

**The use of Oscillatory Positive Expiratory Pressure (OPEP) for airways
clearance in chronic respiratory conditions.**

By

Carwyn G Bridges BSc PgCert

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ABSTRACT

This thesis consists of three intrinsically linked but distinct studies examining the role of airways clearance in chronic lung disease.

Study 1: Analysis of UK data collected multicentre prospective cohort study (Bronch-UK) on airways clearance techniques used in routine hospital care 2015-2022 and factors associated with airway's clearance choice. Data from 1579 patients showed 70% routinely using airways clearance techniques, which is higher than previously reported. Active cycle of breathing technique (ACBT) (77%) and OPEP (38%) being the most common used techniques with 24% using both. No differences in demographics or clinical parameters between those prescribed ACBT versus OPEP. Disease severity was associated with increased use of airways clearance techniques.

Study 2: expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP): A pilot randomised control trial study comparing two airways clearance techniques, ACBT versus OPEP (Aerobika). Recruiting patients that were experiencing an acute exacerbation of chronic obstructive pulmonary disease (COPD) within 3 days from hospital wards or emergency clinics. 19 received OPEP 23 received ACBT, the study struggled to recruit to target and retain data. Although both groups improved significantly and clinically importantly from baseline (during exacerbation), we found no difference in the primary outcome of Leicester cough questionnaire at three months between groups.

Study 3: Three online focus groups explored views on OPEP and what improvements could be made, especially remote monitoring. The 1st group consisted of respiratory physiotherapists working in the NHS with experience prescribing airways clearance techniques in the real word; the 2nd and 3rd focus group was 5 and 2 participants respectively with COPD or bronchiectasis. The main findings were that OPEP was well-tolerated by patients and is valued by healthcare professionals. Smart enabled monitoring of OPEP would be beneficial, depending on cost, data security and technical complexity.

DECLARATIONS AND STATEMENTS

Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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Date 30/05/2025.....

Statements

1. This thesis is the result of my own investigations, except where otherwise stated and that other sources are acknowledged by footnotes giving explicit references and a bibliography is appended.

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2. The metadata and abstract are automatically made available in the University repository to outside organisations. An e-thesis deposit agreement will be supplied to the library if accepted. Access levels to the full text will be managed according to the completed agreement.

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3. The University's ethical procedures have been followed and, locoregional NHS ethical approval and R&D approvals have been granted (see Appendix 3 and 9).

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4. The authors secondment time was funded by Respiratory Innovation Wales who were a not-for-profit organisation funded by Welsh government (2017-2024) and [Trudell Medical International \(TMI\)](#) who help people manage respiratory health with innovative devices. This may be perceived as a potential conflict of interest. The funder had no role in the design of the study; the collection, analysis, or interpretation of data; the writing of the manuscript; or the decision to submit the work for publication.

The author can affirm that the research was conducted independently and objectively, in accordance with the ethical standards of the relevant bodies and conflict of interest policies of Swansea University.

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5. All authors contributed meaningfully to the development and execution of the research. Contributions are outlined below;

Carwyn Bridges: Conceptualisation, study design, data collection, data analysis, interpretation of findings, project administration, coordination with ethical review process. manuscript drafting, editing and finalising.

Prof Keir Lewis: Supervision, funding acquisition, co-conceptualisation, data analysis, critical revision of the manuscript.

TIPTOP: Sarah Bowen: Project administration. Research delivery: Joe Annandale and Dr Scott O'Rourke.

CONNECT: Dr Rachel Gemine: Data analysis, collection and critical revision of the manuscript. Trudell, and all those who publicised the project.

BRONK-UK: Paul McCallion and Dr Jamie Duckers: Interpretation of findings.
Dr Owen Bodger: Statistical support.

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6. The COVID-19 pandemic has had a measurable impact on the timeline and execution of this research project. Although core data collection commenced in September 2021, the preceding period, marked by institutional closures, public health restrictions, and logistical disruptions, caused a radical change in patient pathways resulting in adjustments to the original research plan. This affected stakeholder engagement prior to the start of TIPTOP and impacted recruitment as behaviours of both those receiving and providing healthcare changed.

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TABLE OF CONTENTS

Abstract.....	1-2
Declarations and Statements	1-3
Table of Contents	1-6
Acknowledgements.....	1-11
List of Tables	1-16
List of Figures	1-18
1 Introduction	26
1.1 Mucus and the Healthy Respiratory system	28
1.2 Mucus in Disease	42
1.2.1 Muco-Obstructive lung disease	46
1.3 Airways Clearance Techniques (ACT).....	53
1.3.1 Physical Effects and Mechanisms	55
1.3.2 Breathing Techniques.....	56
1.3.3 Devices.....	63
1.4 Summary.....	90
2 Study: Analysis of Bronch-UK data.....	92
2.1 Introduction	92
2.1.1 Prevalence.....	94
2.1.2 Mortality	96
2.1.3 Socioeconomic Burden.....	96
2.1.4 Pathophysiology	96
2.1.5 Exacerbations.....	102

2.1.6	Pharmacological treatments	107
2.1.7	Airways Clearance.....	113
2.1.8	Pulmonary Rehabilitation.....	115
2.1.9	Smoking Cessation and Vaccination	118
2.2	Aims of Study	119
2.3	Methods	119
2.3.1	Ethics and Approvals	119
2.3.2	Procedure	122
2.3.3	Data Source.....	122
2.3.4	Statistical Analysis	125
2.3.5	Sample	125
2.4	Results	129
2.4.1	Aim One.....	129
2.4.2	Aim Two.....	135
2.5	Discussion	145
3	Study: expectOration of sPutum Techniques real wOrld data in coPd (TIPTOP).....	153
3.1	Introduction	153
3.1.1	COPD Definition	153
3.1.2	Incidence and prevalence.....	156
3.2	COPD Aetiology	162
3.3	Pathophysiological process.....	166
3.4	Diagnosis	171
3.5	Phenotypes.....	175
3.6	Exacerbations.....	178
3.7	Pharmacological Treatments	182
3.8	Non-pharm Treatments.....	194

3.9	Aims and Objectives	205
3.10	Methods	206
3.10.1	Ethics and peer review	206
3.10.2	Participant Selection	208
3.10.3	Participant Identification and Approach	208
3.10.4	Study Visits and Follow-Up	209
3.10.5	Screening procedures	212
3.10.6	Informed Consent	213
3.10.7	Interventions	214
3.10.8	Data collection	218
3.10.9	Outcome Measures	218
3.10.10	Statistical analysis	222
3.10.11	Demographics	223
3.11	Results	225
3.12	Discussion	243
4	Study: CONNECT: Thematic qualitative analysis of Aerobika and Smart Connected Aerobika in chronic respiratory conditions.....	255
4.1	Introduction	255
4.2	Background	256
4.2.1	Objectives	260
4.3	Methods	262
4.3.1	Approvals and Funding	262
4.3.2	Focus group process	263
4.3.3	Thematic Analysis	263
4.3.4	Recruitment	268
4.3.5	Participants/Sampling	271
4.4	Results	276

4.5 Discussion	300
Thesis: Overall conclusions / personal reflections.....	308
Appendix 1: Bronch-UK Study Outline.....	311
Appendix 2: Application for Access to Bronch-UK data	312
Appendix 3: HRA and Health and Care Research Wales (HCRW) Approval Letter (TIPTOP).....	313
Appendix 4: Patient information sheet and Informed consent form (TIPTOP)	314
Appendix 5: Leicester Cough Questionnaire. © 2001 (Birring, 2003)	325
Appendix 6: COPD Assessment Test (CAT)	326
Appendix 7: SF-36 Short form.....	327
Appendix 8: Acceptability and Tolerability (TIPTOP).....	329
Appendix 9: Sample Transcript from HCP Focus Group (CONNECT).....	330
Appendix 10: Questions and areas to be explored - CONNECT	349
Appendix 11: Confirmation of Ethical Approval (CONNECT).....	350
Appendix 12: CONNECT advertisement e-Poster	351
Appendix 13: Patient information sheet and informed consent form (CONNECT).....	352
References	360

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Candidates' role in Thesis

Study: Analysis of Bronch UK data:

I co-designed the project setting out project aims and objectives. I applied for and managed the data working closely with the statistician during analysis. I led the collaboration of a working group that contained leading names in the field, and three professors, working towards publication of the data. I am co-lead of the write-up for publication.

Study: expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP):

I co-designed the research project working to create a protocol and study documents and attended meetings, independently, with the sponsor to gain support and work towards regulatory approval. I prepared the IRAS form and liaised with the ethics committee attending and presenting the project with arm's length support from my supervisor. I led all study set-up activities in site 1 including, protocol, study-specific and intervention teaching. During study delivery, I took on the role of principal investigator managing the research team. I repeated this in the second site taking on study activities including screening, consenting and delivery of intervention in acute and community settings, I sometimes travelled long distances by bike to get the job done! Every follow up was conducted by me contacting, arranging collection, and collating outcome data. Additionally, during the study, I met regularly with peers and supervisors to report on progress and work collaboratively to problem solve. I met with directors of therapies to ensure continued study support, created and managed amendments, led on AE/SAE reporting, and enrolment of Associate PI. Data preparation and analysis was carried out by me with support and guidance from a data checker and supervisor. I was the lead author on any dissemination of results, publications, and write up of thesis.

Study: CONNECT: Thematic qualitative analysis of Aerobika and Smart Connected Aerobika in chronic respiratory conditions:

I co-designed the research project with research, third sector and industry partners working to secure funding for the project. I led protocol development seeking agreement from collaborators and meeting with expert patients to discuss the project. I led gaining necessary approvals from Swansea University ethics committee

creating all the necessary study documents. I liaised with third sector organisations to promote the study and managed all participants from initial response, screening and consent. I led the focus groups alongside an experienced facilitator. I collaborated in the transcription of the data and alongside my co-researcher completed thematic analysis, write-up, and dissemination of the data to industry partners.

Publications

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Other non-Peer reviewed presentations

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Learning and Outcomes from an investigator led trial “TIPTOP”. 7th May 2024 [online]. Hywel Dda Research Quality and Safety Group.

The use of API scheme in an investigator led study. 3rd March 2023. UK Cystic Fibrosis Clinical Trials Day. Newport, South Wales.

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Induced Sputum. 9th March 2023. Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF) Conference. Birmingham.

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LIST OF TABLES

1	Introduction	26
	Table 1.1 Performance characteristics of the OPEP devices at comparable therapy position.....	70
2	Study: Analysis of Bronch-UK data.....	92
	Table 2.3 Mean and SD of scores for the eight domains of the QOL-b.	128
	Table 2.4 Breakdown of ACT types and combinations	131
	Table 2.5 Clinical factors associated with the relative frequency of the use of OPEP and ACBT	133
	Table 2.6. The association between Individual factors and the use of ACT.....	136
	Table 2.7 The association between the dimensions of QoL and the use of ACT	142
	Table 2.8 A combined model for the use of ACT built using stepwise methods.....	144
3	Study: expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP).....	153
	Table 3.1 Post bronchodilator spirometry grades of severity.	172
	Table 3.3 Study Summary Triple therapy inhalers – combinations of ICS+LABA+LAMA	190
	Table 3.4 Amendments dates and summary	207
	Table 3.5. Social demographics at base line.....	223
	Table 3.6. Severity of disease at baseline.	224
	Table 3.7 Means and SD of LCQ at each time point.....	226
	Table 3.8 LCQ Responder rate percentages.....	228
	Table 3.9 Means and SD of CAT at each time point.....	231
	Table 3.10 CAT Responder rate percentages.....	233
	Table 3.11. Means and SD of courses of oral Antibiotics (ABx).....	236

Table 3.12 Means and SD of hospital admissions since last review.....	239
Table 3.13 Serious Adverse Events (SAE).....	241
Table 3.14 Tolerability of interventions	242
Table 3.15 Acceptability of intervention	242
Table 3.16 Methodologies of recent studies for comparison.....	248
 4 Study: CONNECT: Thematic qualitative analysis of Aerobika and Smart Connected Aerobika in chronic respiratory conditions.....	 255
Table 4.1 Connect research questions and TA linkage.....	261
Table 4.2 Table of demographics for Healthcare Professionals.....	273
Table 4.3 Table of demographics Participants with Chronic lung condition	 275
Table 4.4 Summary of Comments on Device Choice	280
Table 4.5 Summary of Comments on Learning and Teaching.....	284
Table 4.6 Summary of comments on the theme of Doing.	289
Table 4.7 Summary of comments on monitoring compliance and adherence	 293
Table 4.8 Summary of comments on tracking and monitoring / smart device	 297

LIST OF FIGURES

1	Introduction	26
	Figure 1.1 Structure of the respiratory system	27
	Figure 1.2 Distributions of mucins in mucus gels and PCL.....	30
	Figure 1.3 A: Diagrammatic representation of Mucosal gland structure B: serous cells, C: mucous cells in mucous tubule, D: non-ciliated cells in collecting duct.	32
	Figure 1.4 Ciliary structure and function.....	35
	Figure 1.5 Cilia compress as they beat.....	37
	Figure 1.6 Archimedes screw	39
	Figure 1.7 Effects of airflow on mucus during cough.	41
	Figure 1.8 Progression from normal to muco-obstructed disease state.	43
	Figure 1.9 Illustration depicting PCL compression with a hyper-concentrated mucus layer.....	45
	Figure 1.10 Mediators of mucin expression and histopathological changes in chronic respiratory diseases.	47
	Figure 1.11 Pathway of mucus in ex-smoker (A) non-smoker (B)	49
	Figure 1.12 Chest physiotherapy interventions overview. ERS statement on airways clearance.	54
	Figure 1.13 Pathways for collateral ventilation	57
	Figure 1.14 Proposed mechanisms by which ACBT results in secretion clearance.	57
	Figure 1.15 Breathing pattern during autogenic drainage.	61
	Figure 1.16 OPEP waveform and physiological mechanisms.	66
	Figure 1.17 A selection of commonly available OPEP devices.	68
	Figure 1.18 Representation of oscillation frequency and amplitude of different OPEP devices.	72

Figure 1.19 Mean (SD) values for oscillation frequency for the different devices and waveforms.	74
Figure 1.20 Mechanism of Aerobika vane and valve.	78
Figure 1.21 Using an Aerobika	80
Figure 1.22 Recyclable Aerobika.....	82
Figure 1.23 Aerobika with manometer and numbered resistor settings.....	84
Figure 1.24 High-Frequency Chest Wall Oscillation (HFCWO)	87
Figure 1.25 Standard approach to MI-E initiation in adults.....	89
2 Study: Analysis of Bronch-UK data.....	92
Figure 2.1 Underlying causes of bronchiectasis in the EMBARC cohort (n=16983).	93
Figure 2.2 Incidence of bronchiectasis in the UK from 2004 to 2013 stratified by age in a) men and b) women.....	95
Figure 2.3 The four key aspects underpinning the vicious vortex of bronchiectasis.	97
Figure 2.4 Cycle of Pseudomonas biofilm development.....	100
Figure 2.5 Results ‘Criteria of an Exacerbation’ Delphi process.....	104
Figure 2.6 Schematic for exacerbation prevention in bronchiectasis.	106
Figure 2.7 Treatment for bronchiectasis according to the vicious cycle concept.....	108
Figure 2.8 Components of pulmonary rehabilitation.....	117
Figure 2.9 Bronch-UK study flow chart.	121
Table 2.2 Demographics of sample.....	127
Figure 2.10 Distribution of people who perform ACT.....	130
Figure 2.11. Visual representation of breakdown of ACT types and combinations.	131
Figure 2.12 Association between clinical factors and the specific ACT (PsA)	133

Figure 2.13 Association between clinical factors and the specific ACT (Exacerbation Rate)	134
Figure 2.14 Association between clinical factors and the specific ACT (mMRC)	134
Figure 2.15. Association between severity and the use of ACT (Exacerbation Rate).....	138
Figure 2.16 Association between severity and the use of ACT (BSI)	138
Figure 2.17 Association between severity and the use of ACT (mMRC)	139
Figure 2.18 Association between severity and the use of ACT (PsA)	139
Figure 2.19 Association between severity and the use of ACT (Asthma)....	140
Figure 2.20 Association between severity and the use of ACT (FEV ₁).....	140
Figure 2.21 Association between severity and the use of ACT (Gender)	141
 3 Study: expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP)	 153
Figure 3.1 Causes and Progression of COPD	154
Figure 3.2 Classification of COPD according to risk factors.	155
Figure 3.3 Inverse distance weighted (IDW) interpolation map of chronic obstructive pulmonary disease (COPD) prevalence in the world.....	157
Figure 3.4 2nd Atlas of variation for respiratory disease in England, map 7c variation in COPD.	159
Figure 3.5 Respiratory admissions and death rates, Wales 2020/21.....	161
Figure 3.6 Taxonomy of COPD.	163
Figure 3.7 Monocyte and neutrophil recruitment in the pathogenesis of COPD.	167
Figure 3.8 Increased oxidative stress drives the pathology of COPD through several mechanisms.....	169
Figure 3.9 Airflow Obstruction spirometry trace.	172
Figure 3.10 Differential diagnosis that may mimic or contribute to an exacerbation of COPD.....	174

Figure 3.11 Increased probability of no readmission against FEV1 and eosinophil.....	177
Figure 3.12 Causes, Pathology and Physiology of Exacerbations in COPD.	179
Figure 3.13 ABE assessment tool for exacerbations.	181
Figure 3.14 Initial Pharmacological Treatments.....	183
Figure 3.15 The distribution of beta receptors in the body.....	185
Figure 3.16 Proposed synergistic effect of LABA and inhaled corticosteroids.	188
Figure 3.17 Proportion of participants free from acute exacerbations of COPD for 1 year.	192
Figure 3.18 Smoking prevalence in the UK	195
Figure 3.19 Smoking attributed mortality in Wales by deprivation.	196
Figure 3.20 MRI ventilation in representative sputum and non-sputum producers.	202
Figure 3.21. Pathway A (Admitted to Hospital)	210
Figure 3.22. Pathway B (Outpatient identification)	211
Figure 3.23 ACBT diagram	216
Figure 3.24 TIPTOP Consort flow Diagram.....	217
Figure 3.25 Graph of mean LCQ Scores over time	227
Figure 3.26 LCQ Score changes from 0 to 4 weeks following OPEP intervention	229
Figure 3.27 LCQ Score changes from 0 to 4 weeks following ACBT intervention	230
Figure 3.28 Graph mean CAT score over time.	232
Figure 3.29 CAT Score changes from 0 to 4 weeks following OPEP intervention	234
Figure 3.30 CAT Score changes from 0 to 4 weeks following ACBT intervention	235

Figure 3.31 Graph self-reported courses of Antibiotics (Abx) since last review.	237
Figure 3.32 Graph self-reported courses of Antibiotics (Abx) Overtime.	238
Figure 3.33 Graph admissions since last review.	240
Figure 3.34. Graph cumulative admissions overtime.	241
 4 Study: CONNECT: Thematic qualitative analysis of Aerobika and Smart Connected Aerobika in chronic respiratory conditions.....	 255
Figure 4.1 Provisional Thematic map	265
Figure 4.2 Social media post to recruit to CONNECT.....	269
Figure 4.3 Response Rate to Advert Over Time.....	270
Figure 4.4 Final Thematic map	277

Abbreviation	Definition
AATD	Alpha-1 Antitrypsin Deficiency
ACBT	Active Cycle of Breathing Technique
ACO	Asthma-COPD overlap
ACPRC	Association of Chartered Physiotherapists in Respiratory Care
ACT	Airways Clearance Techniques
AD	Autogenic Drainage
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
ATS	American Thoracic Society
BMI	Body Mass Index
BSI	Bronchiectasis Severity Index
BTS	British Thoracic Society
CAP	Community-Acquired Pneumonia
CAT	COPD Assessment Test
CCG	Clinical Commissioning Groups
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane regulator
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CT	Computed Tomography
CVD	Cardiovascular Diseases
DNA	Deoxyribonucleic Acid
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
ERS	European Respiratory Society
FEV ₁	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Professionals
HCRW	Health Care Research Wales
HFCWO	High-Frequency Chest Wall Oscillation
HI	Haemophilus Influenza
HR	Heart Rate
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTS	Hypertonic Saline
ICP	Intracranial Pressure
ICS	Inhaled Corticosteroid
IOS	Impulse Oscillometry
IPC	Infection Prevention Control

IQR	Inter Quartile Range
IRAS	Integrated Research Application System
IRR	Incidence Rate Ratio
LABA	Long-Acting Beta Agonists
LAMA	Long-Acting Muscarinic Antagonists
LCI	Lung Clearance Index
LCQ	Leister Cough Questionnaire
LoA	Length of Admission
LTOT	Long-Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
MCID	Minimal Clinically Important Difference
MD	Mean Difference
<i>MDT</i>	Multi-Disciplinary Team
mMRC	Modified British Medical Research Council Dyspnoea Scale
MRI	Magnetic Resonance Imaging
NET	Neutrophil extracellular Traps
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health and Care Research
NIV	Non-Invasive Ventilation
NNT	Number Needed to Treat
NTM	Non-Tuberculous Mycobacteria
OCM	Outcome Measures
OPEP	Oscillatory Positive Expiratory Pressure
OR	Odds Ratio
PCD	Primary Ciliary Dyskinesia
PCL	Periciliary Liquid Layer
PEP	Positive Expiratory Pressure
PF	Pulmonary Fibrosis
PIS-ICF	Participant Information Sheet - Informed Consent Form
PO	Primary Outcome
PR	Pulmonary Rehabilitation
PsA	Pseudomonas Aeruginosa
QoL	Quality of Life
QoL-b	Quality Of Life - Bronchiectasis
RCT	Randomised Control Trial
REC	Regional Ethics Committee
RIP	Rest In Peace
RIW	Respiratory Innovation Wales
ROS	Reactive Oxygen Species
SA	Staphylococcus Aureus
SAE	Serious Adverse Event
SABA	Short Acting Beta Agonist

SD	Standard Deviation
SF-36	Short Form - 36
SGRQ	St George's Respiratory Questionnaire
SITT	Single Inhaler Triple Therapy
SOB	Shortness Of Breath
SPSS	Statistical Package for the Social Sciences
SUMS	Swansea University Medical School
TDI	Transition Dyspnoea Index
TNF	Tumour Necrosis Factor
TMI	Trudell Medical International
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

1 INTRODUCTION

“Marvels of Mucus and Phlegm. The Slime That Keeps You Healthy”

(NIH, 2020)

This chapter will outline the structure and function of mucus in the respiratory system describing its physiological properties, transport, the process of coughing, and consider elements of its dysfunction in chronic respiratory health. Airways clearance is a key nonpharmacological treatment of excess treatments. The author aims to describe the physiological actions and the literature to support each modalities use.

The respiratory system is made up of the nasal cavity, pharynx, larynx, trachea bronchi and lungs with mucus membranes being present throughout, see Figure 1.1. The following sections will focus on the structure and function of mucus and the physiological apparatus in the bronchioles and terminal bronchioles unless explicitly stated.

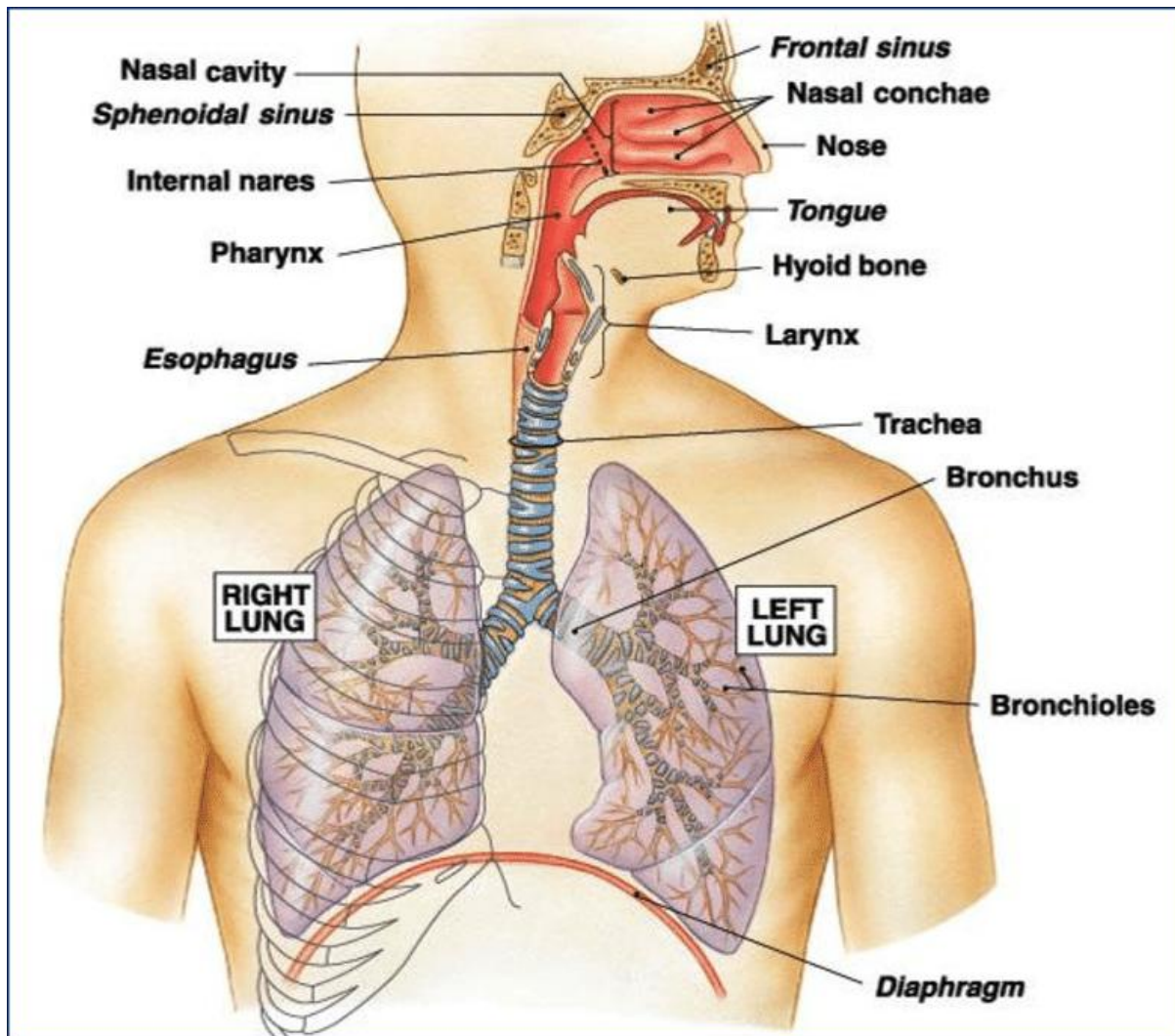


Figure 1.1 Structure of the respiratory system

(Jabbar, 2016)

1.1 MUCUS AND THE HEALTHY RESPIRATORY SYSTEM

Mucus can be considered to have three roles in the lungs.

- Firstly, airway mucus acts to defend the lungs from the environment and the constant barrage of noxious particles and bacteria that are inhaled during the metronomic and constant process of breathing. It is estimated that we inhale 10^4 - 10^6 bacteria and other particles per day, that small and large airways are required to repel and neutralise (Chatterjee et al., 2020).
- Secondly, mucus acts to moisturise the airway ensuring that vital functions operate effectively. This is achieved by the regulation of sodium ions in the epithelium and the aqueous layer creating an osmotic gradient to shift the fluid in the system (Hill et al., 2022).
- Thirdly, mucus traps and facilitates the removal of debris and pathogens acting as the transport agent in mucociliary clearance (Knowles & Boucher, 2002).

Physical Properties and Composition of Mucus

Mucus in the airways is composed mainly of water, ions, mucin glycoproteins, and various other macromolecules, creating a gel-like substance that covers the airway surfaces (Lillehoj et al., 2013). The secreted polymeric mucins, particularly MUC5AC and MUC5B, are crucial for forming this gel and contribute significantly to its rheological properties (Thornton et al., 2008).

The polymeric mucins MUC5AC and MUC5B are the largest in this system and can assemble to create thicker secretions using cysteine-mediated disulfide bonds that link terminal regions of the mucin monomers (Hill et al., 2022).

The viscoelasticity of mucus is crucial to allow it to perform its critical barrier function. The complex nature of mucus means it can act as a viscous liquid, deforming and shearing during mucociliary escalation and behaving like an elastic solid at low frequency to trap bacteria and particles (Song et al., 2020). The rheology of sputum is associated with the quantity of organic matter present in mucus, with an average value of 1.5%, which is considered normal in the in vitro models. However, several

studies have shown the viscosity of sputum at different percentages of organic matter. D. B. Hill et al. (2014) showed 0.5% of organic matter gave a viscosity 10 times that of water whilst Dawson et al. (2003) found sputum in Cystic Fibrosis (CF) containing 10% organic matter to be at least as viscous as honey.

In an updated model known as 'Gel on brush' the description of distinct types of mucins provides a rationale for the presence of distinct gel layers that do not penetrate the inter-cilia spaces (Hill et al., 2022). The periciliary liquid layer (PCL) consists of tethered mucins such as MUC1, MUC4, and MUC16 that form a brush between the cilia and have distinct structures that play critical roles in hydration, lubrication and provide the barrier function of airway mucus (Kesimer et al., 2013), see Figure 1.2.

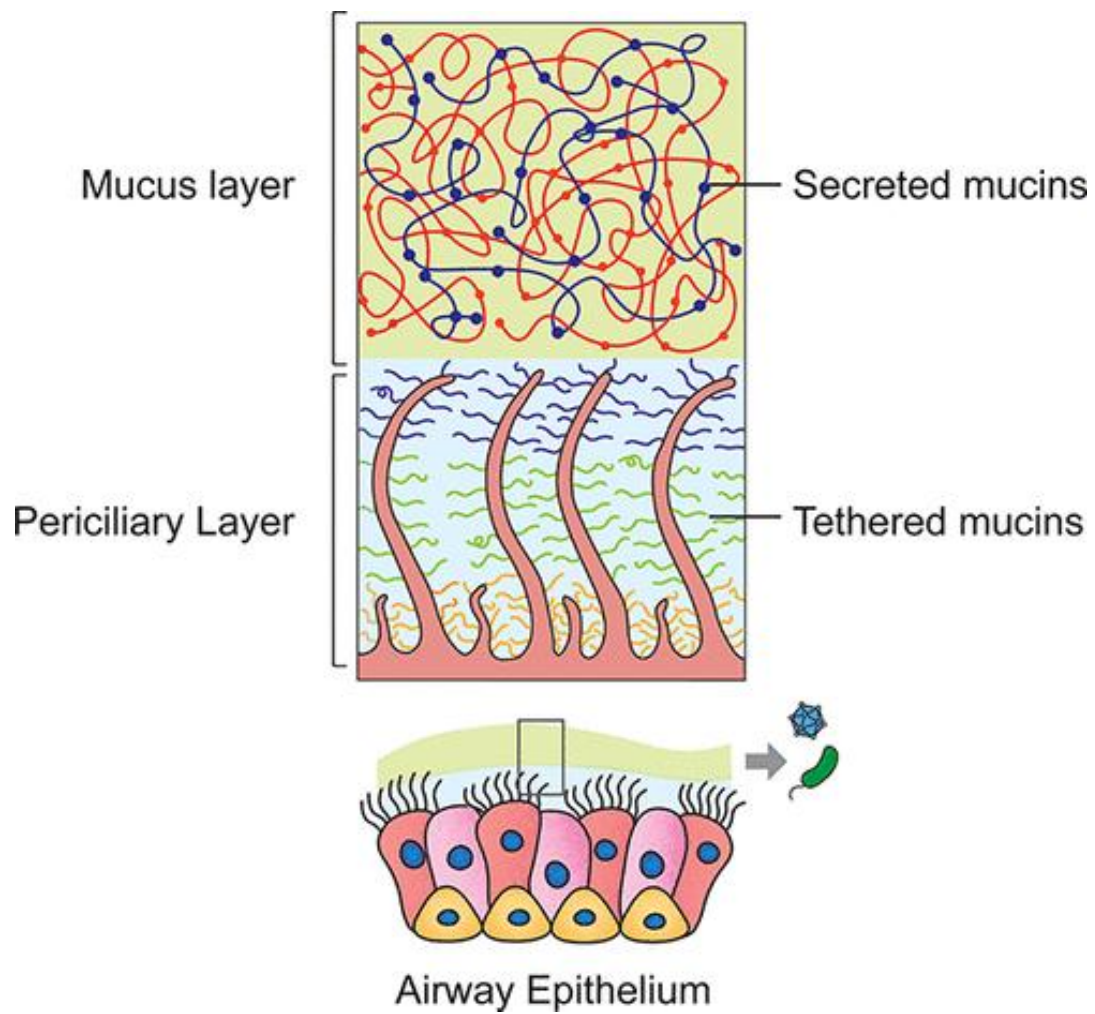


Figure 1.2 Distributions of mucins in mucus gels and PCL.

(Song et al., 2020)

This complex molecular architecture of mucins and the dynamic properties of the mucus gel are essential for maintaining respiratory health and preventing lung damage (Song et al., 2020).

Factors Influencing Mucus Production.

Airways glands produce mucus by secreting the components of airway mucus. These glands have a complex structure, including a single terminal duct, a non-ciliated duct and branching secretory tubules lined with serous cells and mucous cells, as can be seen in Figure 1.3 (Widdicombe & Wine, 2015).

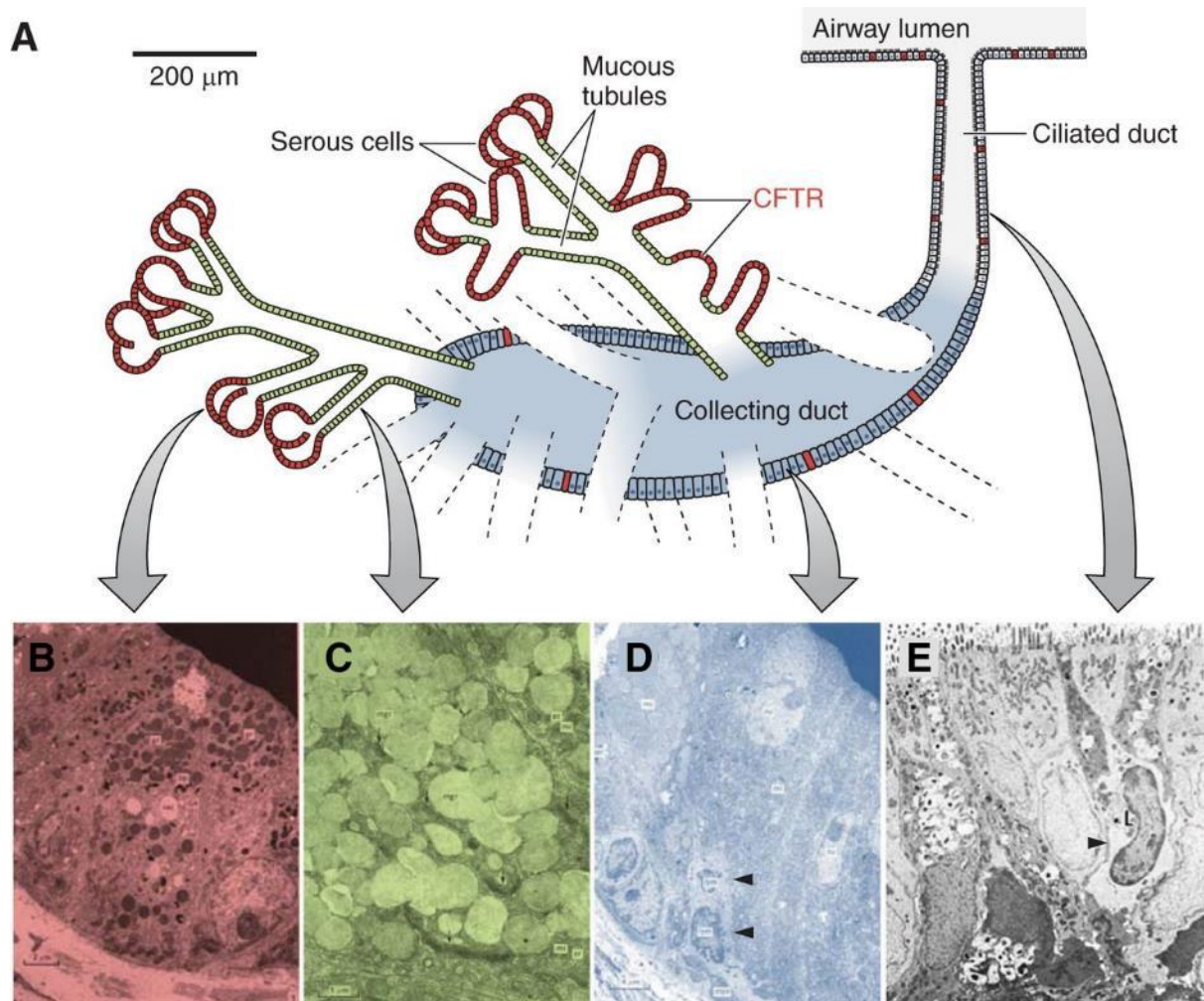


Figure 1.3 A: Diagrammatic representation of Mucosal gland structure B: serous cells, C: mucous cells in mucous tubule, D: non-ciliated cells in collecting duct.

(Widdicombe & Wine, 2015).

The classic view mode of secretion of the key mucins of the gel layer described the MUC5AC as being released from the superficial epithelium of the proximal and distal airways whilst the MUC5B was associated with the submucosal glands of the proximal airways (McShane, Bath, et al., 2021; Widdicombe & Wine, 2015). However, data from Okuda et al. (2019) suggests that MUC5B is secreted from a small granular pathway in club cells in both proximal and distal airways. At the alveolar level the same club cells secrete surfactant rather than MUC5B in order to keep the high surface area of these structures optimised for gas exchange (Brasch et al., 2004).

Mucus production is regulated by neural, hormonal and immune factors and in the healthy lung these factors act to regulate between production for entrapment and transport of particles and pathogens but also control of clearance of mucus through mechanical mechanisms (Widdicombe & Wine, 2015). The level of production at a basal level has been shown to be 1/10th of that in an activated or excited state. Interestingly, and key to the authors understanding, these states have been described as 'Housekeeping' and 'Emergency' (Widdicombe & Wine, 2015).

Neural involvement in the regulation of secretion of mucus has been under investigation since 1864 when Claude Bernard noted that activity of salivary glands diminished after denervation of the parasympathetic nerves (Mandour et al., 1977). Widdicombe and Wine (2015) comment that MUC5B secretion is promoted by the cough reflex in a healthy model. Research in lung transplant patients has shown the stimulation of the transplanted lung below the anastomosis, an area of denervation, produces less mucus in the absence of a cough reflex (Dubin et al., 2004).

Hormonal modulation plays an important role in mucus production. Studies are difficult *in vivo* due to the difficulty in isolating the specific system under investigation therefore *in vitro* studies have been used to demonstrate hormonal modulation. The key hormones responsible for the upregulation of the production of mucus are cholinergic agents (Widdicombe & Wine, 2015).

The secretion of immunological factors such as immunoglobulin A and immunoglobulin M from airway glands play an important role in the innate immune response of the airways (Bartlett et al., 2008). Added to this, the secretion of antimicrobial chemicals and proteins regulate the micro-environment of mucus and

the airways making it inhospitable to bacteria and promoting the action of macrophages (Warszawska et al., 2013).

Mucus secreted in the healthy respiratory system is a fine balance optimised for defence, moisturisation and mucociliary clearance - with all the contributing parts acting as one to regulate the quantity and viscosity of mucus.

The Mucociliary Escalator

Mucociliary clearance is a crucial function of airway mucus with the coordinated beating of cilia and the rheological properties of mucus working together to trap particles and pathogens from the respiratory tract (Hill et al., 2022). The complexity of the mucociliary escalator can be viewed through macroscopic and microscopic scales, with different factors influencing the mucociliary escalator.

Respiratory epithelium in the proximal and distal airways are covered in cilia that are between 5 and 7 μm long with each epithelial cell hosting 50 to 200 cilia. They move in a rhythmically coordinated fashion beating at 20 cycles a second and clearing debris at 2cm per minute (Houtmeyers et al., 1999; Satir & Sleight, 1990), see Figure 1.4. The nature of the beating can be split in two, the first being an effective stroke whose action creates the motion of the gel layer and the return stroke returns the cilia to its starting position through the aqueous periciliary layer (Antunes & Cohen, 2007).

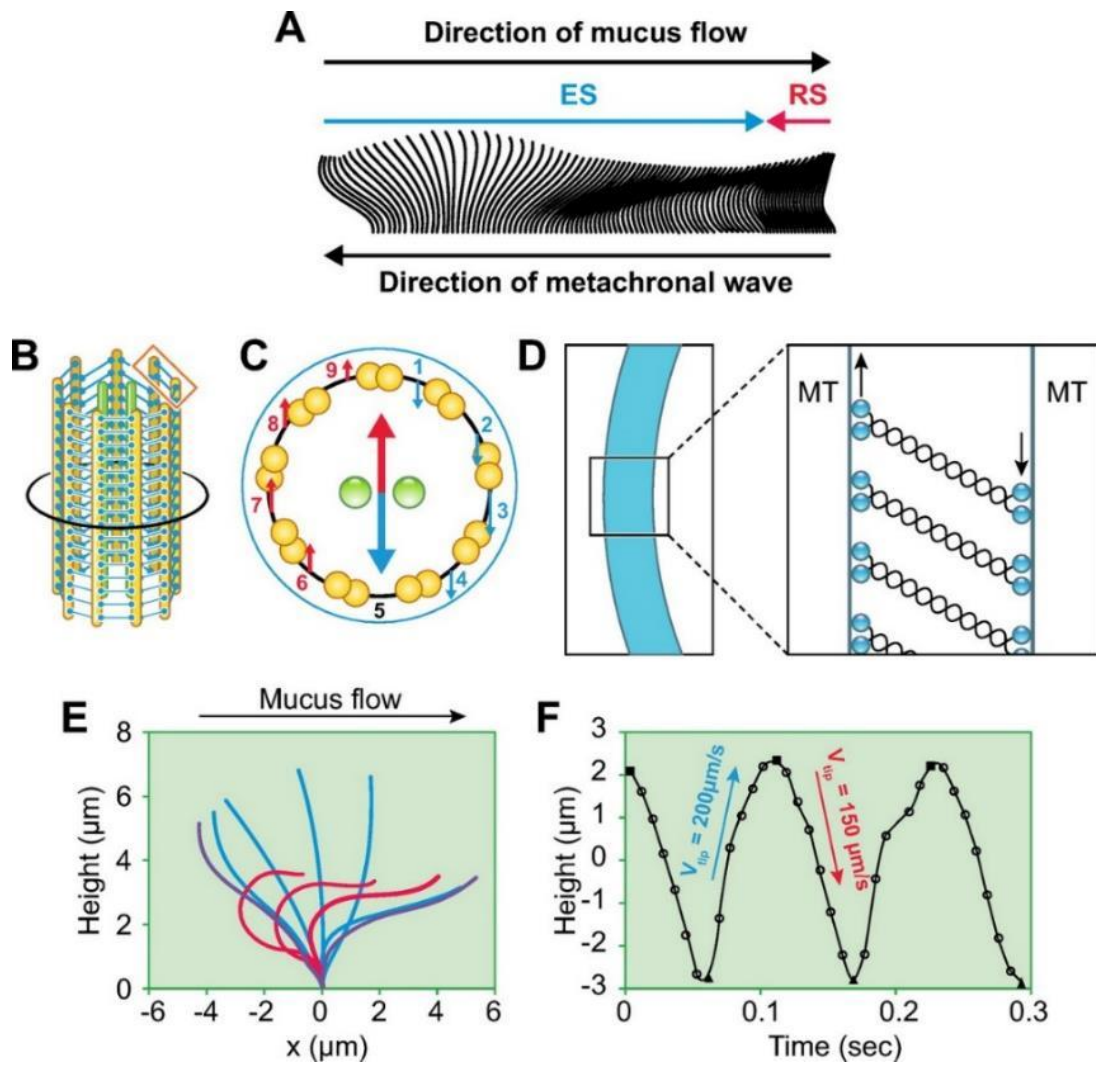


Figure 1.4 Ciliary structure and function.

(Hill et al., 2022)

The cilia are made up of molecular motors inside the axoneme which shorten according to the direction of travel, as can be seen in sections B, C and D of Figure 1.4. The cilia are made up of nine microtubules arranged concentrically with one side contracting using dynein motor proteins to produce the effective stroke and the other side responsible for the return stroke (Satir, 1999). Ciliary activity is regulated through mechanical (Sanderson & Dirksen, 1986), thermal (Mwimbi et al., 2003), chemical (Jain et al., 1993), and hormonal stimuli (Sanderson & Dirksen, 1989), that change the phosphorylation status of axonemal proteins (Gertsberg et al., 2004).

The understanding of the interaction between cilia and mucus has developed over time and as observational techniques improved cilia were thought to interact chemically with secreted mucins in the mucus layer to aid transport (Hill et al., 2022). However, recent studies have suggested that as the motors act to compress the cilia during the active stroke water is displaced from the tip aiding the distortion and movement of the mucus layer, propelling the mucus along and then rehydrating during the return stroke (Guo et al., 2017), see Figure 1.5.

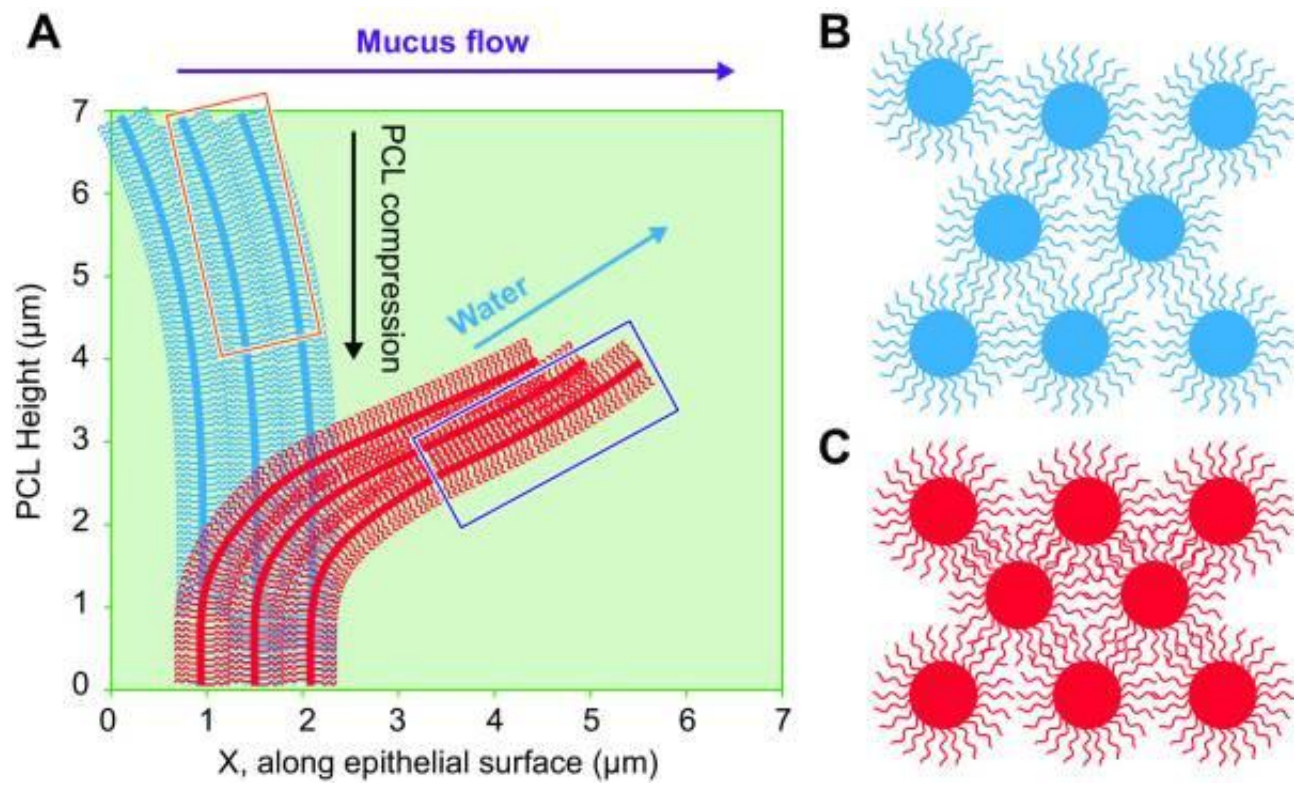
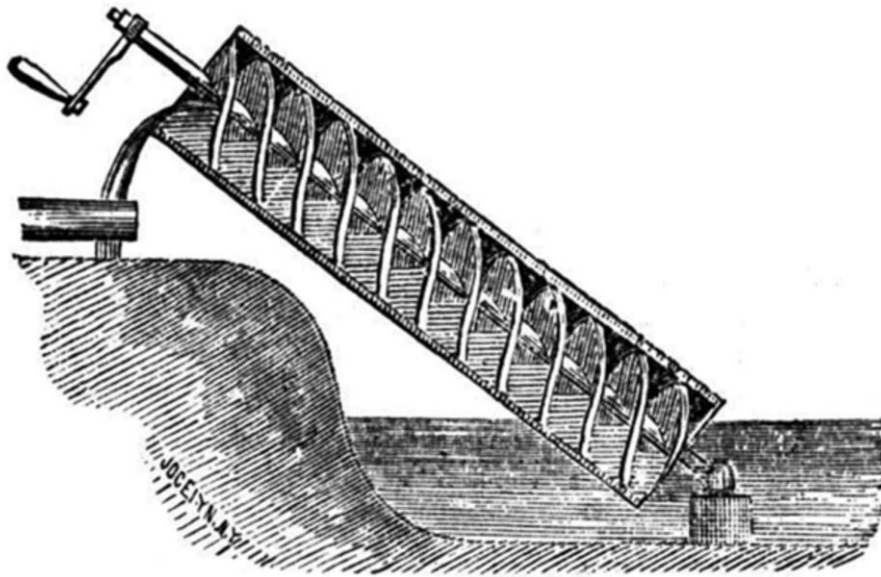


Figure 1.5 Cilia compress as they beat.

(Hill et al., 2022).

The full picture of the way that mucus moves in the airways is a developing story as many studies have reported different outcomes depending on the nature of the research. The difficulty remains that in vivo and in vitro studies provide different information to inform the true biological picture (Hill et al., 2022). However, it is useful to consider previously described mechanisms to give a better understanding of the processes at play. The long-held model described by Morgan et al. (1984) describes the mucus gel layer as a continuous blanket moving 'quickly' proximally allowing older mucus with trapped noxious particles to be expectorated as fresh mucus replaces it. Secondly, it has been proposed that flakes or aggregates made up of insoluble mucus masses 10-100 μm float proximally along the gel layer dealing with detritus (Bennett et al., 2015). Whilst sweepers or strands may act to clear large deposits in the upper airway (Hill et al., 2022). In a paper describing the movement of mucus Abelson et al. (2024) used radiolabelled secretions in human subjects and found that, in healthy individuals, mucus moves proximally in a helical pattern similar to an Archimedes screw, rotating clockwise when viewed from below, see Figure 1.6. This pathway is different in disease and is further discussed in disease-specific sections.

The Archimedes screw profile of an Archimedes screw, the design for which has been used to pump water up slope since Ancient Egyptian and Greek civilisations (image available under Creative Commons/CC BY-SA 4.0).



David Abelson et al. Thorax 2024;79:607-614

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THORAX

Figure 1.6 Archimedes screw

(Abelson et al., 2024)

In the healthy lung, the final stage of mucociliary clearance is the expectoration of mucus where it is swallowed in most cases and cleared by cough in the event of pooling due to temporary dysfunction of the mucociliary escalator (Bennett et al., 1990). Airflow, during cough, in the distal airway aids the movement of mucus with lower velocity air acting to slide mucus proximally (Hasani et al., 1994). However, in the larger proximal airways higher airflow acts to produce shearing forces in the mucus layer causing the mucus to peel from the airway surface (Walker et al., 1990). Studies have shown that the shear forces needed in this process are correlated with the quantity of organic solids in the mucus (Button et al., 2012), see Figure 1.7.

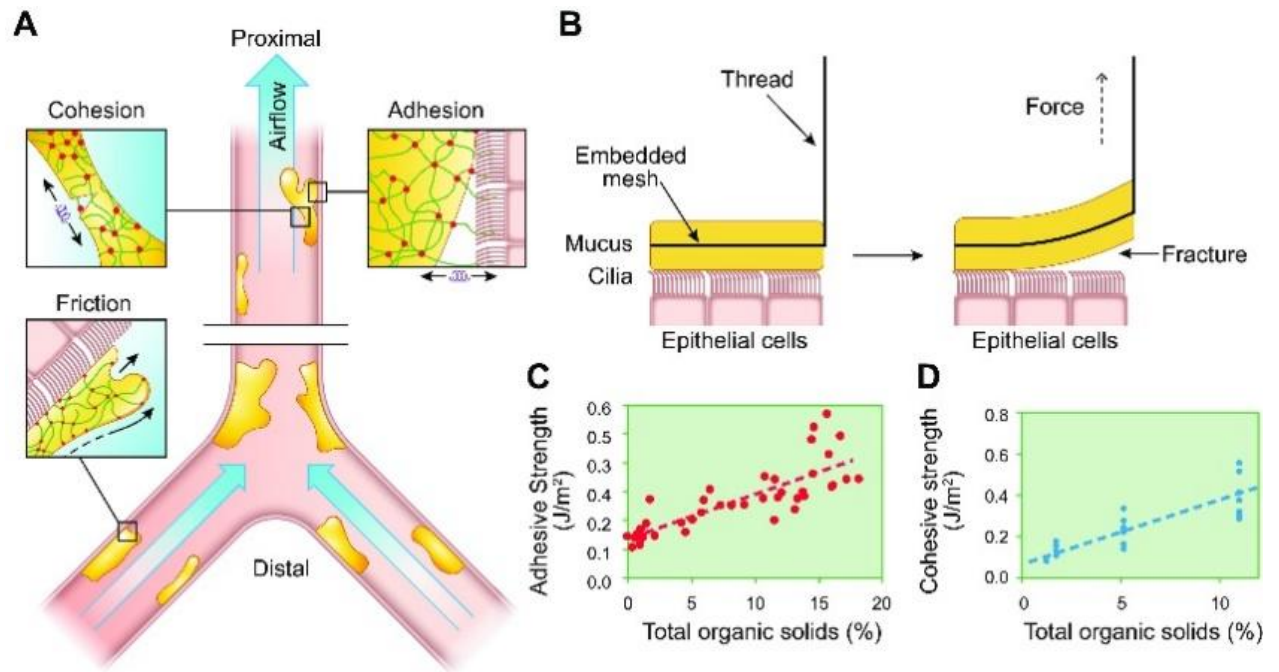


Figure 1.7 Effects of airflow on mucus during cough.

(Hill et al., 2022)

1.2 MUCUS IN DISEASE

There are several chronic respiratory conditions that are hallmarked by an increase in mucus viscosity and volume and can be termed muco-obstructive lung disease (Singh et al., 2023). Figure 1.8 shows the progression from a healthy to a muco-obstructed disease state with the balance of sodium ion absorption and calcium ion secretion affecting the hydration of the airway liquid layer. This happens from within the epithelium by osmotically compressing the PCL (Hill et al., 2022).

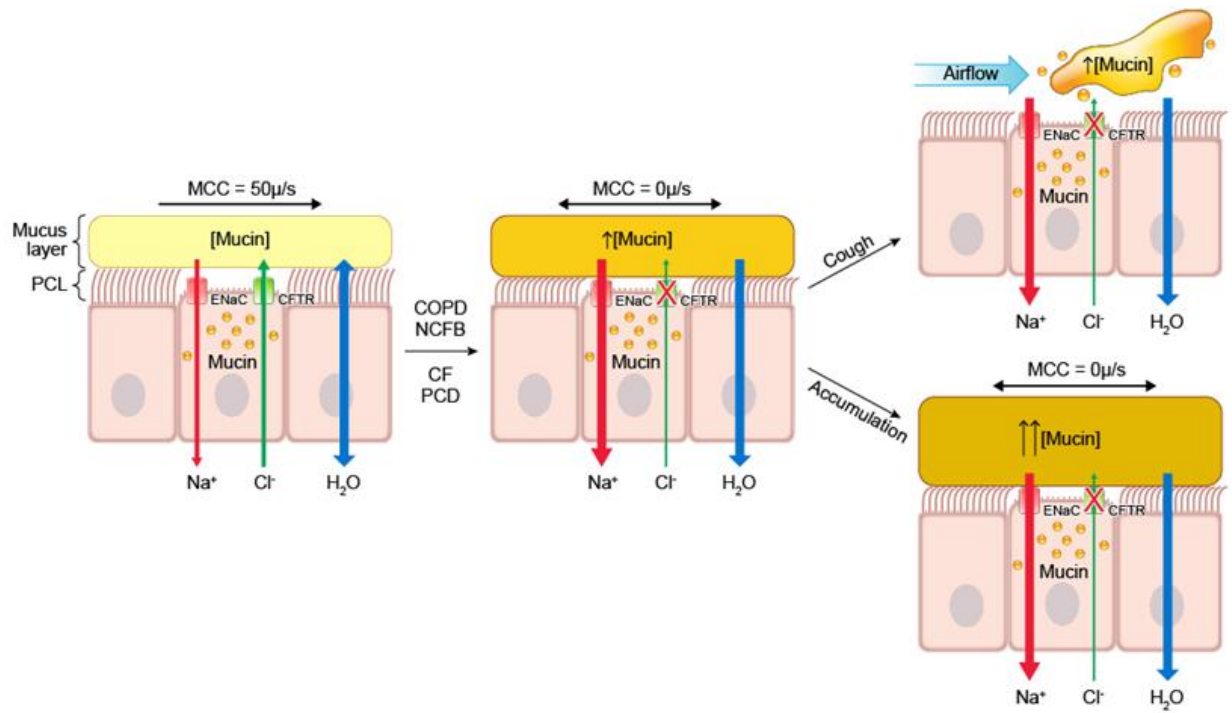


Figure 1.8 Progression from normal to muco-obstructed disease state.

(Hill et al., 2022)

An imbalance of this process alongside the secretion of excess mucins acts negatively on the mucociliary escalator. When the mucus layer becomes hyper-concentrated and its osmotic pressure exceeds that of the PCL, water is drawn from the underlying PCL into the mucus layer leading to compression of the cilia and inhibiting the beating of the cilia, as can be seen in Figure 1.9 (Button et al., 2012).

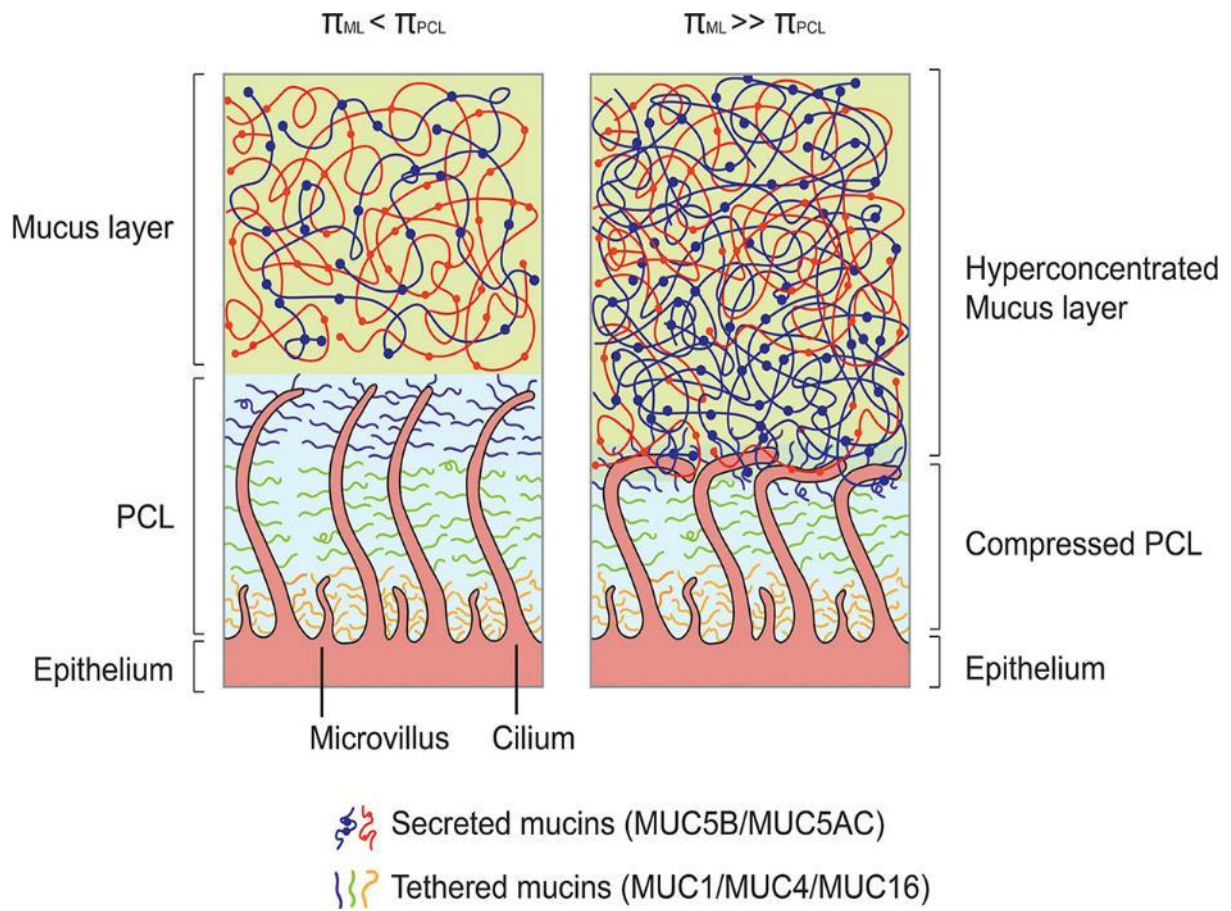


Figure 1.9 Illustration depicting PCL compression with a hyper-concentrated mucus layer.
 (Song et al., 2020)

1.2.1 Muco-Obstructive lung disease

Conditions of muco-obstruction share the common problem of excess mucus resulting in a build-up of sputum; however, the intricacies of getting to this point and the make-up and structure of sputum differ by condition (Abrami et al., 2024).

Chronic Obstructive Pulmonary Disease (COPD)

In the chronic bronchitis phenotype of chronic obstructive pulmonary disease (COPD), the presence of sputum created by mucus hypersecretion is a prominent feature contributing to airway obstruction (breathlessness) but also to inflammation and fibrosis of the small airways (Burgel et al., 2009). The failure of this defence mechanism in COPD increases the risk of patients experiencing acute exacerbations that are mediated by bacterial and viral infections (Wedzicha, 2015). Figure 1.10 shows mediators that contribute to changes in sputum attributing them to the epithelial structures in COPD.

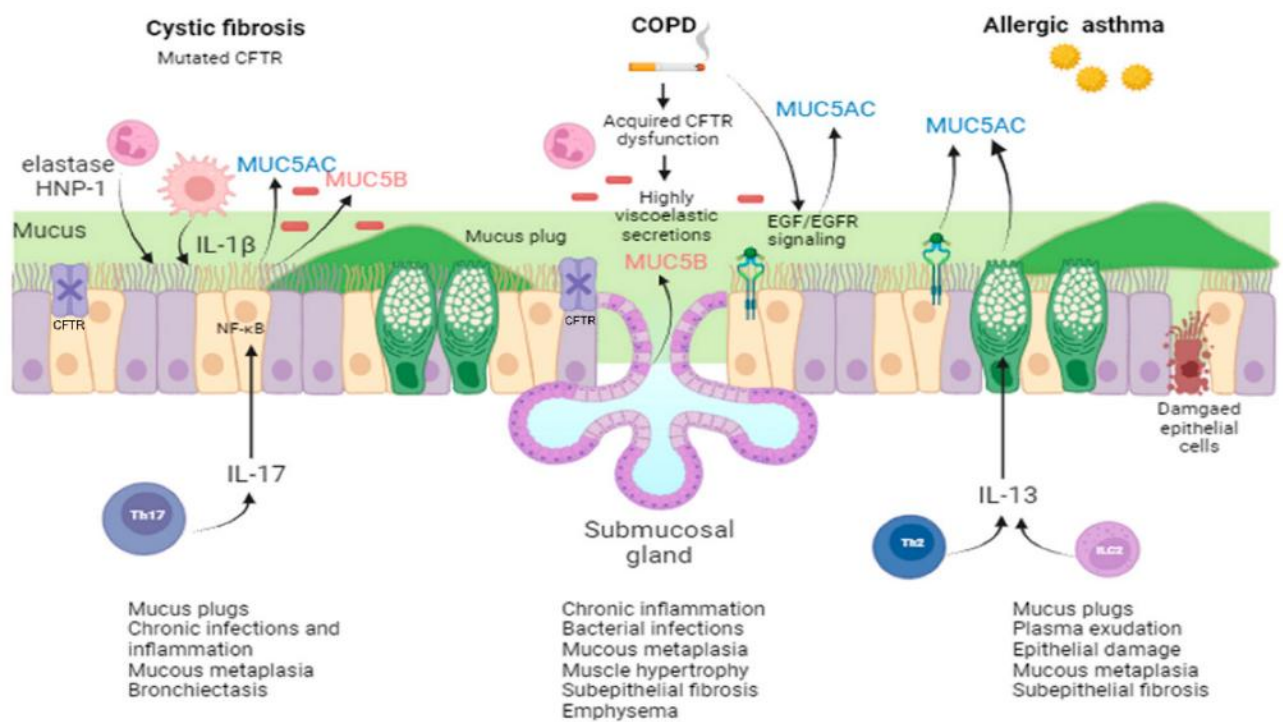
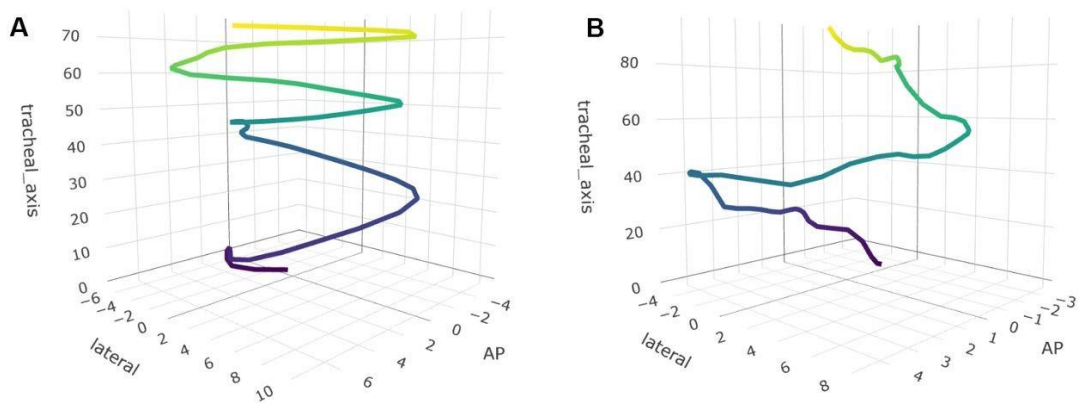


Figure 1.10 Mediators of mucin expression and histopathological changes in chronic respiratory diseases.

(Abrami et al., 2024)

COPD sputum has a high viscosity and contains much higher levels of MUC5AC and MUC5B than normal with this abnormally high level modulated by smoking (Abrami et al., 2024; Kirkham et al., 2002). Higher levels of albumin secreted due to goblet cell hyperplasia and submucosal gland hypertrophy result in airway inflammation driven by excess and activated macrophages and neutrophils (Chung & Adcock, 2008; GOLD, 2024a). Additionally, the helical pathway of the mucociliary escalator is disrupted in COPD. Abelson et al. (2024) recruited 20 participants including, three younger non-smokers (mean (IQR) age 37 (10) years 34% female), 12 ex-smokers (mean (IQR) age 71 (16) years 34% female) with median predicted forced expiratory volume in one-second (FEV₁) of 61% and a diagnosis of COPD, and five people with primary ciliary dyskinesia (PCD). Described the pathway of radiolabelled tracked sputum in ex-smokers (COPD) as moving in a similar helical pattern but travelling a greater distance before expectoration, as seen in Figure 1.11. Abelson et al. (2024) describe the helical angle as *not fixed* varying in speed and proximal motion negatively with disease, age and smoking history.



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Figure 1.11 Pathway of mucus in ex-smoker (A) non-smoker (B)
(Abelson et al., 2024)

Therefore, the need to manage excess sputum through physiological processes such as cough and the use of pharmacological and non-pharmacological treatments such as airways clearance techniques (ACT) are considered key cornerstones of treatment (Ramos et al., 2014). The pathophysiology of COPD is further discussed in Chapter 3.

Asthma

Asthma is characterised by reversible airflow obstruction that causes persistent cough, wheeze, and chest tightness; however, the process of inflammation leads to thickening of airway walls and increased smooth muscle mass (Fabbri et al., 2003). Viscous sputum in asthma also contains more MUC5AC than normal with mucus plugs, in the small airways, made up of high levels of mucins that are tethered to the airway epithelium (Shimura et al., 1996). Figure 1.10 shows mediators that contribute to changes in sputum attributing them to the epithelial structures in asthma.

Computed tomography (CT) changes in asthma have shown that mucus plugging is a key feature of asthma pathophysiology (Dunican et al., 2018). Svenningsen and Nair (2022) suggest that these mucus plugs should be a target for novel pharmacological therapies but recognise the importance of considering established therapies such as ACT in patients with persistent cough.

Cystic Fibrosis (CF)

CF is a recessive heterogeneous genetic life-limiting condition that involves a fault in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that dysregulates the mucus environment in the CF lung. Factors generated by the faulty CFTR gate are numerous and include the creation of an acidic and dehydrated environment due to abnormal Cl^- and HCO_3^- secretion and dysregulated activity of the sodium channel (ENaC) resulting in PCL dehydration (Morrison et al., 2019). See Figure 1.8.

CF sputum has been shown to contain higher levels of mucins including MUC5B and MUC5AC and bundles of deoxyribonucleic acid (DNA) and F-actin from dead inflammatory cells (Chalmers et al., 2023; Tang et al., 2005). In CF the CFTR channel is responsible for causing the hypersecretion of mucins and influencing the

hyper concentration of sputum (Morrison et al., 2019). Due to the environment and disruption in clearance people with CF are prone to opportunistic bacterial infections that manifest in exacerbations that are empirically linked with disease progression (Thornton & Parkins, 2023). Figure 1.10 shows mediators that contribute to changes in sputum attributing them to the epithelial structures in CF.

ACT are seen as a mainstay of treatment for mucus plugging for people with CF with guidelines recommending its use as a primary intervention for dealing with sputum, reducing symptoms and slowing disease progression (Smyth et al., 2014).

Bronchiectasis

In bronchiectasis, it is recognised that the levels of DNA present in the sputum are elevated above normal levels at a ratio of 1:13 (Ramsey et al., 2020). This increase in DNA present in sputum should not alter the osmotic properties of sputum however it is predicted to increase the viscosity of secretions (Zahm et al., 1995). Neutrophil elastase, a product of bacterial infection, present in sputum drives the vicious cycle of bronchiectasis promoting airway damage, a hallmark of the condition (Chalmers et al., 2017). The pathophysiology of bronchiectasis is further discussed in Chapter 2.

Management of sputum in bronchiectasis is viewed as an essential component to the management of the condition with guidelines from the British Thoracic Society (BTS), and European Respiratory Society (ERS) both suggesting that ACT are a first-line treatment (Hill et al., 2019; Polverino et al., 2017). Again, further details around treatment options and management for bronchiectasis can be found in Chapter 2

Primary Ciliary Dyskinesia (PCD)

Primary Ciliary Dyskinesia (PCD) a rare genetic condition that affects the proteins in the cilia shafts causing a dysregulated and ineffective beat that results in poor function of the mucociliary escalator has traditionally been considered a motor problem (Knowles et al., 2016). This was also highlighted in Abelson et al. (2024), described previously, with the lack of any discernible helical movement of secretions in the mucociliary escalator. Sputum has also been shown to be abnormally concentrated in PCD (Bush et al., 2006).

It is recognised that excess sputum promotes bacterial infection and inflammation with the cycle of exacerbations leading to damaged airways. Airways clearance and the use of mucolytic agents are recommended treatments (Paff et al., 2021).

1.3 AIRWAYS CLEARANCE TECHNIQUES (ACT)

Muco-obstructive conditions are characterised by the presence of an excess of mucus that builds up in the airways providing a breeding ground for bacteria and resulting in a reservoir of infection. This results in symptoms including chronic productive cough, fatigue, shortness of breath (SOB) and hypoxia (Singh et al., 2023).

There are many different types of ACT each with different merits. They aim to affect the viscoelasticity of secretions and cause sputum to be mobilised from the distal to proximal airways (McIlwaine et al., 2017). ACT can be categorised in several ways, described elsewhere, with Polverino et al. (2017) recognising that exercise and muscle weakness play an important role in interventions by a respiratory physiotherapist. However, although exercise and muscle training are of great importance, this thesis will primarily focus on techniques aimed directly at addressing mucus problems using ACT, see Figure 1.12.

Barker et al. (2017) evaluated prescription data around medications such as carbocysteine and ACT adjuncts in 2013-2015. They suggested that spending was 100 times greater on medication rather than adjuncts. Marmor and McShane (2024) comment that ACT is recognised for its merits across the medical community despite the lack of compelling evidence, due to the shortage of robust studies with longitudinal follow up. This highlights the need for more research to provide better evidence for physiotherapists to promote ACT and adequately prescribe devices such as oscillatory positive expiratory pressure (OPEP).

Chest physiotherapy interventions flow chart based on clinical experience from the task force panel.

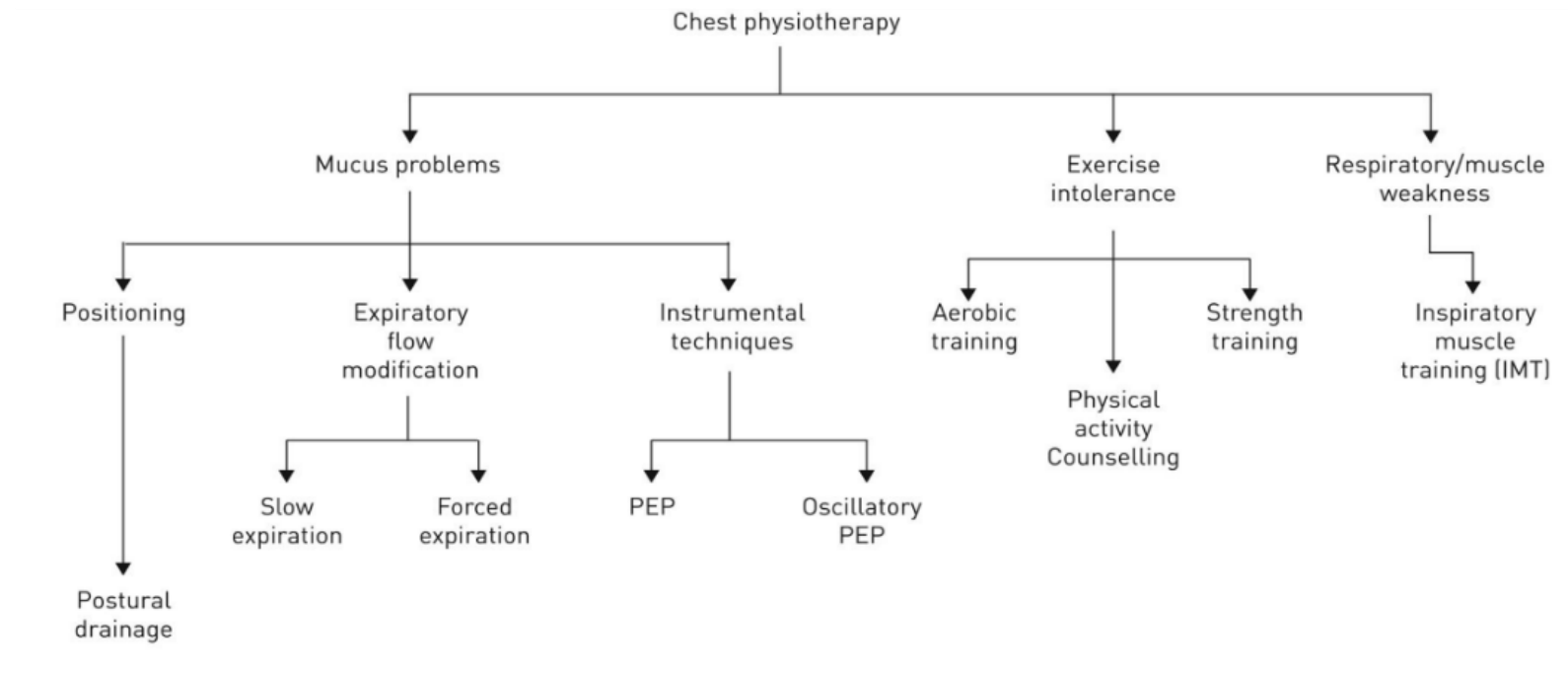


Figure 1.12 Chest physiotherapy interventions overview. ERS statement on airways clearance.

(Polverino et al., 2017)

1.3.1 Physical Effects and Mechanisms

Optimising ventilation in the obstructive lung is a key target for mobilising secretions. Sputum causes a narrowing of the airways that leads to decreased ventilation in the obstructed region requiring the recruitment of more peripheral ventilation (further described in the following sections), to get air beyond the obstruction leading to dynamic hyperinflation but also providing an opportunity for ACT to act (McIlwaine et al., 2017).

The process of coughing is a reflex that the body uses to expel excess secretions, cough receptors responsible can be found up to seven-eight airway levels deep (Kendrick, 2007). A cough is normally preceded by deep inspiration and closure of the glottis to increase intrathoracic pressure (Lapin, 2002). The resulting pressure is released at >500L/min as the airways contract creating flow and shear forces that propel mucus proximally (Lapin, 2002).

A huff is a manoeuvre described by Mead et al. (1967), that is taught by a respiratory therapist that aims to replicate high flow (+/-300L/min) and shear forces with an open glottis avoiding the effort needed to generate a cough see Figure 1.14. McIlwaine et al. (2017) describe the increased expiratory flow rate generated by cough, huff, and ACT as a mechanism to overcome the adhesive properties and viscosity of secretions. A short video can be found by following the [Link](#) (Asthma Australia, 2022).

Positioning to enhance ACT, using gravity to assist mucociliary motion was long thought to be a useful tool (Matthews et al., 1964). However, research in CF has shown an increased likelihood of gastric reflux when the head is held lower than the abdomen with the growth in sputum cultures of associated microbiological pathogens (Button et al., 1998). There is little evidence in other conditions however, the argument remains compelling.

The following sections aim to outline the physical effects and mechanisms at play when using a variety of cough / ACT that are routinely used by respiratory physiotherapists, in the United Kingdom (UK) (Herrero-Cortina et al., 2023). This is not an exhaustive review and will concentrate on methods pertinent to the research of this thesis and some novel areas of research that have an active body of research.

1.3.2 Breathing Techniques

Breathing techniques are considered as any actions that act to modify lung expiratory flow to mobilise secretions, the descriptions below are intended to give a clear understanding of the benefits and parts of each technique.

1.3.2.1 ACBT

The Active Cycle of Breathing Technique (ACBT) changes some of the constraints, such as time, pressure and physiological actions, present in normal breathing to elicit improved mobilisation of secretions (McIlwaine et al., 2017). Interdependence, a mechanism described by Otis et al. (1956) demonstrated that well-ventilated alveoli exert traction forces on obstructed alveoli assisting in re-expansion. Whilst, collateral ventilation between lung segments allows air to move behind obstructions through the pores of Kohn, channels of Lambert and channels of Martin (McIlwaine et al., 2017; Van Allen et al., 1931), see Figure 1.13. In healthy lungs, collateral ventilation or interdependence are rarely used as air takes the path of least resistance through unobstructed airways (McIlwaine et al., 2017). However, in the obstructed lung these alternative pathways become an important aspect of ventilation with both deep breathing and the three-second breath hold, components of ACBT that promote collateral ventilation and interdependence (Pryor, 2016). The interplay between these different mechanisms and the parts of ACBT can be seen in Figure 1.14.

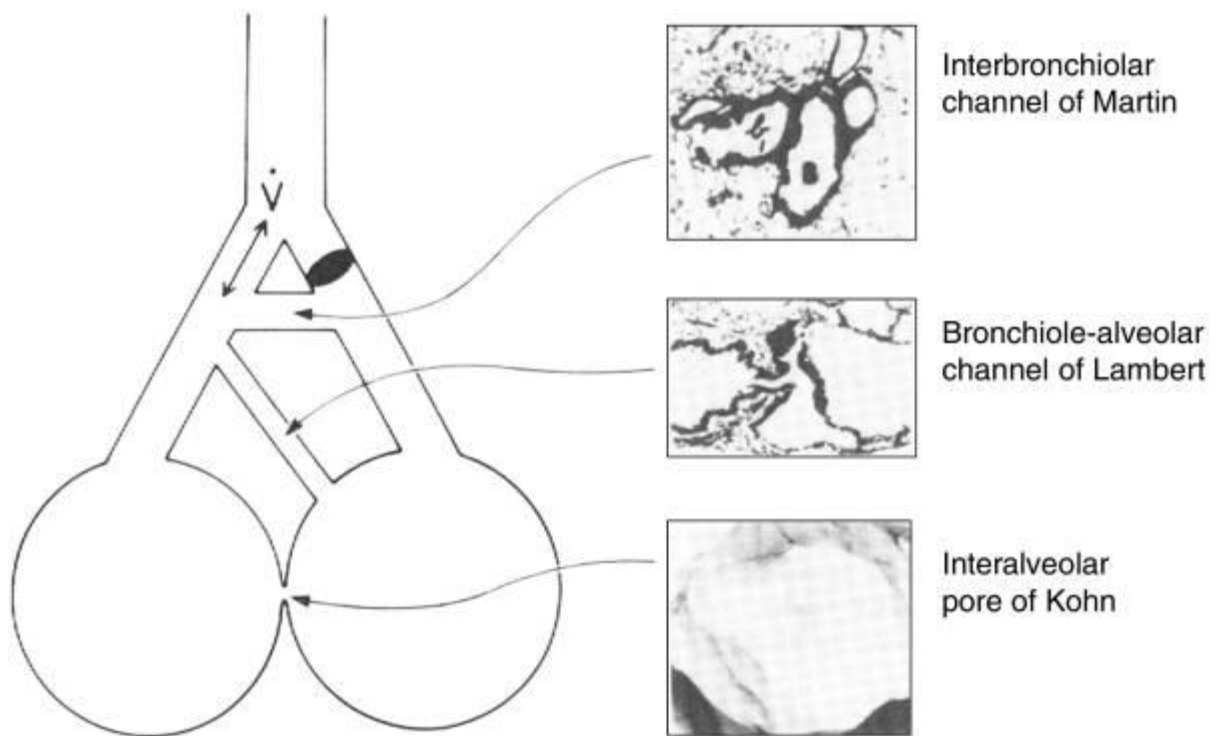


Figure 1.13 Pathways for collateral ventilation

(Terry & Traystman, 2016)

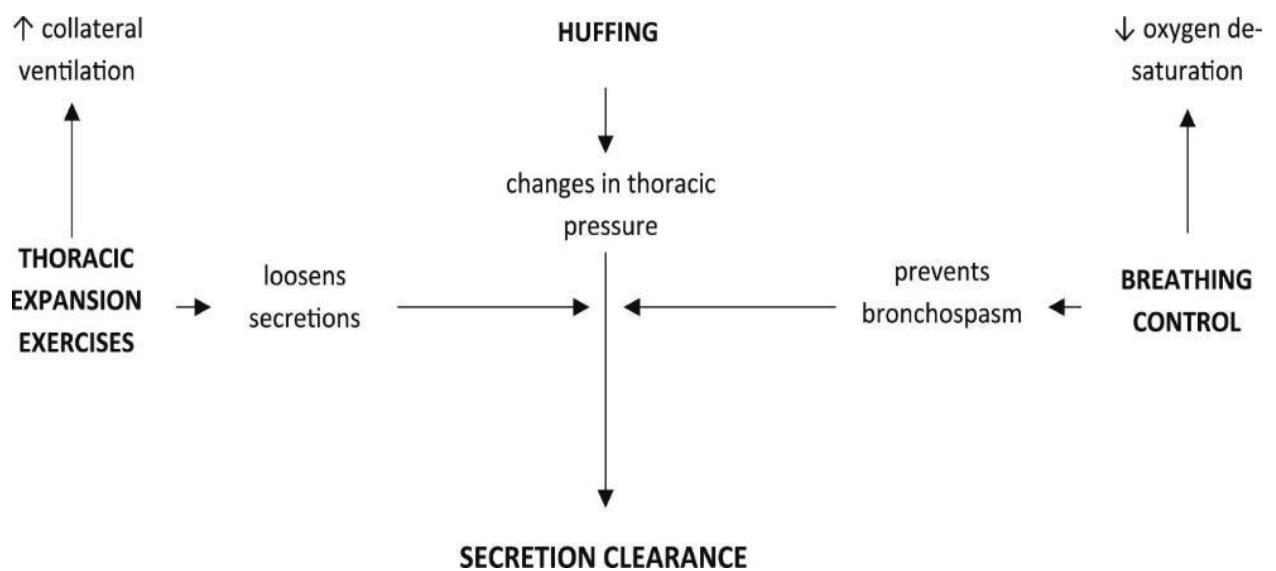


Figure 1.14 Proposed mechanisms by which ACBT results in secretion clearance.

(Lewis et al., 2012)

The other components of ACBT, that can be seen in Figure 1.14, include cough and huff. Huff, as previously described, is an expiratory manoeuvre aimed at promoting an equal pressure point at different lung volumes to aid the mobilisation of secretions proximally and increase flow rates to exert shear forces on secretions (Mead et al., 1967; Pryor, 2016).

ACBT is widely used in hyper muco-obstructive conditions with several papers outlining its usage in different populations. A. L. Lee et al. (2021) reported data from 56 patients with bronchiectasis in Australia with 64% (n=36) using ACBT. McLeese et al. (2023) surveyed 201 patients with bronchiectasis, in Northern Ireland, with 86% reporting performing ACT of which 64% (n=129) used ACBT. McShane, Philley, et al. (2021) conducted a survey in the United States of America (USA) of health professionals during the Coronavirus pandemic (2019) with 86% reported teaching ACBT to people with bronchiectasis or with pulmonary infections with non-tuberculous mycobacteria (NTM). An Australian survey of 121 respiratory physiotherapists by Phillips et al. (2021) reported 89% of them regularly prescribed ACBT.

ACBT is ubiquitous with ACT and has been present in the research since the 1980's with Lewis et al. (2012) and Zisi et al. (2022) providing systematic reviews. Zisi et al. (2022) included 11 studies between 2008 and 2021 in patient populations with COPD, bronchiectasis or CF, outcomes used included lung function, sputum weight, and disease-specific measures including quality of life (QoL). Lewis et al. (2012) included 24 studies on ACBT with participants with various respiratory conditions characterised by chronic sputum production (COPD, bronchiectasis, CF, and PCD) with similar clinical outcomes. Both reported that most studies were short-term comparing ACBT to manual techniques or positive expiratory pressure (PEP) and that ACBT was at least as good as the other methods evaluated. Both Lewis et al. (2012) and Zisi et al. (2022) recognising the limited ability to extrapolate this to longer term effects of ACBT with the small sample sizes, limited outcomes and short time frames of the currently published literature. However, both systematic reviews identify the value of ACBT as a treatment for retained secretions.

Sputum weight as an outcome is difficult in longer term studies with the practicalities of collecting research samples over a large geographical area impractical. Added to

this processing and measuring the samples is difficult and requires extra equipment and resources. However, due to the COVID-19 pandemic the use of this as part of this research was not an option.

Patterson et al. (2004) compared ACBT to a test of incremental respiratory endurance (TIRE) in a cross-over design in 20 patients with bronchiectasis. They found that the ACBT group expectorated significantly ($p=0.02$) more sputum during and immediately after treatment. However, no change in lung function was observed. Patterson et al. (2005) compared ACBT to OPEP in bronchiectasis reporting no difference in breathlessness, weight of sputum or oxygen saturations between the modalities concluding that both were effective methods of airway clearance. In a short-term study (seven-days) by Eaton et al. (2007) 36 participants with bronchiectasis received ACBT, OPEP (flutter), or ACBT augmented with postural drainage in a supervised ACT session, with the primary endpoint of sputum weight and tolerability. They concluded that ACBT augmented with postural drainage was superior in sputum weight production ($p<0.01$) with all ACT being well tolerated although the addition of postural drainage was significantly less comfortable and time-consuming ($p<0.01$).

Compared to bronchiectasis and CF few clinical trials have explored the use of ACBT in COPD. Shen et al. (2021) randomised 100 participants in China, with a mean (SD) age of 54.89 (± 12.06) 60% female, with no other concurrent respiratory conditions to receive ACBT or usual care (no ACT) in a one-week interventional study whilst admitted to hospital for acute exacerbation of COPD (AECOPD). Demographics at baseline showed 81% were Global Initiative for COPD (GOLD) one–two and 58% had been stable for >12 months with the ACBT group recording a COPD assessment test (CAT) score of 7.3 (± 2.55) and the usual care group 6.4 (± 2.43). Results showed a greater amount of sputum 24-hours post-intervention ACBT 16.73ml (± 6.72) Usual care 14.78ml (± 10.5) ($p=0.025$) with improvements in FEV₁ / forced vital capacity (FVC) ratio ($p<0.0001$), although from the report it was difficult to interpret the actual volumes to gauge the clinical impact. Whilst the CAT showed no change between group with both groups significant improving from base line ($p<0.001$). Shen et al. (2021) reported that 100% of participants were productive of sputum, but this was not an inclusion criterion, and 905 were approached to achieve the sample size. This demonstrates the difficulty in recruiting

for trials of ACT. The population for this study is younger than you may expect, and a higher rate of sputum production is seen compared to what would be expected in a cohort of this severity. Ethical approval for this study was granted however NICE (2018) guidelines recommending ACBT as usual care may have made this difficult in the UK.

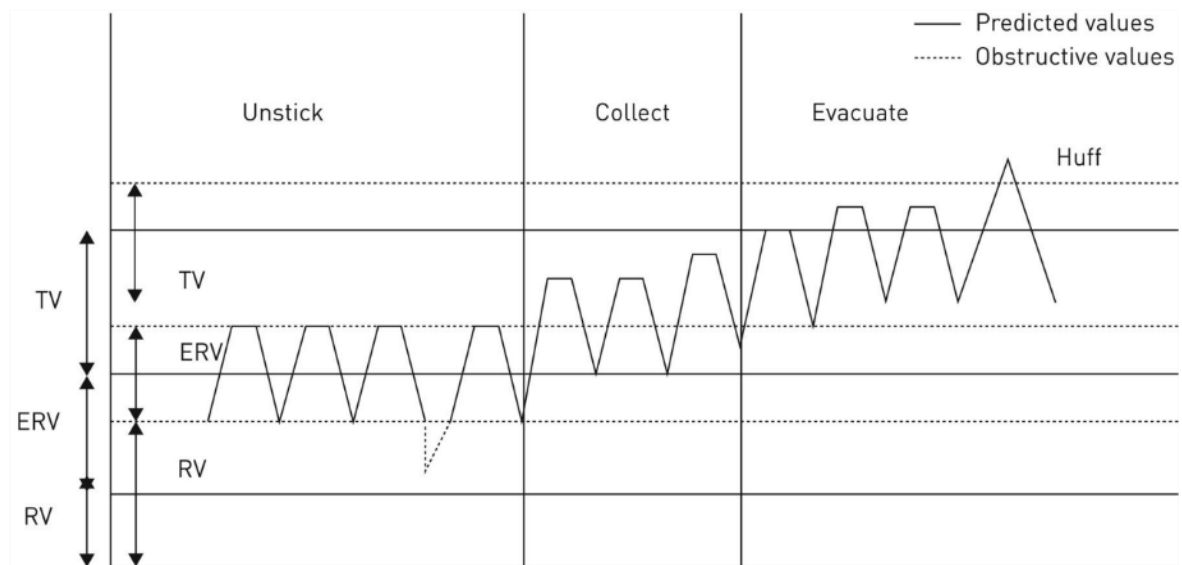
Although the physiological mechanisms of ACBT have been well researched few well-designed studies have reported the medium to long term clinical impacts of performing ACBT. A protocol by Phillips et al. (2023) proposes a multicentre randomised control trial (RCT) in participants hospitalised due to an acute exacerbation of bronchiectasis, randomising to ACBT, OPEP or walking and huffing. Outcomes included sputum weight (acute phase), Leicester Cough Questionnaire (LCQ), QoL bronchiectasis (QoL-b) and admission rates over six months. At the time of writing. Phillips et al. (2023) have completed recruitment achieving a sample size of 55 against a target of 90 with an estimated end to data collection late in 2024, we look forward to reading the results.

1.3.2.2 Autogenic Drainage (AD)

Autogenic drainage (AD) is a series of respiratory manoeuvres aimed at ventilating different lung volumes progressively moving secretions proximally (Belli et al., 2021), as can be seen in Figure 1.15. Each breath is augmented with a three-second breath hold to promote interdependence and collateral ventilation (McIlwaine et al., 2017). The processes are completed with a huff, cough clear as necessary to expel secretions.

In a Cochrane review of AD in CF Burnham et al. (2021) included 37 studies n=212 participants where AD was compared to another ACT or no treatment for greater than 2 sessions. Outcomes included FEV₁, sputum weight, and QoL. However, the review concluded that the level of evidence was low or very low and that further well-designed long-term studies are required.

Breathing pattern during autogenic drainage.



TV: tidal volume; ERV: expiratory reserve volume; RV: residual volume.

Figure 1.15 Breathing pattern during autogenic drainage.

(McIlwaine et al., 2017)

Shteinberg et al. (2020) studied a cohort of people with bronchiectasis (n=49) comparing OPEP and AD on lung clearance index (LCI), sputum volume, and QoL-b. No change was observed in LCI or QoL-b, however, sputum quantity decreased after one-month ($p=0.044$). Poncin et al. (2017) reported the effects of AD on LCI in n=24 people with bronchiectasis. Each participant completed LCI pre and post AD sessions. LCI scores improved significantly ($p=0.04$). However, only 5 participants improved by greater than the expected measurement variability. Therefore, any clinical interpretation of these results is difficult.

In the author's experience, AD is useful in those with a good level of understanding and breathing control and can be valuable in those with reactive airways. A short demonstration video can be seen by following the [Link](#) (Bronchiectasis Toolbox, n.d)

1.3.2.3 Expiration Lentte Totale Glotte Overerte en decubitus Lateral (ETGOL)

ETGOL is a technique involving expiration with an open glottis in a lateral position with the goal being the control of expiratory flow preventing airway collapse and aiding the mobilisation of secretions (Wong et al., 2018). Muñoz et al. (2018) in a RCT compared ELGOT to placebo in patients with bronchiectasis (n=44) and reported primary outcome of sputum volume increased by 17ml ($p<0.001$) in the intervention group. Secondary outcomes of exacerbations decreased by 0.35 ($p=0.04$) over 12 months and improvement above the MCID were seen in LCQ (1.89 $\pm$ 4.03) $p<0.001$.

Herrero-Cortina et al. (2016) enrolled 31 bronchiectasis outpatients in a crossover trial of AD, ELTGOL and temporary positive expiratory pressure. Outcomes included sputum expectoration (24hr) and LCQ with no difference in sputum expectoration and an improvement seen in all groups LCQ scores. These studies show that ELTGOL as an alternative breathing technique that should be considered as part of a toolkit for treating retained secretions

1.3.2.4 Singing

Singing for lung health has recently become prominent in the literature with a growing body of evidence to support its holistic benefits to those with muco-obstructive lung conditions (Lewis et al., 2016). Breathing and singing share a number of physiological parameters which become disordered in conditions such as COPD (Lewis et al., 2021). Philip et al. (2024) conducted an assessor blinded RCT in COPD comparing singing for lung health versus usual care. Participants (n=115) median (Inter Quartile Range (IQR)) age 69 years (62-74) the Modified British Medical Research Council Dyspnoea Scale (mMRC) three (3-4) 56.5% females, and 80% previously attended pulmonary rehabilitation (PR), groups were well matched at baseline. Singing for lung health involved a one-to-one set-up session followed by 12 weekly online group sessions, Outcome measure (OCM) included SF-36, CAT,

mMRC and depression and anxiety scores. Philip et al. (2024) reported a between-group improvement in physical health. Analysis of the responder rates (>10%) showed 32% in the singing for lung health and 12.7% in the usual care group ($p=0.02$) in physical health domain of the SF-36. This study showed that online completion of interventions like this is possible however it should be recognised that this occurred during the COVID-19 pandemic. Although it is not considered a direct ACT its effect on QoL (SF-36) has been shown, and it may be appropriate to add to usual care (McNamara et al., 2017; Philip et al., 2024).

1.3.3 Devices

Devices for ACT include any instrument used to promote the physiological mechanisms necessary to mobilise excess secretions. These devices can be driven by the patient's own respiratory function or by external mechanical sources. Patient-driven devices are regularly used in chronic respiratory conditions as both acute and long-term therapy, while mechanically externally driven devices are more often used in the acute hospital setting.

1.3.3.1 Positive Expiratory pressure (PEP)

Using a mouthpiece or mask, PEP can be achieved by exhaling against a constant resistance. There are several ways that this can be achieved, from the use of a spring to the delivery of air pressure during expiration to provide resistance (Demchuk & Chatburn, 2021). However, most devices used in current practice use a leakage port of a set size to create a therapeutic back pressure between +15 -20 cm H₂O (Demchuk & Chatburn, 2021). The physiological result of this is to promote collateral ventilation and mobilise sputum proximally as the airways shut down (Franks et al., 2019). A handheld manometer is often used to provide performance feedback, ensuring therapeutic pressures are achieved.

A systematic review of PEP devices in CF by McIlwaine et al. (2019) found 28 studies of various designs, including crossover and short-term comparisons. They found that the most common primary outcome was FEV₁ and the number of exacerbations. The results showed little or no difference in the FEV₁ between the

comparators but a significant decrease in exacerbations from 833/1000 to 609/1000 RR 0.73 ($p < 0.05$) with PEP therapy. McIlwaine et al. (2019) commented that most studies had short follow-up times and that the robustness of methodology in the studies reported in the literature was poor. This variety of short-term studies with differing methodological approaches is seen across ACT and may result in systematic reviews' ability to draw clear conclusions on the evidence.

However, evidence in COPD and bronchiectasis is limited. Osadnik et al. (2014) recruited 90 participants, 32 female, mean age of 68.6 years, FEV₁ 40.8%p, to PEP or usual care (no ACT) during an AECOPD. OCM data was collected at eight-weeks and six-months from hospital discharge. They found no significant difference between groups in hospital admissions, St Georges or the breathlessness, cough and sputum scale at eight-weeks or six-months. However, the study did report a decrease in breathlessness (mMRC 2.8 to 2.2) at eight-weeks ($p = 0.006$) but this was not maintained to the end of the study. In summary, whilst implementation of PEP therapy is common in the CF community with recommendations in the guidelines for care (Smyth et al., 2014), there is little evidence to support its use in other muco-obstructive conditions.

1.3.3.2 Oscillatory Positive Expiratory Pressure (OPEP)

As an additional adjunct to PEP devices, OPEP offers rapid changes in pressure that cause vibrations aiding the movement and expectoration of secretions. Oscillations are caused by changes in resistance and flow (McIlwaine et al., 2017). These devices have been developed and have become an important adjunctive ACT since the 1990s (McIlwaine et al., 2019; Olsén et al., 2021).

Physiological mechanisms mirror those of PEP with the addition of oscillations between 11-15Hz that aim to mirror ciliary beat frequency. Additionally, oscillations aim to help thin the secretions and shake adherent sputum from the airway surfaces as can be seen in Figure 1.16 (Poncin et al., 2020). The manoeuvre consists of a slightly larger than tidal volume inhalation followed by a purposeful exhalation through the device, followed by a huff cough to expectorate secretions (Van Fleet et al., 2017).

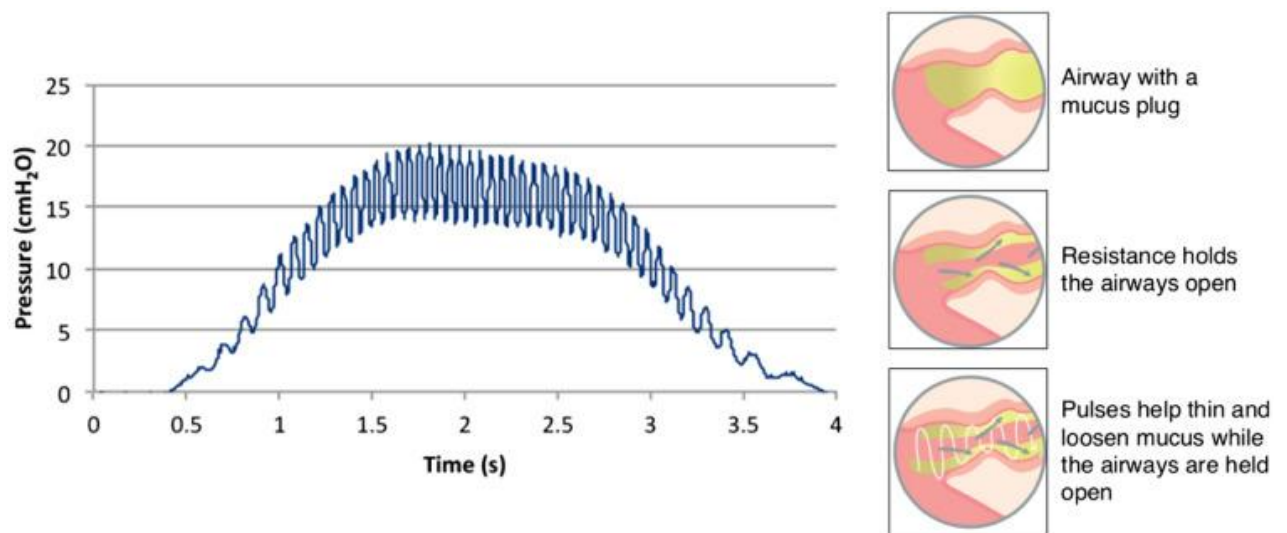


Figure 1.16 OPEP waveform and physiological mechanisms.

(Coppolo et al., 2022)

The choice of OPEP device is often a result of clinical practice, cost and personal (therapist) preference with little robust evidence to support the use of one device over another (Herrero-Cortina et al., 2023). Constraints including flow rate, PEP, oscillation frequency, and amplitude vary between devices and are important to consider when evaluating the research (Lewis & Osadnik, 2023). For instance, Tse et al. (2020) in a propensity-matched retrospective cohort study in COPD sputum producers comparing Aerobika (n=619) and Acapella (n=1857) users, found Aerobika users were less likely to exacerbate within 30 days ($p=0.01$), 12 months ($p=0.01$) and experience a longer time to first exacerbation ($p=0.01$). This suggests that Aerobika devices may be superior and that devices vary in clinical effectiveness (Tse et al., 2020).

There are several different devices available, as can be seen in Figure 1.17, that all have different performance characteristics, with the comparative literature outlining some of the key performance differences as summarised below.



(A): acapella* green
and blue versions
With acapella*
Choice† green below



(B) Aerobika*



(C) Flutter*



(D) Lung Flute*



(E) PocketPep*



(F) Quake*



(G) RC-Cornet*



(H) ShurClear*



(I) Vibralung*



(J) vPEP*



(K) VibraPEP*

Figure 1.17 A selection of commonly available OPEP devices.

(Coppolo et al., 2022)

Morgan et al. (2019) in a bench study looked at the flow rates necessary to generate target expiratory pressure in four different devices. The Acapella DH (green), Aerobika, VibraPEP and vPEP were tested at three pressures, low (13cm H₂O), medium (15cm H₂O) and High (17cm H₂O) and the results can be seen in Table 1.1. replicated from (Morgan et al., 2019).

Table 1.1 Performance characteristics of the OPEP devices at comparable therapy position.

Performance characteristics at varying steady-state pressures, position 1			
Low pressure	Steady-state pressure (cm H ₂ O)	Frequency (Hz)	Steady-state flow (L/s)
Acapella DH	12.7 (12.6–12.8)	14.6 (14.4–14.8)	0.71 (0.69–0.72)
Aerobika	12.6 (12.6–12.7)	14.8 (14.5–15.2)	0.84 (0.83–0.86)
VibraPEP	13.5 (13.4–13.5)	19.4 (18.9–20.0)	0.37 (0.36–0.39)
vPEP	12.6 (12.4–12.9)	16.0 (15.3–16.6)	0.85 (0.82–0.88)
Medium pressure			
Acapella DH	14.5 (14.4–14.6)	16.0 (15.8–16.3)	0.76 (0.74–0.78)
Aerobika	14.4 (14.3–14.5)	16.0 (15.6–16.4)	0.93 (0.92–0.95)
VibraPEP	15.3 (15.3–15.3)	19.3 (18.7–20.0)	0.46 (0.44–0.48)
vPEP	14.6 (14.3–15.0)	16.9 (16.1–17.6)	0.96 (0.93–0.99)
High pressure			
Acapella DH	17.3 (17.2–17.4)	18.3 (17.9–18.6)	0.84 (0.81–0.86)
Aerobika	16.9 (16.8–17.0)	17.4 (17.0–17.9)	1.04 (1.02–1.05)
VibraPEP	18.2 (18.1–18.2)	20.3 (19.7–20.9)	0.53 (0.51–0.55)
vPEP	N/A	N/A	N/A

Note: Data is denoted as mean (95% C.I.). No data was collected for vPEP at the high target pressure.

As can be seen, the different devices offer different pressures, frequencies and flow rates during this lab-based test and could explain some of the variability found in the research and clinical practice. Morgan et al. (2019) commenting on the clinical consequences of these differences suggested that the size, weight, and clinical severity of patients will all influence the achievable flow rate. Mechanical OPEP designs (vPEP, Aerobika and Acapella DH) require higher flow rates than oscillating designs (VibraPEP) to achieve a therapeutic expiratory pressure $>10\text{cm H}_2\text{O}$. In a similar study Demchuk and Chatburn (2021) showed consistency in expiratory pressure across flow rates was achieved using different settings on the devices.

Oscillation frequency and amplitude are driven by flow rate and resistance which is a hallmark of OPEP devices. Several evaluations have been performed under different lab-based simulations replicating clinical characteristics in various patient groups. Van Fleet et al. (2017) in a model based on a paediatric CF, patients reported statistically significant variation in peak pressure ($p<0.01$), PEP ($p<0.01$), amplitude ($p<0.01$) and oscillatory frequency consistent with manufacturer-reported values. A graphical representation of this can be seen in Figure 1.18 with the Aerobika providing the most consistent amplitude, frequency and mean PEP across resistance settings (Van Fleet et al., 2017).

In clinical practice, it is the authors experience that the duration and amplitude of oscillation seen in Figure 1.8 means that the effective treatment time during each breath experienced when using an Aerobika makes it the device of choice. However, as seen in Table 1.1 the differences in mean pressure experienced during lab test is within normal treatment parameters, and the oscillations remain between 14.8 and 17.4 across the tests. This is in keeping with the authors clinical experience.

Representative waveforms for each of the devices tested from which the oscillatory frequency was counted.

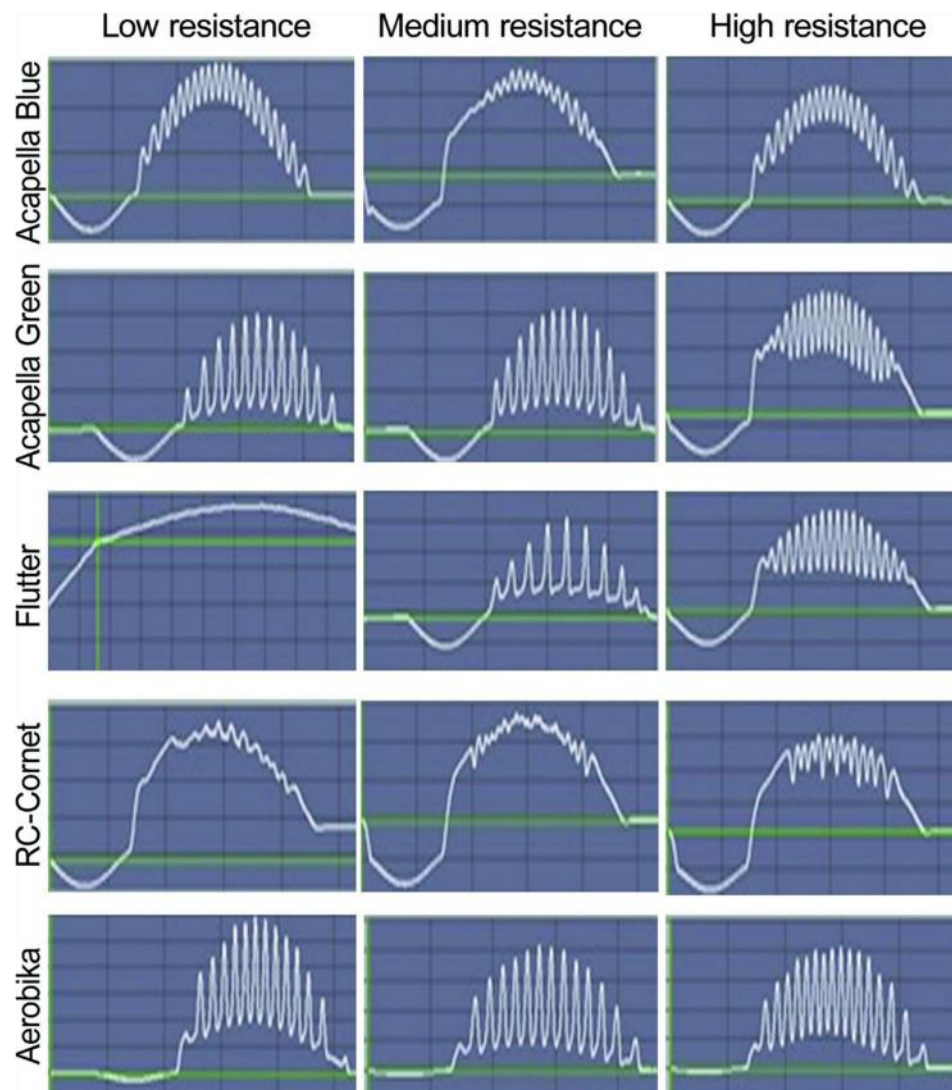


Figure 1.18 Representation of oscillation frequency and amplitude of different OPEP devices.

Adapted from (Van Fleet et al., 2017)

Poncin et al. (2020) replicated several different clinical representations by developing wave forms to simulate COPD 50% predicted FEV₁, COPD 71% predicted, FEV₁, CF 25% predicted FEV₁, and healthy flow volume loops. Reporting consistency in oscillation frequency through Flutter, Gelomuc, Pari and Shaker devices and found greater variance in Acapella and Aerobika devices, as can be seen in Figure 1.19. They concluded that therapeutic efficacy may depend on clinical presentation and device settings.

Mean (SD) values for oscillation frequency for the different devices and waveforms.

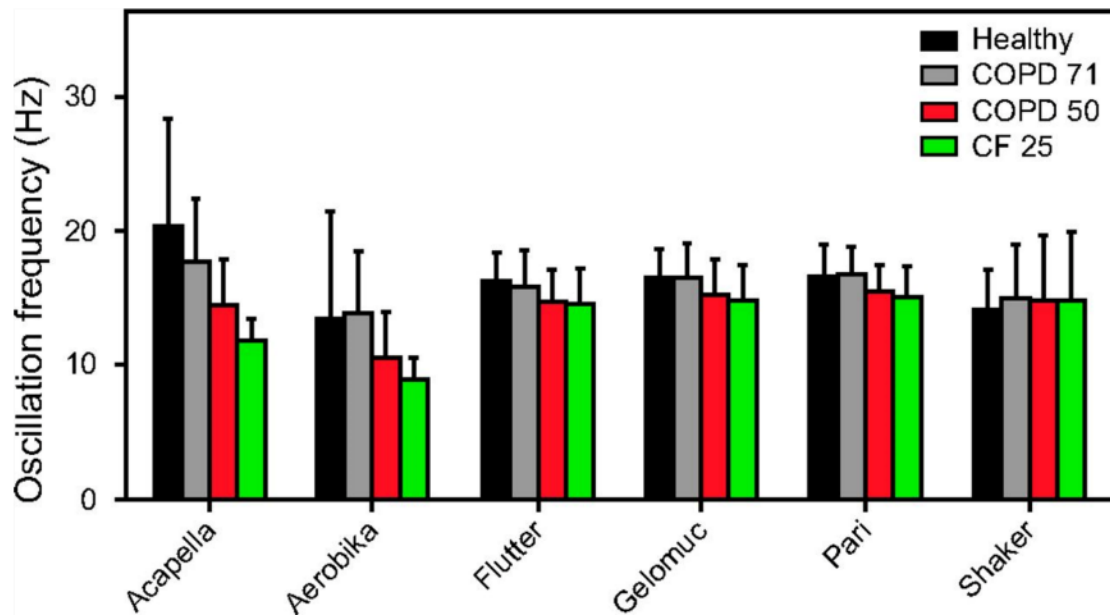


Figure 1.19 Mean (SD) values for oscillation frequency for the different devices and waveforms.

(Poncin et al., 2020)

Coppolo et al. (2022) summarise the key points of these comparative studies reporting the variation in performance characteristics across the available devices but recognising that lab-based methods may not translate to clinical practice. It is suggested that one possible solution to this is to use radio-labelled imaging techniques to add real-world evidence to the body of literature.

Clinical research into the application of OPEP in conditions of muco-hypersecretion is numerous in bronchiectasis with few studies in COPD. However, at the time of writing, this is changing with the number of recently published and planned trials increasing. This may be due to the recent recognition of the role of sputum in the chronic bronchitis phenotype of COPD (GOLD, 2023).

Phillips et al. (2021) surveyed physiotherapists in Australia and New Zealand and received 121 responses with 89% prescribing ACT in acute exacerbations of bronchiectasis. Of the modalities prescribed OPEP was considered effective by 97% of responders, second only to exercise. S. M. Alghamdi et al. (2023) reported on a perspective from Saudi Arabia that analysed responses from 1188 healthcare providers with fewer but still the majority (75%) considering prescribing mucus clearance devices such as OPEP for those with COPD and excessive sputum. In a European statement on airways clearance in bronchiectasis by Herrero-Cortina et al. (2023), it was recognised that OPEP offered an important alternative to be considered when prescribing ACT.

In a systematic review of COPD studies between 1996-2014 by Alghamdi et al. (2020) eight articles were considered suitable to be included. Most participants (n=381) were enrolled in stable state COPD whilst only 45 subjects were recruited into trials during AECOPD. Of the eight trials, two were crossover and six were parallel-group RCTs. The devices used varied across the studies and included, Flutter, RC-Cornet Plus, Acapella Plus, Lung flute plus, and Aerobika with the control arms being usual care, ACBT or sham devices. OCM included lung function, exercise tests, breathlessness, healthcare utilisation and HRQoL scores St George's Respiratory Questionnaire (SGRQ) and CAT. Those that were admitted for AECOPD using OPEP saw no difference in lung function but experienced shorter admissions of three versus five-days. Analysis of the eight studies concluded that most had a high risk of bias, due to methodological and blinding issues with rates for dropout of

8%, acceptance 81%, and completion 91% of the studies. Alghamdi et al. (2020) concluded the trials with longer time frames, using validated measures, and designs that allow participants to remain in the studies through acute episodes were needed to compare ACT modalities.

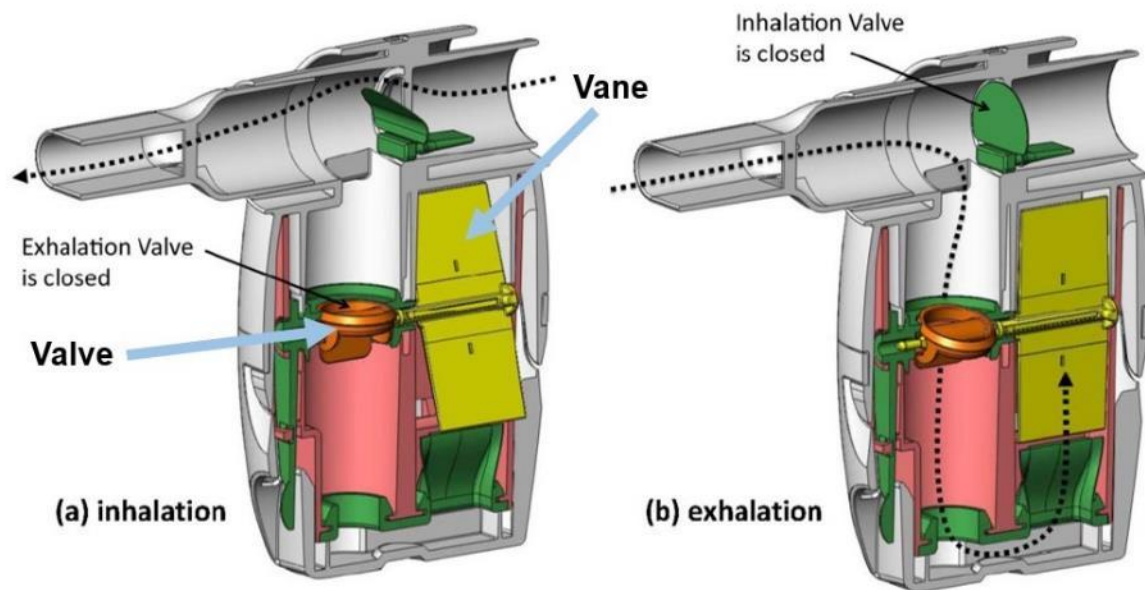
Shteinberg et al. (2020) studied a cohort of people with bronchiectasis (n=49) comparing OPEP and AD on LCI, sputum volume, and QoL-b no change was observed in LCI or QoL-b, however, sputum quantity decreased after one-month (p=0.044).

The rationale for use, wider body of evidence, physiological mechanisms, and performance characteristics of OPEP devices have been outlined in this section to provide a background to its place in current clinical practice. Due to the comprehensive systematic review by Alghamdi et al. (2020), which matched the study design timeline of TIPTOP, a full systematic review was not completed. This choice was taken due to the lack of robust trials outside of the scope of the previous review and the feeling that this would not add to the body of literature currently available.

Due to the authors' clinical practice, availability of OPEP devices at the two research sites, and the indirect support of Trudell Medical International (London, Ontario) Chapters 3 and 4 of this thesis will centre around the Aerobika device whilst Chapter 2 describes OPEP more generally.

1.3.3.3 The Aerobika

The Aerobika OPEP device was launched in late 2013. The device creates positive pressure pulses as the patient exhales, which has been shown in a magnetic resonance imaging (MRI) study to help recruit poorly ventilated lung areas (Svenningsen et al., 2016). The mechanical workings of the device can be seen in Figure 1.20. The vane provides oscillation by a system of valves that create back pressure and allow the connection of a nebuliser pot, providing the ability to add inhaled therapies such as hypertonic saline to augment therapy.



Pivoting vane and valve mechanism

Figure 1.20 Mechanism of Aerobika vane and valve.

Reproduced with permission of Trudell Medical International.

Using the Aerobika requires the user to maintain good posture in sitting or side-lying. A good seal should be made around the mouthpiece of the device and a deep inhalation should be performed with a two to three second breath hold before a long steady expiration. This process should be repeated between 10 and 20 times, or as instructed by your HCP; each set should be followed by a huff, cough, clear technique. Figure 1.21 provides diagrammatic instructions and, a [YouTube instructional video](#) can be found by following the link (Trudell Medical International, 2021).

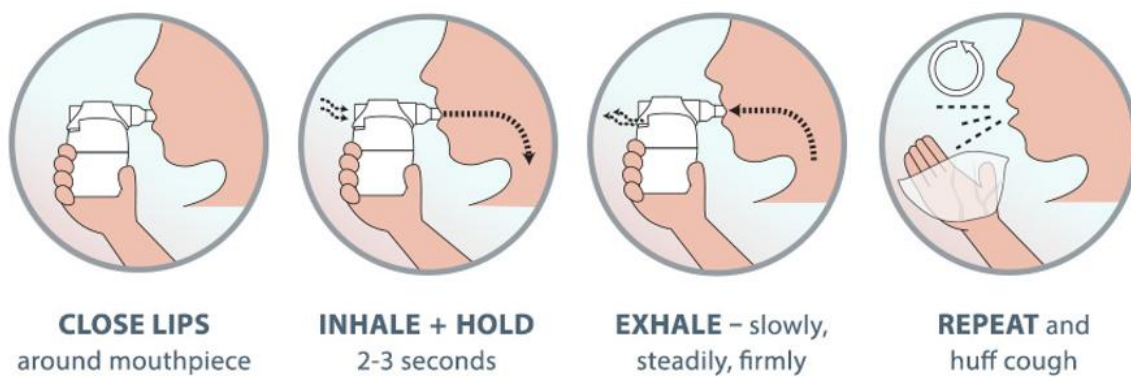


Figure 1.21 Using an Aerobika

Reproduced with permission of Trudell Medical International.

Some additional key iterations of the device are:

- Introduction of a silicone spring to the vane mechanism in the valve cartridge component of the device, added to ensure that the device does not stall ensuring consistent oscillations.
- Numbers from 1 (low) to 5 (high) were added to the resistance indicator scale.
- A flared lip was added to the mouthpiece to allow patients to form a better grip and more effective seal around the mouthpiece when using the device.
- The device is now made from recyclable plastic and does not use bisphenol A (BPA), natural rubber latex, phthalates, lead, or polyvinyl chloride (PVC), see Figure 1.22.



Figure 1.22 Recyclable Aerobika

Reproduced with permission of Trudell Medical International.

Resistance in the device can be altered using a scale of one to five to change the resistance and the achievable back pressure as measured in cm H₂O (Van Fleet et al., 2017), as previously described in Section 1.3.3.2. as can be seen in Figure 1.22

The Aerobika OPEP device with a manometer adapter was launched in 2015. It aims to provide visual feedback during instruction by a healthcare provider and during independent therapy. The manometer adapter provides visual feedback about a patient's exhalation whilst using the Aerobika device. A manometer can be seen in Figure 1.23 The value here is 3-fold:

Train

- Develop proper exhalation technique

Encourage

- Receive visual feedback

Confirm

- Achieve therapeutic pressure every time
- Maximise treatment effectiveness



Figure 1.23 Aerobika with manometer and numbered resistor settings.

Reproduced with permission of Trudell Medical International.

The next generation of devices is under development and will be blue tooth enabled providing the user and their healthcare team with data on performance on usage in real time. At the time of writing the device is still under development and information from Chapter 4 has been used to inform product development.

1.3.3.4 Mechanical Devices

Several different devices are available to deliver the mechanical forces necessary to mobilise secretions. Devices such as high-frequency chest wall oscillation (HFCWO) involve the patient wearing a vest that is driven by pulses of air at 25-40Hz aiming to promote the movement of secretions and induce a productive cough (Barto et al., 2020). See Figure 1.24.



Figure 1.24 High-Frequency Chest Wall Oscillation (HFCWO)
(RespirTech, n.d)

An RCT with 107 participants in CF showed little benefit from the use of HFCWO as a primary ACT (McIlwaine et al., 2013). Osman et al. (2010) also showed significantly less sputum ($p < 0.001$) over 24 hours when using HFCWO compared to other methods of ACT. Conversely, Bridges et al. (2018) in a retrospective data collection compared data one-year pre and post-initiation of HFCWO in six (three female) adults with CF aged 19-42 years. Baseline data showed a median predicted FEV₁ of 41%, and BMI 23.1kgm² results saw a trend in the reduction of intravenous antibiotic days (69.5 to 62.5) and hospital admissions (2.2 to 1.5) in the year post initiation of HFCWO.

Alternatively, the use of positive pressure delivered directly into the airways can be provided by non-invasive ventilation (NIV). This aims to increase lung volume during inspiration and provide positive end-expiratory pressure during expiration, to support collateral ventilation (Johnson et al., 2020). Whilst mechanical insufflation – exsufflation (MI-E) delivers air to increase lung volume on inspiration and negative pressure on expiration using the swing in pressures +/-40 cm H₂O to promote shear forces in secretions. Peak cough flow >160 L/min is considered insufficient to mobilise secretions and the point at which cough augmentation should be considered. Settings should be personalised to the individual patient, but a suggested algorithm can be seen in Figure 1.25 by (Chatwin & Wakeman, 2023).

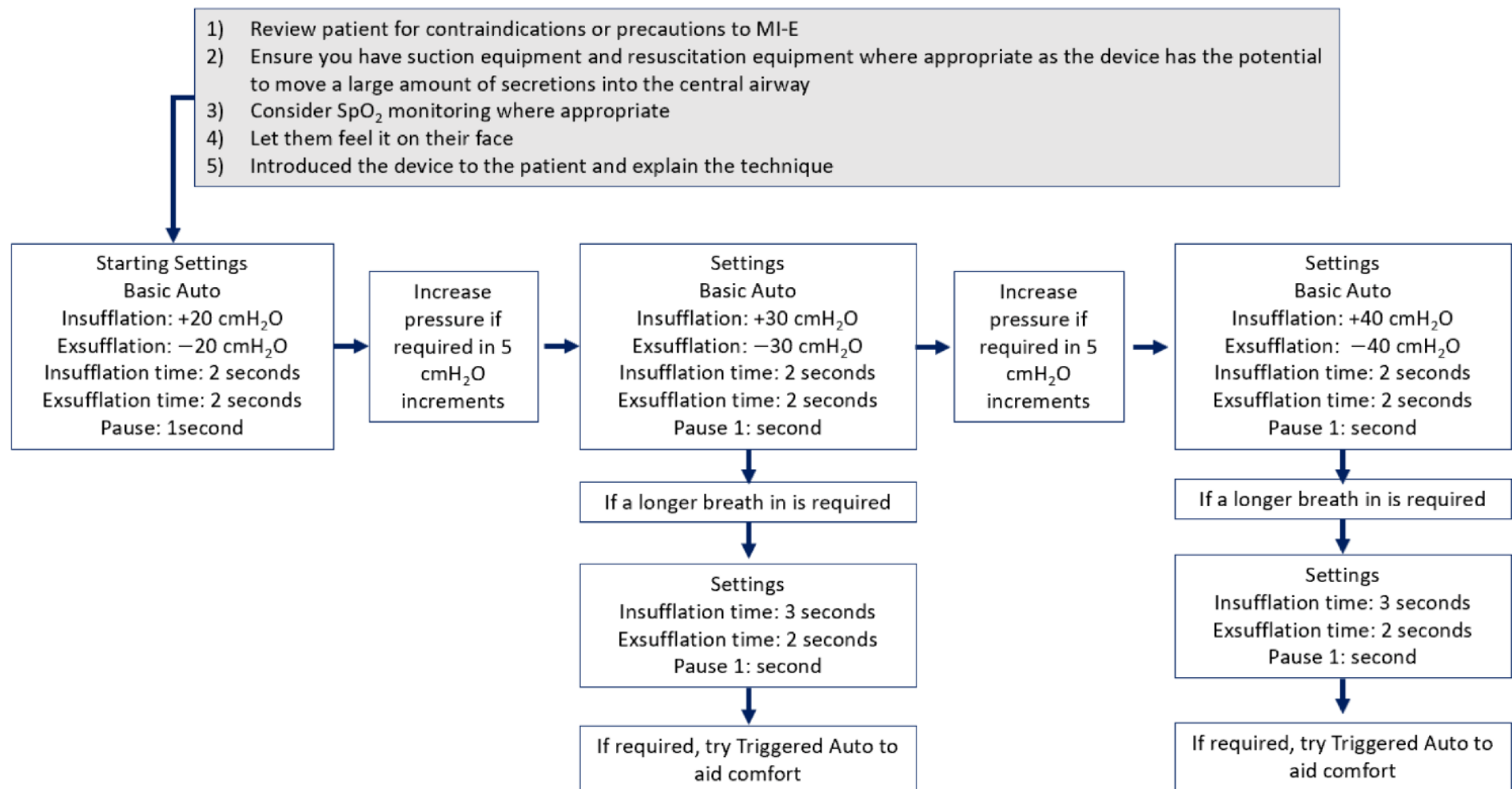


Figure 1.25 Standard approach to MI-E initiation in adults

(Chatwin & Wakeman, 2023)

Early research conducted by Beck and Barach (1954) involving 103 acutely ill patients—27 with neuromuscular disease and 72 with respiratory disease—demonstrated clinical and radiological improvements in 92 individuals. Chatwin et al. (2003) recruited 22 neuromuscular patients median age of 21 years and 19 matched controls recording unassisted peak cough flow baseline and during assisted coughs including MI-E. Results showed that MI-E increased the peak cough flow from 169 (± 90) Lmin⁻¹ to 235 (± 111) Lmin⁻¹ ($p=0.01$) which was more than any other adjunct in this patient group. Ferreira de Camillis et al. (2018) in a randomised parallel group ($n=90$) trial of intubated patients showed that MI-E increased mucus clearance rates. Results showed that mucus weight was 2.42 (± 2.32) g in the MI-E group and 1.35 (± 1.56) g in the control group. Demonstrating that MI-E promotes mucus clearance in sedated patients. Hov et al. (2023) in a cross-sectional study collecting health-related outcome data in 73 children, 30 female, median age of 10 (IQR 6-14) years, who used MI-E regularly at home. Hov et al. (2023) reported a decrease in hospital admissions by 42% and respiratory infections by 38% in the one-year pre- and post-data.

This device is often used in neurological conditions where cough is ineffective despite a paucity of robust evidence (Chatwin, 2008). Guidelines for motor neurone disease recommend that a cough assist should be considered if cough is weak, or ineffective and secretions are a problem (NICE, 2016).

1.4 SUMMARY

The role of mucus in the healthy respiratory system is to perform three vital roles protection, hydration and entrapment of debris including pathogens. Mucus in disease states changes in quantity, structure and viscosity leading to progression of disease through pathological mechanisms. ACT is an umbrella term for a group of non-pharmacological treatments to help clear excess mucus, aiming to alleviate symptoms and slow disease progression including decreasing the number of lung infections and minimising lung function decline.

The following chapters describe three studies that the author undertook, to enhance the knowledge in the use of OPEP, as an ACT in chronic respiratory disease. The

studies ran concurrently with each looking to address a different aspect of this field of research.

2 STUDY: ANALYSIS OF BRONCH-UK DATA

2.1 INTRODUCTION

Bronchiectasis is a heterogenous condition that is often characterised by irreversible bronchial dilation and thickening of the bronchial wall (Long et al., 2024). The radiological appearance was first described by Laennec in the 19th century and then the histopathological characteristics were associated with the condition in the 1950's (O'Donnell, 2022). It has been referred to as one of the most neglected respiratory conditions (Aliberti et al., 2022; Goeminne et al., 2019).

People with bronchiectasis live with daily symptoms including productive cough and breathlessness. Impaired mucociliary clearance is linked to the pathological process of bronchiectasis leading to disease progression (Ramsey et al., 2020). This results in mucus retention and a vicious cycle of bronchial inflammation with increased sputum load particularly during exacerbation (Chalmers et al., 2018; Hill et al., 2018; Polverino et al., 2017).

Chalmers et al. (2023) describing the data from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) identified that 38% (n=6466) of people had an unidentified cause and 21% (n=3600) had disease that was attributed to previous infection. The full list of associated pathogens and infections is unclear however tuberculosis, episodes of pneumonia, allergic aspergillosis and chronic *Pseudomonas aeruginosa* (PsA) infections have been associated with the development and rapid progression of the condition (Reynolds & Kollef, 2021), see Figure 2.1.

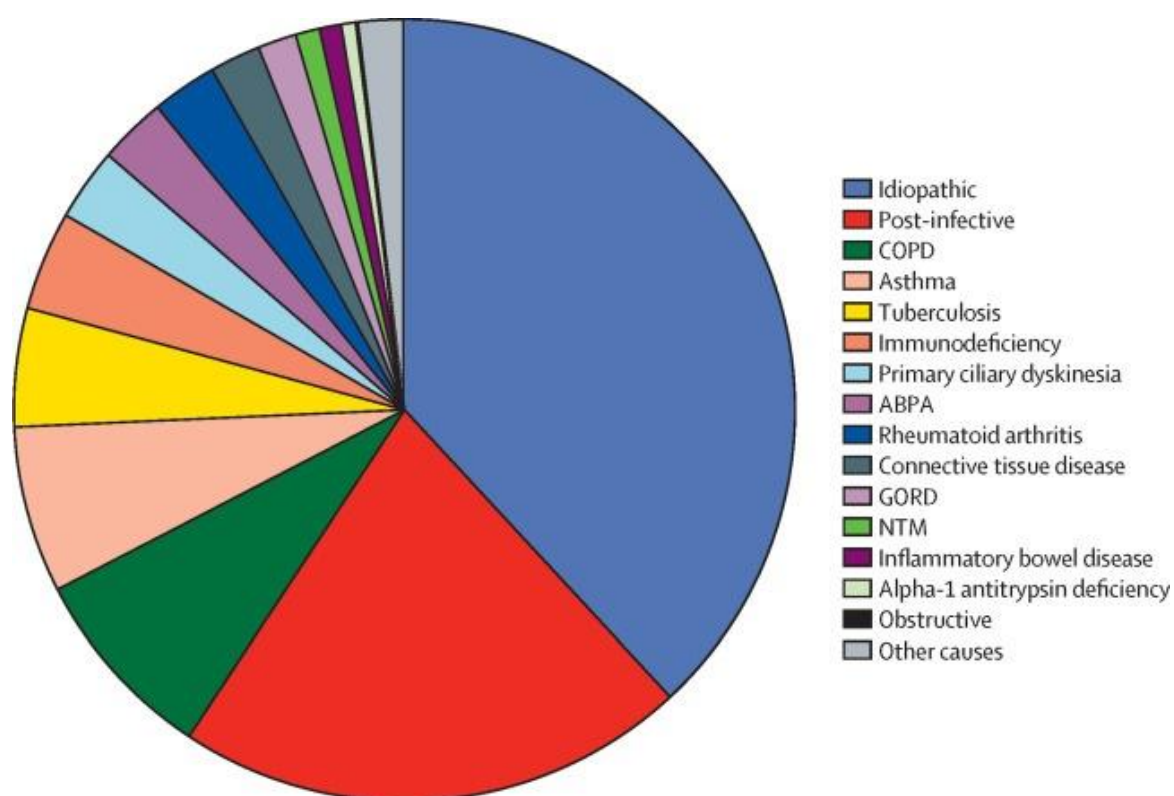


Figure 2.1 Underlying causes of bronchiectasis in the EMBARC cohort (n=16983).

Adapted from (Chalmers et al., 2023)

The cause of bronchiectasis is often unknown, but it represents the final common pathway of several respiratory conditions. Associated conditions that are risk factors for the development of bronchiectasis lung disease include CF, PCD, and COPD (Keir & Chalmers, 2021).

ACT is a key component of care in bronchiectasis and the community of respiratory physiotherapists who deliver the training, and interventions strive to use evidence-based practice to inform clinical decision making. There is a lack of data measuring performance against the guideline recommendations in the literature.

2.1.1 Prevalence

The prevalence of bronchiectasis in the UK has shown a marked increase between 2004 and 2013 increasing from 351 to 566 per 100,000 in women and 301 to 486 per 100,000 in men, see Figure 2.2 for prevalence across age range. The overall figures are corroborated in, Germany and Spain (Monteagudo et al., 2016; Ringshausen et al., 2015) and slightly higher in the USA 701/100,000 (Henkle, Chan, et al., 2018). The reason for this increase over time is not clear but contributing factors may include changes in the risk factors that cause bronchiectasis, improved diagnosis due to the increased availability of CT scans, patients living longer, and a spotlight increasing the labelling of the condition alongside other respiratory conditions (Quint et al., 2016).

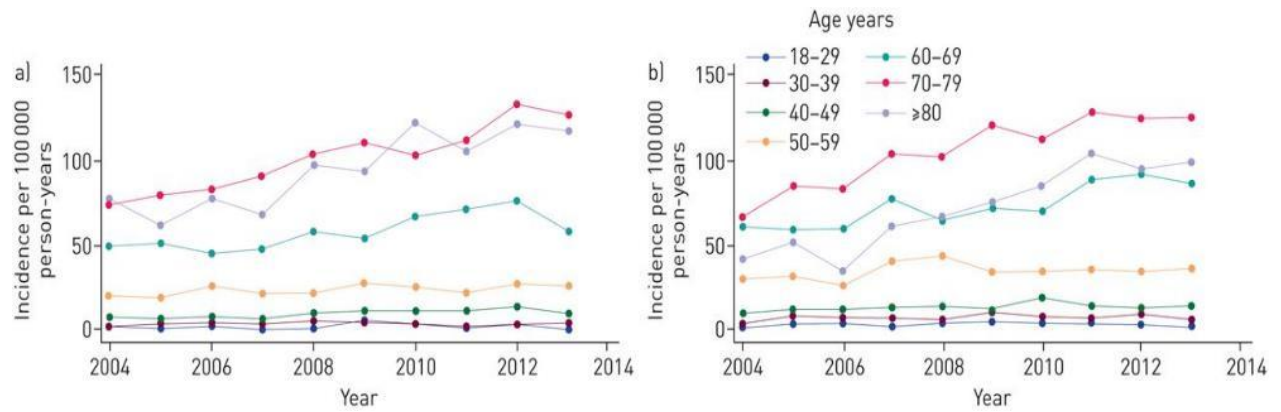


Figure 2.2 Incidence of bronchiectasis in the UK from 2004 to 2013 stratified by age in a) men and b) women.

(Quint et al., 2016)

2.1.2 Mortality

Mortality is considerably higher than in an age-matched population. Quint et al. (2016) using data from England and Wales in 2010 estimated that a comparative mortality rate for women was 2.26 and men was 2.14 times higher for those with bronchiectasis. Goeminne et al. (2014) in a prospective cohort analysis of 245 admissions, in Belgium, due to bronchiectasis found a mortality rate of 20% over 5 years and 70% in those with concurrent COPD. Loebinger et al. (2009) following 91 UK participants over 13 years showed that 30% of patients did not survive with 58% of deaths recorded from respiratory causes.

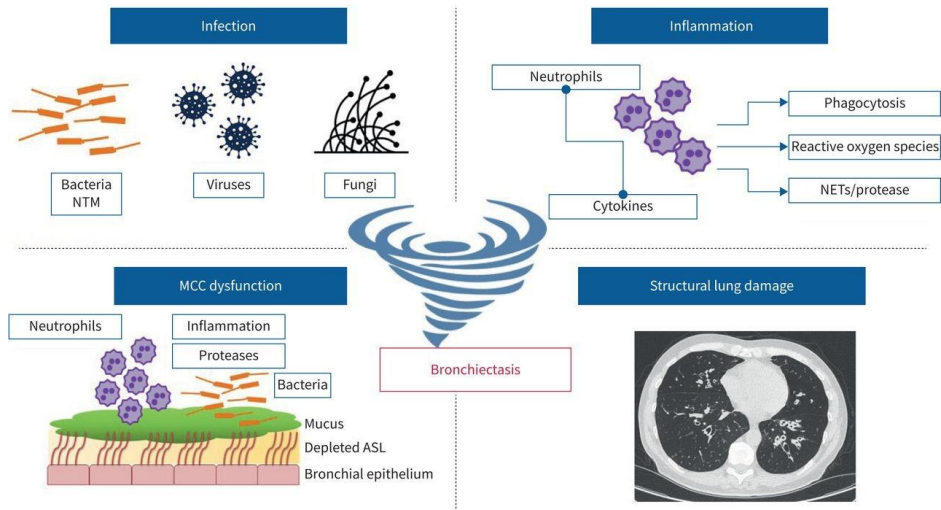
2.1.3 Socioeconomic Burden

The cost of treating people with bronchiectasis is substantial. The EMBARC data reports people with bronchiectasis experience a median of two exacerbations a year (IQR 1-4) and 26% were hospitalised by an exacerbation in the previous 12 months (Chalmers et al., 2023). Costs of management of bronchiectasis patients were \$2,500 higher than age-matched controls in the USA and European studies at around €7520 per year per patient who experiences >2 exacerbations. However, the biggest driver of the cost was hospitalisation and the management of PsA could increase to \$56,000 (Goeminne et al., 2019) per patient per year. These figures should be interpreted with caution as the UK has a different healthcare system. However, they do highlight that costs are considerable. The indirect costs of bronchiectasis to society (e.g. time off work, carer costs etc) have not been reported.

2.1.4 Pathophysiology

As discussed previously there are multiple risk factors associated with the development of bronchiectasis with the initial insult often provided by an infection that initiates the vicious cycle of exacerbation and airway inflammation. Figure 2.3 displays the four key aspects of the vicious cycle of bronchiectasis that were first described by Cole (1986) and have been added to by decades of translational science and clinical research.

The four key aspects underpinning the vicious vortex of bronchiectasis.



James D. Chalmers et al. Eur Respir Rev 2023;32:230015

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Figure 2.3 The four key aspects underpinning the vicious vortex of bronchiectasis.
(Chalmers. et al., 2023)

Infection

The healthy lung is not a sterile environment with the balance of organisms, unique to an individual, described as a microbiome. The advent of rRNA sequencing technologies has allowed the study of the microbiome in bronchiectasis, revealing a complex and varied bacterial landscape (Faner et al., 2017). The microbiome during periods of clinical stability often includes dominant species like PsA and Haemophilus influenza (HI) (Cox et al., 2017). Notably, a less diverse microbiome, especially when dominated by PsA, correlates with increased disease severity, more frequent and severe exacerbations, and a higher mortality risk (Dicker et al., 2021). However, further studies are needed to understand the causes of reduced microbiome diversity, its connection to culture-detected bronchial infections, and the feasibility of targeting the microbiome with treatments.

Infections from bacteria, viruses, fungi, or NTM contribute to both the development and exacerbations of bronchiectasis, with Gram-negative bacteria like PsA and HI being the most prevalent in-patient airway secretions, alongside Gram-positive Staphylococcus aureus (SA) and Streptococcus pneumoniae (Mac Aogáin et al., 2018; Metersky et al., 2021; Sibila et al., 2015).

Instead of fighting infection, neutrophils in the bronchiectasis lung often exacerbate the situation. These immune cells release enzymes and sticky DNA traps that fight infection but also damage lung tissue. Neutrophil elastase increases mucus production and makes it thicker and harder to clear. This thick mucus is worsened by altered fluid regulation and infection. Over time, the body's repair systems are overwhelmed, allowing inflammation and damage to continue, see section below inflammation. Increasingly bronchiectasis is seen as a chronic inflammatory problem, not a chronic infection problem (Long et al., 2024).

Chronic infections by HI and PsA directly damage lung tissue, with HI disrupting mucociliary clearance by inhibiting protein kinase resulting in a change in beat frequency of cilia and PsA through elastase secretion, which breaks down lung extracellular matrix components and neutralises anti-neutrophil elastase capacity (Bailey et al., 2012; Nair et al., 2014).

Biofilms also play a crucial role in the survival of PsA in the lung by shielding it from immune responses and enhancing antibiotic resistance. Neutrophils' unintended actions support biofilm stability by favouring the emergence of antibiotic-resistant strains. Within biofilms, PsA becomes immobile, further protecting it from immune cells. Biofilm formation begins through quorum sensing; as bacterial population density increases, signalling molecule levels rise, enhancing communication among bacteria. Reaching a threshold triggers these molecules to activate genes essential for biofilm development, producing mushroom-shaped structures and allowing further dispersal, as shown in Figure 2.4 (Thi et al., 2020). PsA ability to rapidly mutate enables it to adapt and thrive under varying environmental, immune, and antibiotic pressures by modulating gene expression (Solarat et al., 2023).

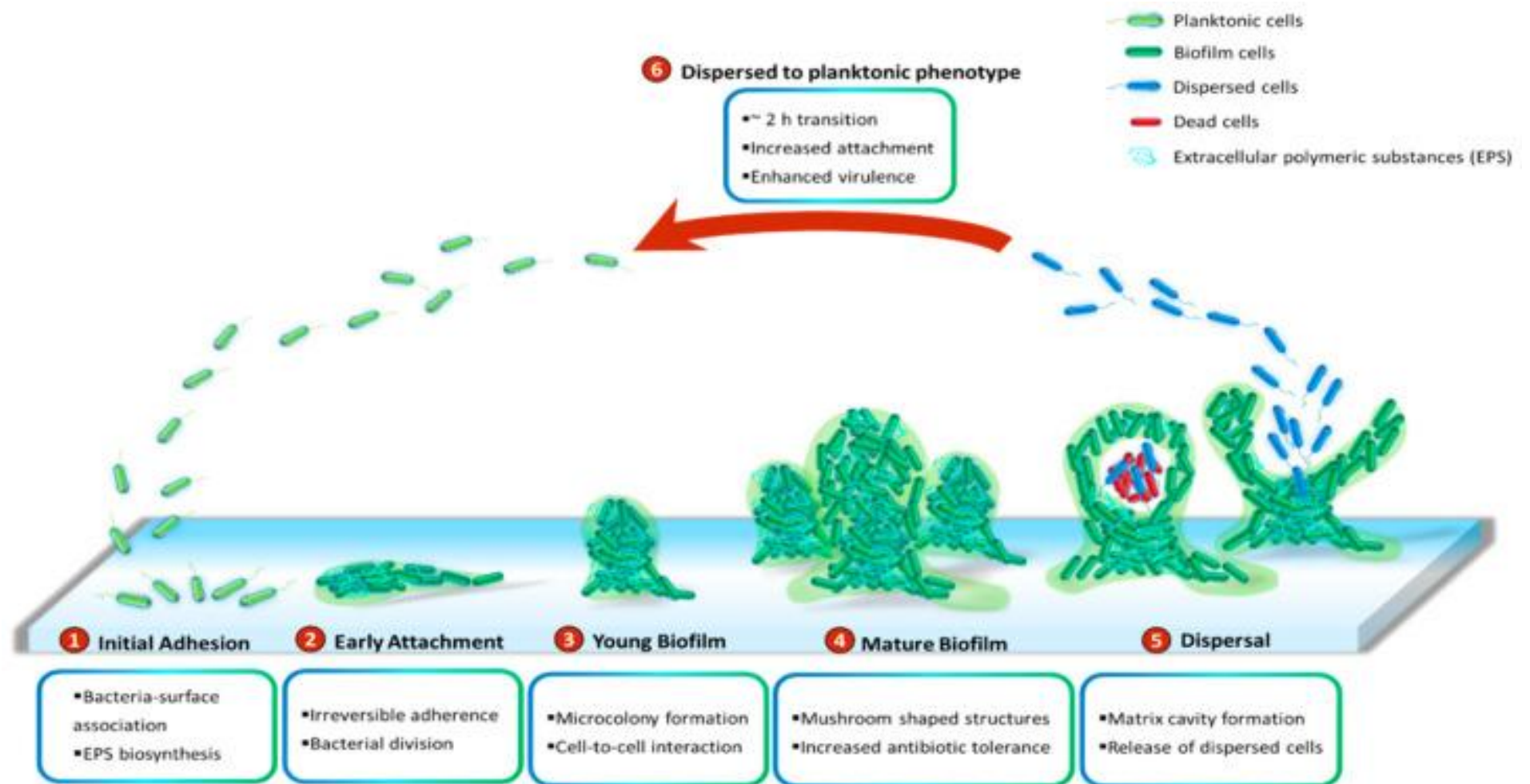


Figure 2.4 Cycle of *Pseudomonas* biofilm development
(Thi et al., 2020)

Inflammation

Bacterial load in bronchiectasis is directly linked to airway inflammation, with neutrophils being the predominant inflammatory cells, driving disease severity and progression (Chalmers et al., 2012). Up to 30% of patients show signs of T-helper cell type 2 (Th2)-mediated inflammation, indicated by elevated blood eosinophil counts. Neutrophils, attracted by cytokines and chemotactic factors such as IL-8, IL-1 β , IL-17, TNF- α , and leukotriene B₄, which are needed for bacterial phagocytosis, releasing reactive oxygen species and proteases, forming neutrophil extracellular traps (NET) (Mikami et al., 1998; Tan et al., 2011). NET, which are made of DNA, histones, and proteases like neutrophil elastase, aim to trap and neutralize microbes are linked to severe bronchiectasis when unregulated. This dysfunction results in reduced pathogen clearance, tissue damage from excessive neutrophil enzymes, and harmful NET activity (Brinkmann et al., 2004).

Additionally, chronic inflammation is exacerbated by continuous neutrophil recruitment and delayed apoptosis by macrophages. Key to these processes is anti-neutrophil elastase, which can disrupt host defence mechanisms by cleaving proteins critical for immune response and tissue integrity (Kavanaugh et al., 2019; Young et al., 2011). High bacterial loads of PsA are associated with neutrophilic-driven inflammation and more exacerbations (Rogers et al., 2014).

Mucociliary clearance dysfunction

As previously discussed, mucociliary clearance is a process which involves the trapping and upward expulsion of debris and pathogens by mucus and cilia on epithelial cells, which is disrupted in bronchiectasis (Button et al., 2012). This dysfunction is one of the four key components of the vicious cycle, see Figure 2.3, result in dehydration and increased viscosity of the airway surface liquid. The process is best understood in the CF lung but is extrapolated to bronchiectasis by Chalmers et al. (2023). Factors include increased mucus production driven by neutrophil elastase, induced mucin gene upregulation, an abundance of mucus-producing cells from goblet cell hyperplasia and metaplasia that can lead to ciliary dysfunction (Fernandez et al., 2018). Leading to potential primary or secondary ciliary dysfunction, loss of ciliated cells, and inflammation-induced excessive mucus production and dehydration, possibly including compromised CFTR function, fuelling

current research studies looking at the effects of CFTR modulators in bronchiectasis (Mirra et al., 2017).

Structural lung damage

Bronchiectasis involves a complex interaction where structural lung damage can be both a trigger and a result of the condition. Factors leading to damage include genetic disorders like CF, PCD, birth defects, airway blockages, connective tissue disorders, and damage from infections as previously discussed. The cycle of damage from infections, cilia dysfunction, inflammatory damage, and elevated neutrophil elastase levels results in compromised mucociliary clearance (Glasgow & Greene, 2022). Hence the importance of airways clearance as a treatment

Progressive destruction of elastin and collagen are exacerbated by the bronchiectasis disease process (De Rose et al., 2018). Neutrophil elastase is linked to the early stages of bronchiectasis and can break down vital structural proteins, damaging airway integrity (Glasgow & Greene, 2022). Matrix metalloproteinases play a critical role in inflammation, tissue remodelling, and healing (Chen et al., 2009). Structural damage is a result of repeated infection and chronic inflammation in this condition, characterised by muco-hypersecretion, paired with impaired mucociliary dysfunction a key target for pharmacological and non-pharmacological treatments.

2.1.5 Exacerbations

The daily ebb and flow of symptoms experienced by people with bronchiectasis makes it difficult to differentiate between a sub-exacerbation level and that associated with an exacerbation. Exacerbations are intrinsically linked to disease progression, poor prognosis and high healthcare costs (Chalmers et al., 2018; Goeminne et al., 2019).

Hill et al. (2017) worked with an expert panel to establish a consensus definition for 'bronchiectasis exacerbations' that could be used in clinical research. They proposed a definition that an exacerbation was characterised by worsening of three or more symptoms such as cough, changes in sputum volume or consistency, sputum

purulence, breathlessness or decreased exercise tolerance, fatigue, and haemoptysis. 81% of the panel agreed a clinical decision to alter the treatment plan was necessary. However, 90% of the panel agreed that this did not exclusively include antibiotic treatment alone and could entail initiating a new treatment regimen that included a course of oral or intravenous antibiotics, the use of systemic steroids, optimising ACT, adjusting inhaled therapies (bronchodilators, mucolytics or antibiotics) or implementing other interventions, as can be seen in Figure 2.5 (Hill et al., 2017). An increase in symptoms over five to seven days can take many weeks to resolve and people often experience a decline in clinical status that never returns to baseline (Brill et al., 2015).

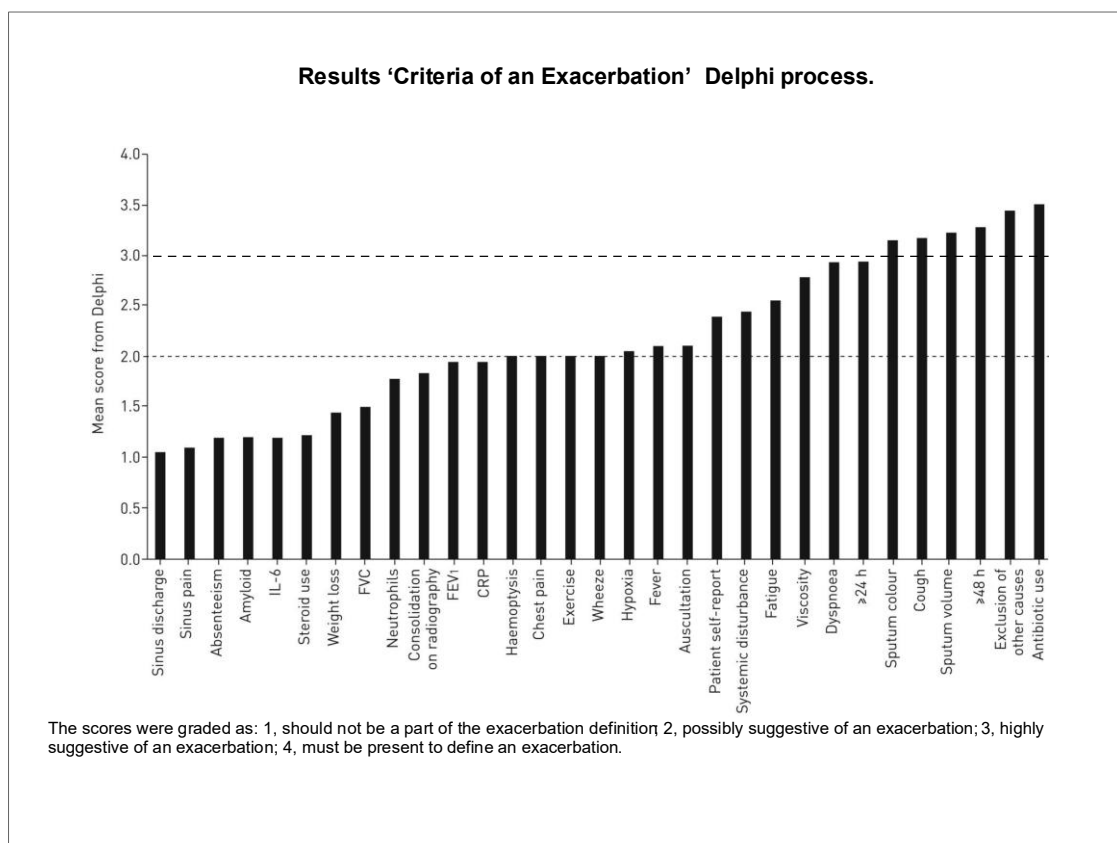
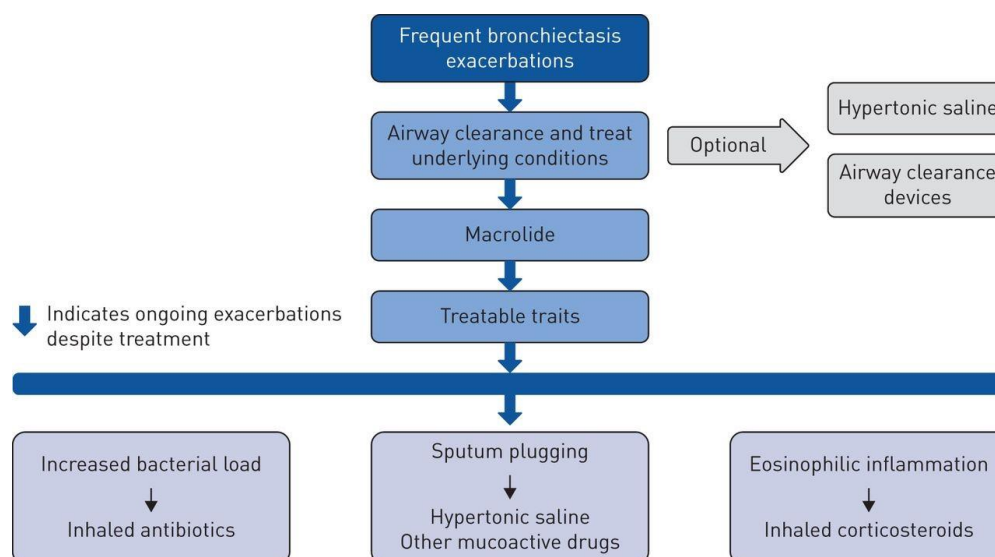


Figure 2.5 Results 'Criteria of an Exacerbation' Delphi process.

Adapted from (Hill et al., 2017)

The prevention of exacerbations, alongside the improvement of symptoms and QoL, is a key component in guidelines with ERS (Polverino et al., 2017), and BTS, (Hill et al., 2019) making several recommendations regarding strategies to decrease the severity and frequency of these debilitating episodes. Recommendations include ACT, mucolytics, long-term antibiotic use and pulmonary rehabilitation (PR). Figure 2.6 shows a simple schematic for exacerbation prevention and the topics will be discussed in the following sections.

A simple schematic for exacerbation prevention in bronchiectasis



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Figure 2.6 Schematic for exacerbation prevention in bronchiectasis.

(Laska & Chalmers, 2019)

2.1.6 Pharmacological treatments

At the time of writing, no medications are licenced specifically for use in bronchiectasis. The BTS and ERS Guidelines provide recommendations based on small cohort studies and evidence-informed by studies in other conditions, that have similar symptoms, physiological characteristics and clinical manifestations (Flume et al., 2018; Hill et al., 2019; Polverino et al., 2017). The following sections highlight current research and classes of medicines commonly used in clinical practice. Figure 2.7 shows how the therapies are considered against the pathophysiology of bronchiectasis.

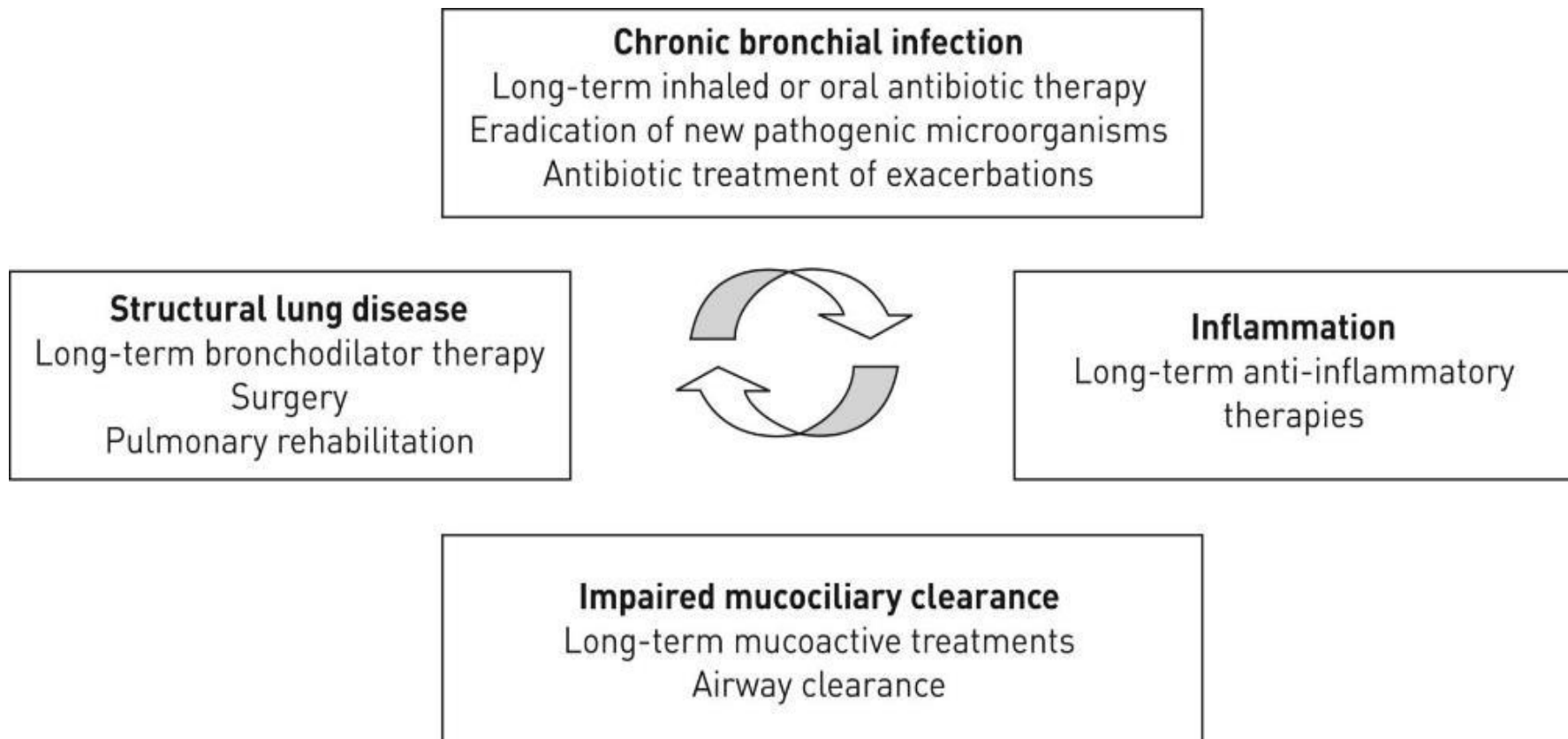


Figure 2.7 Treatment for bronchiectasis according to the vicious cycle concept.

(Polverino et al., 2017)

Antibiotics

Treatment of exacerbations with systemic antibiotics is commonplace in clinical practice. Current guidelines recommend considering intravenous antibiotics for complex patients, those with resistant pathogens, or those not responding to oral antibiotics (Henkle et al., 2017). Guidelines previously suggested a 14-to-21-day course, despite limited evidence supporting this duration (Polverino et al., 2017). A shorter seven-day course may be considered (Polverino et al., 2017). A proof-of-concept RCT explored the viability of shortening antibiotic treatment based on bacterial load (Bedi et al., 2021).

The use of prophylactic oral antibiotics such as macrolides was recommended for patients without PsA infection (Polverino et al., 2017). Take up of this in the UK is shown in EMBARC data with 20% of patients taking macrolides (Chalmers et al., 2023). Research has shown that they target the key components of the vicious vortex of bronchiectasis (Figure 2.3) pathophysiology (Chalmers, 2017; Haworth et al., 2014).

Research into macrolides have small cohorts, several meta-analyses have been conducted into the historical studies to increase the meaningfulness of the data. Gao et al. (2014) analysed data from 559 participants in nine trials identifying a 64% (IRR 0.42 95%CI 0.29-0.61 $p<0.001$) reduction in exacerbation frequency in adults and improvements in FEV₁ ($p=0.002$ adults) and QoL ($p<0.001$). In the PROSPERO study meta-analysis data from 341 participants over three RCTs were included reporting a decrease in frequency of exacerbations, IRR 0.49 with 95% CI 0.36-0.66 $p<0.0001$ and time to first exacerbation IRR 0.46 95% CI 0.34-0.61 $p<0.0001$. However, reductions in frequency and likelihood of exacerbation were not matched by a meaningful improvement in clinical symptoms (Chalmers et al., 2019).

Anti-inflammatories

Inflammation is a key component of bronchiectasis (Figure 2.3), as previously discussed, with sputum neutrophil elastase levels being linked to increased

exacerbation frequency, and a predictor for admission due to exacerbation, time to next exacerbation and mortality ($p < 0.0001$) (Chalmers et al., 2017).

Treatment of bronchiectasis has traditionally focused on antibiotics, but the EMBARC group believes that the development of new anti-inflammatories:

*“Holds the promise of transforming the management of the condition”
(Chalmers et al., 2020).*

There is ongoing research to identify compounds that will interact with the cascade of processes in bronchiectasis. One of these compounds currently under investigation is Brensocatib, is an oral selective reversible inhibitor of dipeptidyl peptidase¹ acting as an anti-inflammatory, the phase two RCT double blind, placebo-controlled trial (WILLOW) recruited those with two or more exacerbations with purulent sputum ($n=256$). At the 24-week mark, an increase in time to first exacerbation ($p=0.03$) was observed, and a decreased risk of next exacerbation with an IRR of 0.58 (95% CI 0.35-0.95 $p=0.03$), however, reported adverse events included dental and skin issues (Chalmers et al., 2020).

Inhaled antibiotics

The BTS and ERS guidelines suggest using inhaled antibiotics alongside macrolides to treat PsA colonisation. A three-month course should follow up an initial two-week phase with sputum sampling to monitor infection status (Hill et al., 2019; Polverino et al., 2017). Davison et al. (2023), in a qualitative study exploring patients' attitudes and lived experience of using nebulised antibiotics, found that only 10% of participants wanted to remain on nebulised therapy as it was an imposition to their daily routine. Reaching consensus that easier treatments that were well researched and effective, were preferable.

Inhaled colistin has long been a first-line therapy in cystic fibrosis but has not been licenced for use in bronchiectasis (Polverino et al., 2017). In a prospective cohort study, Blanco-Aparicio et al. (2019) recruited 67 participants with a median age of 67 years, with confirmed bronchiectasis and positive PsA cultures. Reporting eradication rates of 61% after 3 months, falling to 40% at one year with one-year

pre- and post- decreasing exacerbation rates from 3.4 to 2 ($p=0.001$). Noting that colistin is part of guideline therapy and commonly used in clinical practice de la Rosa-Carrillo et al. (2022) recognised that there is still a paucity of high-grade evidence to support its use.

Inhaled tobramycin has been shown to reduce PsA density ($p=0.01$) in people with bronchiectasis ($n=37$) (Hill et al., 2017). Terpstra et al. (2022), in an RCT of adults with bronchiectasis experiencing two or more exacerbations, found a reduction in the number of exacerbations ($p=0.00$) and a significant reduction in the LCQ total score ($p=0.02$). However, a similar significant reduction in exacerbations was seen in the placebo group ($p=0.00$). Supporting that additional research is necessary to strengthen the evidence supporting this therapy.

Ciprofloxacin dry powder phase II trial showed >3 fold log reduction in bacterial load in sputum PsA, SA and HI, with the most significant reduction being seen up to day eight +/- one and therefore, a 14-day arm was considered a valuable research target in RESPIRE (De Soyza et al., 2018). RESPIRE recruited 416 people to various dosing regimens, including a 14-day on/off regimen. Only the 14-day on/off regime showed significant results with time to first exacerbation >336 days in the treatment group versus 186 in the placebo group ($p=0.0005$). Risk of exacerbations (IRR 0.61 $p=0.0061$) also saw a significant decrease (Aksamit, Bandel, et al., 2017).

An alternative preparation of inhaled ciprofloxacin has been proposed as a once-a-day preparation of inhaled medication designed to have a lower side effect profile than dry powder. ORBIT-4 showed a significant reduction in frequency of exacerbation IRR 0.4 95% CI 0.22-0.74 ($p=0.0031$) (Haworth et al., 2019). We await the publication of the next iteration of the guidelines to see if any of these medications are recommended or even licensed for bronchiectasis.

Bronchodilators

Bronchodilators are not recommended in bronchiectasis as there is no evidence to support their use. However, long-acting bronchodilators should be offered to those with confirmed significant dyspnoea or airflow obstruction, as found in COPD and asthma, and only continued if a positive clinical effect can be seen (Polverino et al.,

2017); however, registry data highlights the overuse of these medications (Chalmers et al., 2023; Henkle, Aksamit, et al., 2018). Martínez-García et al. (2022), in a recent systematic review article, commented that there are no RCTs or long-term observational studies influencing the body of evidence. Guan et al. (2016) identified that bronchodilator response was negatively correlated with lower lung function and that there was a weak but non-significant reduction in exacerbation rate.

The BTS guidelines recommended that bronchodilators only be initiated in those with co-existing asthma and COPD, similar to the recommendations of the ERS (Hill et al., 2019; Sobala & De Soyza, 2022). COPD and bronchiectasis often overlap, with this group exacerbating more often, producing more sputum and having poorer outcomes, including mortality (Choi et al., 2021; Sobala & De Soyza, 2022). Interestingly, In a sample of 16963 people, Polverino et al. (2024) found that people with asthma and bronchiectasis were more likely to exacerbate but had a lower mortality rate. There is a definite need for further research, including well-designed and well-powered studies, to identify subgroups in the population who would benefit from the therapy.

Inhaled corticosteroids

Registry data from Europe and the USA showed that 55% and 39% respectively, of patients reported using ICS (Aksamit, O'Donnell, et al., 2017; Chalmers et al., 2023). This is likely driven by the perceived overlap with other airways diseases. However, there is little support for its use in the literature. Henkle et al. (2017), reported a sample of 511 responses from people with bronchiectasis, the authors noted that 61% had taken ICS for greater than a year, but only 17% had concurrent asthma and 19% COPD. Further research is needed to establish the safety and efficacy of ICS in bronchiectasis.

Mucolytics

Dominant symptoms of bronchiectasis include cough and sputum production, with the guidelines recommending the use of ACT as first-line treatment for these symptoms. However, the use of mucolytics is not recommended, but recognises their use in patient-by-patient cases as good practice (Hill et al., 2019).

Hypertonic saline (HTS) is commonplace in CF care and is recognised as an important supportive adjunct to ACT (Elkins & Dentice, 2020). HTS aims to improve mucociliary clearance by increasing hydration in the airway surface liquid and improving sputum hydration (Lee, 2023). However, evidence to support its use in bronchiectasis is poor. A meta-analysis by Xie et al. (2020) found four RCTs comparing the effects of HTS to normal saline pooled the data of 120 people with bronchiectasis and reported no significant effect on FEV₁ (p=0.18), FVC (p=0.30), sputum expectorated (p=0.99) or LCQ (p=0.68). There is limited evidence to support the use of HTS in place of normal saline in bronchiectasis.

Another agent that is used in CF is Mannitol, a sugary dry powder inhaler, when taken it acts as an osmotic agent, drawing water into the airways, aiming to loosen and mobilise secretions (Daviskas et al., 2005). Bilton et al. (2014), in an RCT comparing a treatment dose of Mannitol (400mg) twice daily for 52 weeks against a low sub-therapeutic dose recruited (n=461) people with bronchiectasis who had experienced ≥ 2 exacerbations in the last year. Baseline demographics matched, and participants were randomised 1:1. The results showed a non-significant reduction in exacerbation rate (p=0.31). However, a significant result in health-related quality of life (HRQoL) (St Georges, p=0.046) and time to first exacerbation (p=0.022) was demonstrated. A potential weakness of this study is the use of a lower dose of the active ingredient in the control arm, which could have affected the outcomes.

2.1.7 Airways Clearance

Airways clearance is an important non-pharmacological treatment in bronchiectasis that aids in the removal of secretions from the airways (O'Neill et al., 2019). Its techniques and application have previously been described in Airways Clearance Techniques (ACT), in chapter 1. This section will highlight specific considerations pertinent to bronchiectasis, particularly to the study's aims.

There are a variety of ACT applied in clinical practice, including positioning, gravity-assisted drainage, manual techniques, ACBT, PEP, OPEP and mechanical tools such as high-frequency chest wall oscillation devices that are applied to the chest

wall (Lee et al., 2017). Many of these techniques may be used in isolation or choreographed together to create an individual, tailored regime.

The BTS advocates a stepwise plan for ACT linking clinical judgement, disease severity, and an individualised self-management plan (Hill et al., 2018). Quality standards propose that people with bronchiectasis are taught ACT by a specialist respiratory physiotherapist (A. T. Hill et al., 2022). Although the acceptability and tolerability of ACT are valued and reported as high by both clinicians and people with bronchiectasis (Bracey et al., 2019; A. L. Lee et al., 2021), guideline recommendations are poorly applied (Basavaraj et al., 2020; A. T. Hill et al., 2014).

Despite these recommendations, reported use of ACT varies significantly across time and location. Spinou et al. (2024) using data from 28 countries from EMBARC (n=16,732) mean age 67 (57-74) years, 39% male, with 72% regular sputum producers. 52% (CI 51-53%) of patients performed regular ACT. Regional variation was reported in the UK (59%), Ukraine (92%), and Bulgaria (2.9%). Interestingly, Spinou et al. (2020), using an earlier dataset from EMBARC (n=13,512), reported 48% performing regular ACT with rates in different countries ranging from 10% to 92% in Sweden and Denmark, respectively. Which shows an encouraging change over time. Whereas USA registry data showed higher use of daily ACT, 59% (n=905) (Basavaraj et al., 2020).

Studies suggest that higher use of ACT is associated with greater disease severity and lower Health-Related Quality of Life (HRQoL) (Herrero-Cortina et al., 2023). Spinou et al. (2024) reported those who did use ACT as having a higher median BSI (7 IQR 5-11), PsA infection in 23% versus 13.2% (p=0.0001) and >3 exacerbations in the last year in 45% versus 32% (p=0.0001). However, this is not cause and effect.

Treatment adherence can be an important consideration that affects both perceived treatment burden and disability caused by respiratory symptoms. McCullough et al. (2014) recruited 75 patients from an NHS cohort in Northern Ireland for a one-year study to identify links between adherence and health outcomes. Participants' adherence was calculated using a medicine possession ratio and a self-reported adherence to ACT, with $\geq 80\%$ considered adherent. Health outcomes were

measured by number of exacerbations, FEV₁, and QoL-b. The results showed that those with adherents $\geq 80\%$ to inhaled antibiotics experienced fewer exacerbations ($p=0.00$) and that $\geq 80\%$ adherence to ACT was inversely related to the QoL-b treatment burden domain ($p=0.01$) and respiratory symptoms ($p=0.05$) (McCullough et al., 2014).

Additionally, the specific use of adjunct ACT is also associated with greater disease severity, lower HRQoL and increased breathlessness in comparison to non-adjunct ACT (McLeese et al., 2023). These descriptions are based on the use of ACT across Europe (Herrero Cortina et al., 2017; Spinou et al., 2024) and in smaller cohorts in Northern Ireland (McLeese et al., 2023) and Australia (A. L. Lee et al., 2021). A recent publication by Basavaraj et al. (2024) demonstrated that increased severity of bronchiectasis predicted the use of and adherence to high-frequency chest wall oscillation therapy. This specific type of ACT is rarely used in the UK and Europe (Spinou et al., 2020). Spinou et al. (2024) described a breakdown of ACT use: 52% used ACT, with ACBT used in 28.4%, regular exercise in 9.3%, postural drainage in 8%, AD 6.5%, and the use of OPEP not reported. However, Spinou et al. (2024) reported that multiple ACT modalities were used: single (37.5%), double (18.1%), and triple (10.5%), with common combinations of ACT, including devices, in 21.6%.

Other than Spinou et al. (2024), who describe a large cohort of European data, providing an opportunity for comparison, there are few data sets describing associations between ACT use and specific types of ACT use (adjunct or non-adjunct) and co-morbidities in bronchiectasis, in the UK. Additionally, there are no large UK studies showing real-world data and exploring the associations of ACT usage and specific types of ACT usage with the Bronchiectasis Severity Index (BSI) and QoL.

2.1.8 Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is an individualised comprehensive intervention-based assessment, including exercise training, education, and self-management strategies, see Figure 2.8, aimed at improving physical and psychological status and promoting chronic condition management (Spruit et al., 2013). A six-to-eight-week program has

been recommended as guideline therapy for COPD and bronchiectasis (Hill et al., 2018; Hopkinson et al., 2019). Referral rates to PR are made up of 50% from primary care, with only 50% of those eligible in Wales referred in 2017 (Stone et al., 2020). PR is recommended by both the BTS (Hill et al., 2019) and ERS (Polverino et al., 2017). Hill et al. (2019) suggest that those who are functionally limited by shortness of breath, scoring ≥ 1 on the mMRC should be offered PR.

Courses of PR should be tailored to suit the needs of the individual and contain resistance training and cardiovascular activity and advice on physical activity levels and healthy living (Bolton et al., 2013; Man et al., 2023). Since its inception, PR has expanded to include other interventions, including those aimed at emotional support and education about symptoms and management tailored to address physical and psychosocial aspects of chronic disease management (Wouters et al., 2018).

Chapter 3 provides further commentary on the delivery of PR. PR is a hotbed of innovation, and the literature is peppered with quality improvement projects aimed at improving the delivery and content of PR to suit the populations they serve. Recent research supporting the strong recommendations in bronchiectasis includes a study by Zanini et al. (2015).

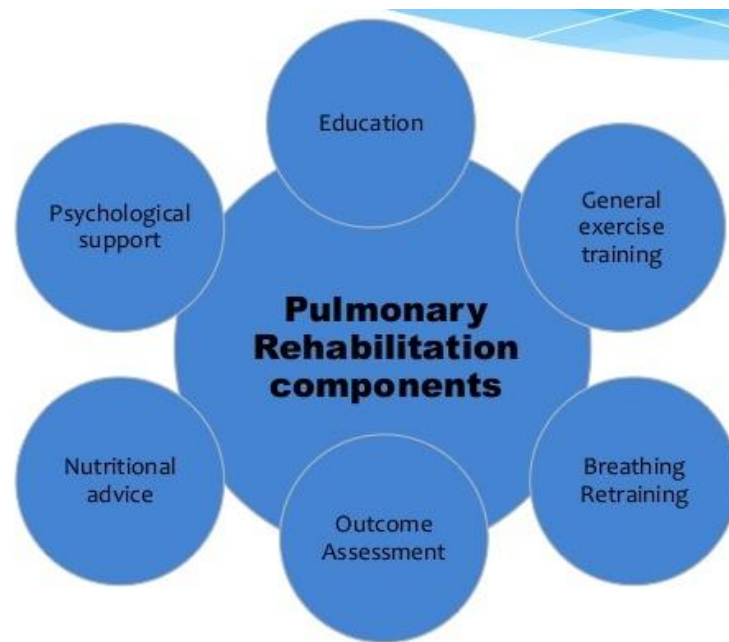


Figure 2.8 Components of pulmonary rehabilitation.

2.1.9 Smoking Cessation and Vaccination

The BTS and ERS guidelines make little specific mention of these strategies and instead point towards public health documents (Hill et al., 2019; Polverino et al., 2017). The guidance for smoking cessation and vaccination is the same across respiratory conditions and can be viewed in smoking cessation in Chapter 3.

2.2 AIMS OF STUDY

Bronch-UK (Bronchiectasis Observational Cohort and Biobank UK) is a multicentre, prospective, observational cohort study working collaboratively with the EMBARC project (DeSoyza et al., 2021). Over 1600 patients with bronchiectasis in the UK enrolled, providing longitudinal real-world data on patient and disease characteristics, treatments and outcomes. This study obtained data from Bronch-UK

Aim (1)

- 1) Describe the most common methods of ACT use in the UK and identify associations between types of ACT and disease severity.

Null-Hypothesis (1)

There is no association between types of ACT and disease severity.

Aim (2)

- 2) Identify associations between the use of ACT and model patient risk factors.

Null-Hypothesis (2)

There is no significant association between patient risk factors and the use of ACT.

2.3 METHODS

2.3.1 Ethics and Approvals

Bronch-UK underwent review and received approval from the National Research Ethics Service Committee Northeast—Newcastle and North Tyneside 1 on July 17th, 2015. A copy of the study outline is in Appendix 1.

- IRAS: 173303
- REC REF: 15/NE/0172
- ISRCTN: 17489966 <https://doi.org/10.1186/ISRCTN17489966>

Bronch-UK Study Design

Bronch-UK is a national research database and biobank of adults with bronchiectasis. Similarly to the European EMBARC database, the database aims to facilitate clinical trials and academic research studies in order to improve our understanding of what causes bronchiectasis and to find better, more effective treatments for people with this condition (DeSoyza et al., 2021).

The inclusion criteria were adults with a clinical history consistent with bronchiectasis (cough, chronic sputum production, and/or recurrent respiratory infections) and a historical CT of the chest demonstrating bronchiectasis (bronchial dilatation) affecting one or more lung lobes.

The exclusion criteria were patients who were unable or unwilling to provide informed consent, bronchiectasis due to known cystic fibrosis or bronchiectasis is not the main or co-dominant respiratory disease, prior lung transplantation for bronchiectasis, and patients already enrolled in EMBARC.

See Figure 2.9 For study flow chart.

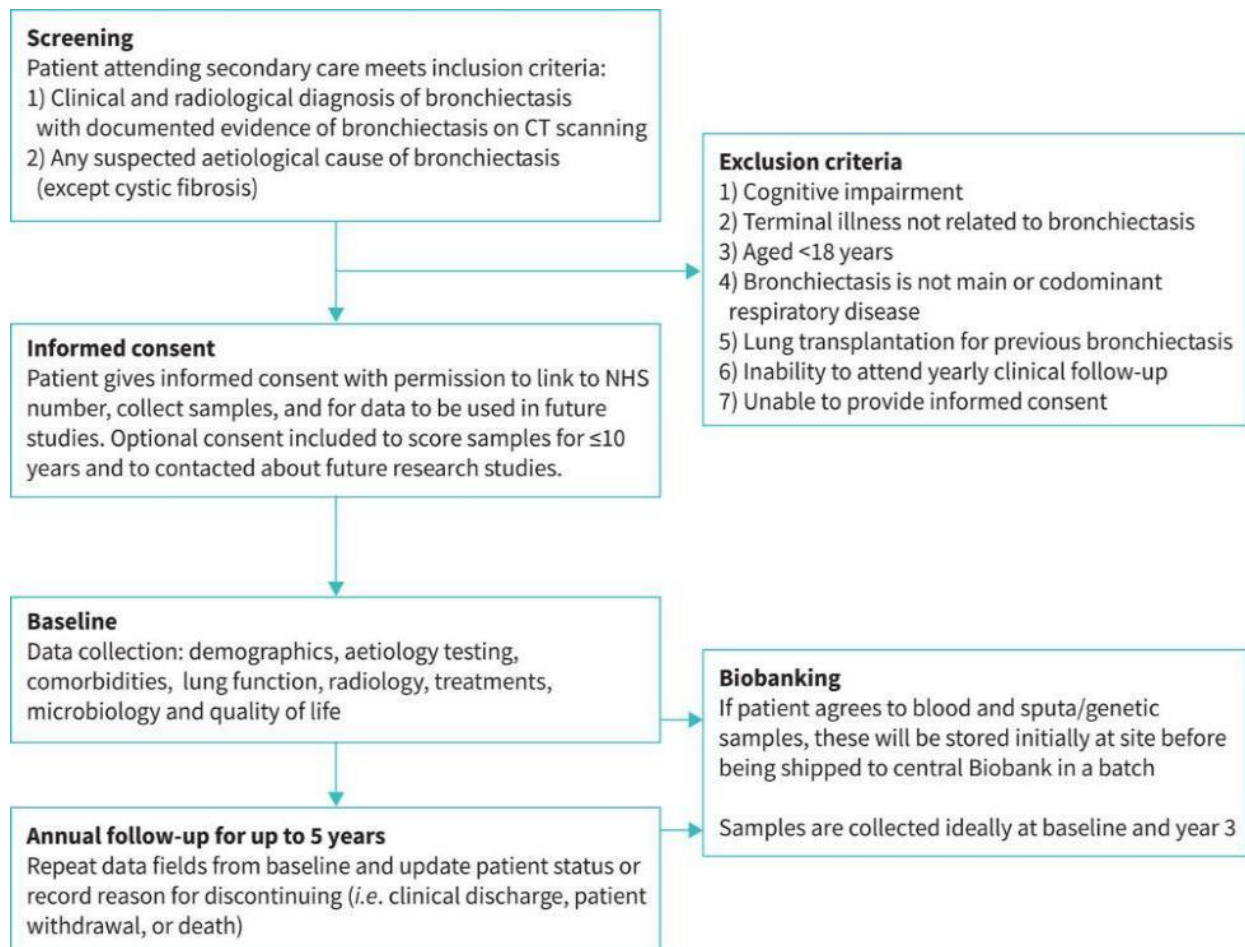


Figure 2.9 Bronch-UK study flow chart.

(DeSoyza et al., 2021)

2.3.2 Procedure

An application to access data from the Bronch-UK registry was submitted on 1st July 2021. Our study was the first application received by Bronch-UK to access baseline data for participants with full data sets. See Appendix 2 for our letter of application.

2.3.3 Data Source

The dataset was the baseline data from the patient's first visit. Clinical data incorporating demographics, co-morbidities, medications, aetiological testing, microbiology, radiology, lung function and disease history were recorded. Spirometry was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards (Quanjer et al., 2012). The investigators recorded and verified aetiology using data from the results of the aetiological testing. Radiological severity was evaluated using CT scan. Disease severity was evaluated using the BSI, see below (Chalmers et al., 2014). Exacerbations were defined as use (a course) of antibiotics for acute respiratory symptoms and were recorded from a combination of patient history, hospital and prescription records (Hill et al., 2017).

Outcome measures

Disease severity was calculated using the BSI, a composite score incorporating lung function, breathlessness, exacerbation frequency, hospitalisations, cough severity, sputum production and microbiological status (Costa et al., 2018). BSI scoring and implications of parameters can be seen in Table 2.1 adapted from Chalmers et al. (2014).

Table 2.1 BSI scoring and parameters

Parameter	Details
Age	Increasing points for older patients
Body Mass Index (BMI)	Score +2 for BMI < 18.5 kg/m ²
FEV₁ % predicted	Lung function; lower % = higher score
Hospitalisations in previous year	≥1 score +5
Exacerbations in previous year	≥3 exacerbations score +2
MRC Dyspnoea Score	1-3, 4, 5 Score +0, 2, 3 respectively
Chronic colonisation with <i>Pseudomonas aeruginosa</i>	Score +3
Chronic colonisation with other pathogens	Score +1
Radiological extent of disease	≥3 lobes +1

BSI total score 0-4 points mild, 5-8 points moderate, ≥9 points severe

Strong associations have been established between these markers of clinical deterioration. The interplay between markers of disease severity and clinical deterioration is well documented, with an exacerbation rate (Chalmers et al., 2018), sputum purulence (Aliberti et al., 2024), and BSI (McDonnell et al., 2016) being indicators of increased risk of future exacerbations and deterioration, therefore, negative disease trajectory. National and international guidelines recognise ACT as a key component to the management of bronchiectasis and have clinical importance over the disease trajectory (Chalmers et al., 2015; Chang et al., 2015; A. T. Hill et al., 2022; Polverino et al., 2017).

HRQoL and mental health were evaluated using the QoL-b version 3.1 (Hill et al., 2017; Magge et al., 2019) and the Hospital Anxiety and Depression Scale (HADS) questionnaire. A score of 7+ in each category indicates having significant symptoms (Bjelland et al., 2002). The QoL-b measure is a disease-specific measure comprising of 37 items and eight domains, with each item rated on a Likert scale. Scores range from 0-100, with a higher score generally indicating a better QoL (Quittner et al., 2015). The HADS was developed in the 1980s, comprising seven items for each anxiety and depression, showing reliability and validity in assessing symptoms in medical patients (Bjelland et al., 2002).

2.3.4 Statistical Analysis

The First research question was to describe the most common ACT use in the UK and identify associations between the use of a specific ACT and disease severity, QoL and additional clinical factors. Patients may use ACBT or OPEP, both, or neither of these types of ACT; therefore, factors will be assessed by making a comparison of the odds of using each type of ACT using a Chi-square test of association based on a null hypothesis that they should be the same.

The second research question aimed to identify associations between disease severity, QoL and additional clinical factors and the use of ACT, which is a binary outcome variable, necessitating the use of logistic regression.

Factors identified as significant in the logistic regression are reported using p-values and point estimates of confidence intervals for the OR. The Nagelkerke pseudo-R² value also measures effect size. The Nagelkerke score is itself a standardised effect score. It represents the proportion of the dependent variable explained by the model.

When building a combined model with multiple independent variables, Using a stepwise methods, comparing both the forward and backward algorithms. Although we acknowledge the limitations of this approach, we determined that the final models remained robust despite these constraints.

For the chi-square test, we report p-values and rates of use. A meaningful odds ratio cannot be calculated in this case as the outcome is not a simple choice between two binary outcomes.

Summary figures for continuous measures are generally quoted as mean and standard deviation although age is reported using median and interquartile range. Categorical results are reported using counts and percentages. Cronbach's alpha is used to assess the internal consistency of the QoL scores.

2.3.5 Sample

The study sample consisted of 1,579 individuals between the ages of 18 and 92, with a median (interquartile range, IQR) age of 67 (59,73). Demographic data is displayed in Table 2.2.

Table 2.2 Demographics of sample

Age	Median (IQR) 67 (59,73)
Gender	M 62% n=602 F 38% n=977
HADS	
Anxiety	Score 1-6 60%) 7+40%
Depression	Score 1-6(73%_ 7+ n=411 (27%)
BSI	
Mild (0-4)	22%
Moderate (5-8)	49%
Severe (≥9)	29%
QoL- B	Mean (SD)
Physical	51 (34)
Role	65 (27)
Vitality	46 (24)
Emotion	79 (23)
Social	60 (27)
Treatment	69 (24)
Health	46 (24)
Resp	61 (22)
Exacerbation in previous 12 months	Median 2 (0-18 range)
MRC	
≤2	n=87%
≥3	n=13%
Microbiology	
Pseudomonas	n=36%
Co-Morbidities	
Asthma	n=38%
COPD	n=16%

The mean scores for each QoL-b dimension are given in Table 2.3.

Table 2.3 Mean and SD of scores for the eight domains of the QOL-b.

Dimension	Physical	Role	Vitality	Emotion	Social	Treatment	Health	Respiratory
Mean (SD)	51 (34)	65 (27)	46 (24)	79 (23)	60 (27)	69 (24)	46 (24)	61 (22)

2.4 RESULTS

2.4.1 Aim One

Describe the most common methods of ACT use in the UK and identify associations between types of ACT and disease severity.

Null-Hypothesis (1)

There is no association between types of ACT and disease severity.

Null hypothesis not rejected.

While most (70%) (n=1099/1579) people in the Bronch-UK data said they performed ACT (see Figure 2.10), we see distinct differences in the types of ACT used by patients. The most common ACT used individually was ACBT, (53% n = 566/1099); OPEP alone was used by 14% (n=151/1099) and around 24% of the sample used both (262/1099), a further 11% (120/1099) used another, unspecified type of ACT.

See Table 2.4. and Figure 2.11

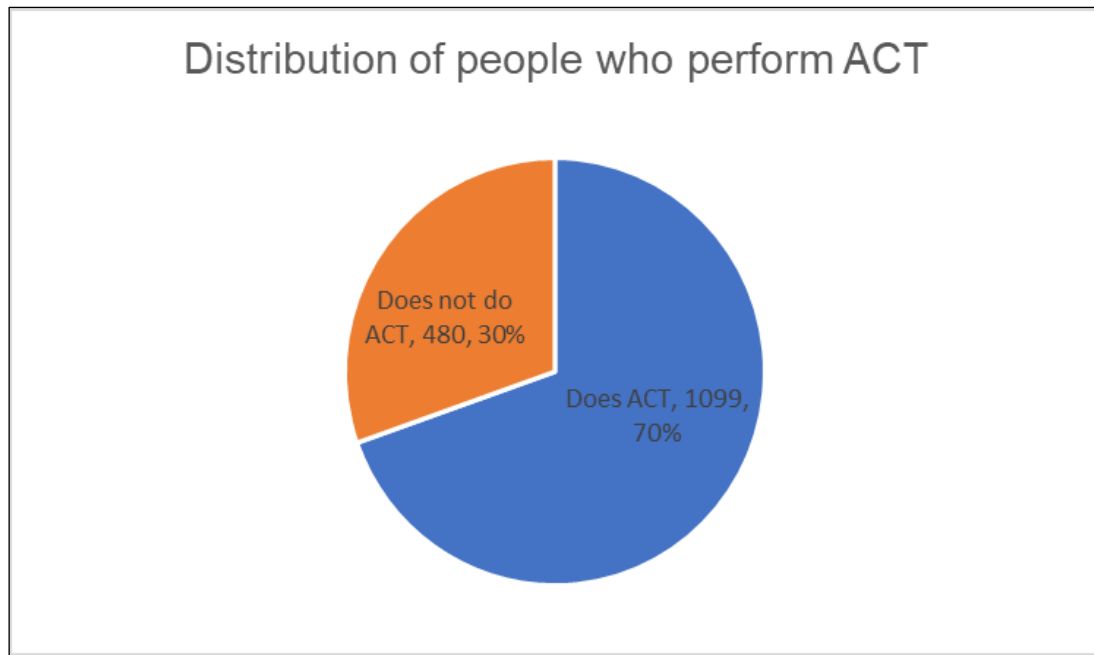


Figure 2.10 *Distribution of people who perform ACT.*

Table 2.4 Breakdown of ACT types and combinations

ACBT (alone)	OPEP (alone)	ACBT + OPEP	OTHER
566 (53%)	151 (14%)	262 (24%)	120 (11%)

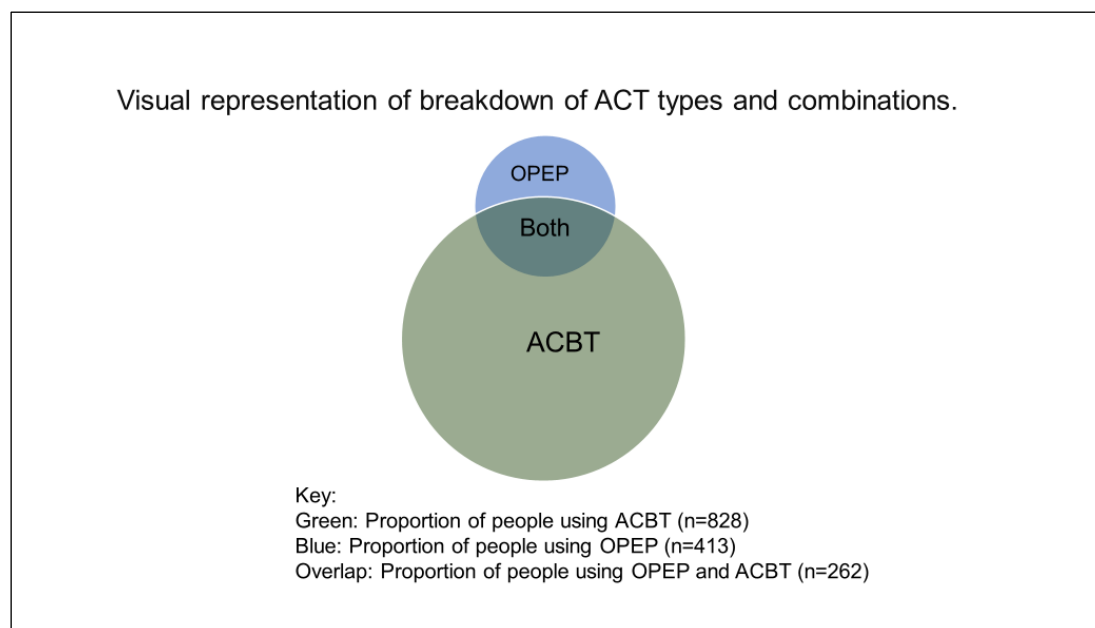


Figure 2.11. Visual representation of breakdown of ACT types and combinations.

Patients with PsA are more likely to use OPEP compared to any other ACT ($n = 199$) ($p < 0.001$). Additionally, patients with PsA are also more likely to use two specific ACTs (OPEP and ACBT) compared to those without PsA (see Table 2.5 and Figure 2.12). There is also a significant association with asthma ($p < 0.001$ for both) with asthmatics using OPEP 34% of the time compared with 22% for non-asthmatics. There is no association between patients using ACBT who have asthma as an additional clinical diagnosis (59%) versus 'no asthma' (OPEP use 49%). The choice between the two methods of ACT does not appear to be affected by severity, with neither exacerbation (see Figure 2.13) nor breathlessness (see Figure 2.14) affecting the relative frequency of ACBT versus OPEP.

Table 2.5 Clinical factors associated with the relative frequency of the use of OPEP and ACBT

Clinical Factor	Comparison	P
PsA	Presence vs absence	<0.001
Asthma	Presence vs absence	0.033
Exacerbation rate	Variation across levels	0.110
Sputum	Purulence vs Muroid	0.289
Gender	Male vs female	0.322
mMRC	Variation across levels	0.582
COPD	Presence vs absence	0.888

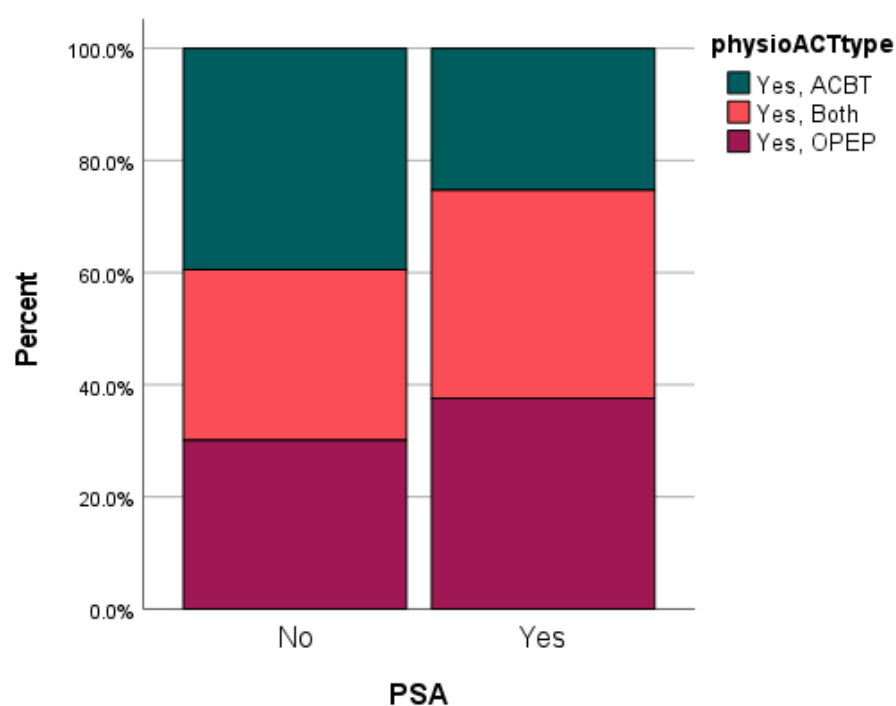


Figure 2.12 Association between clinical factors and the specific ACT (PsA)

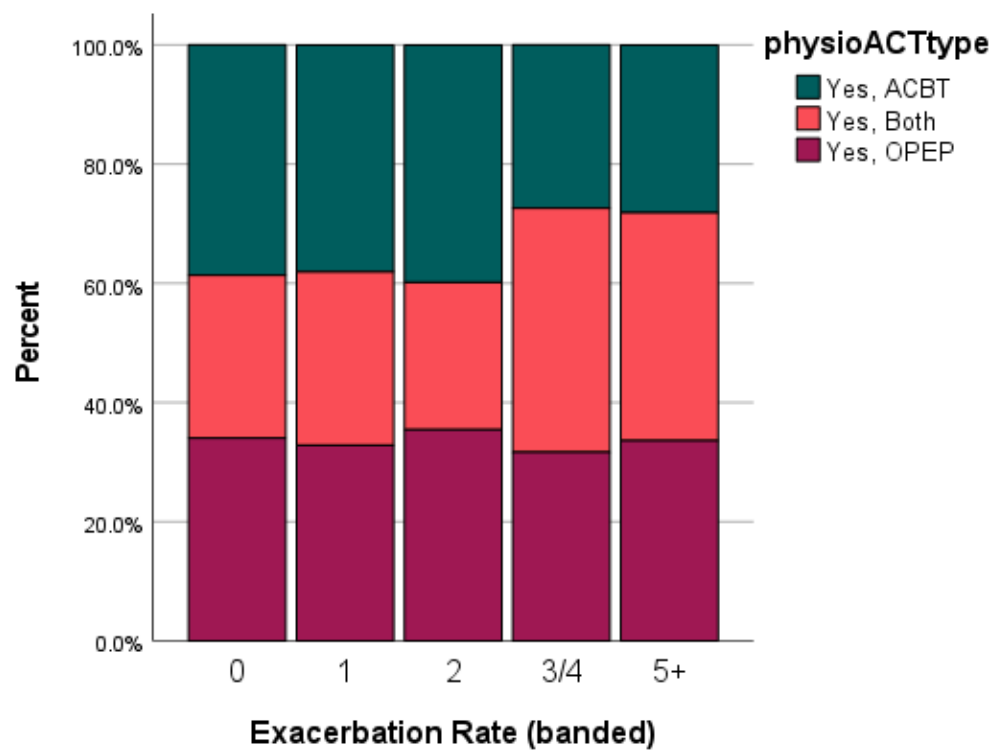


Figure 2.13 Association between clinical factors and the specific ACT (Exacerbation Rate)

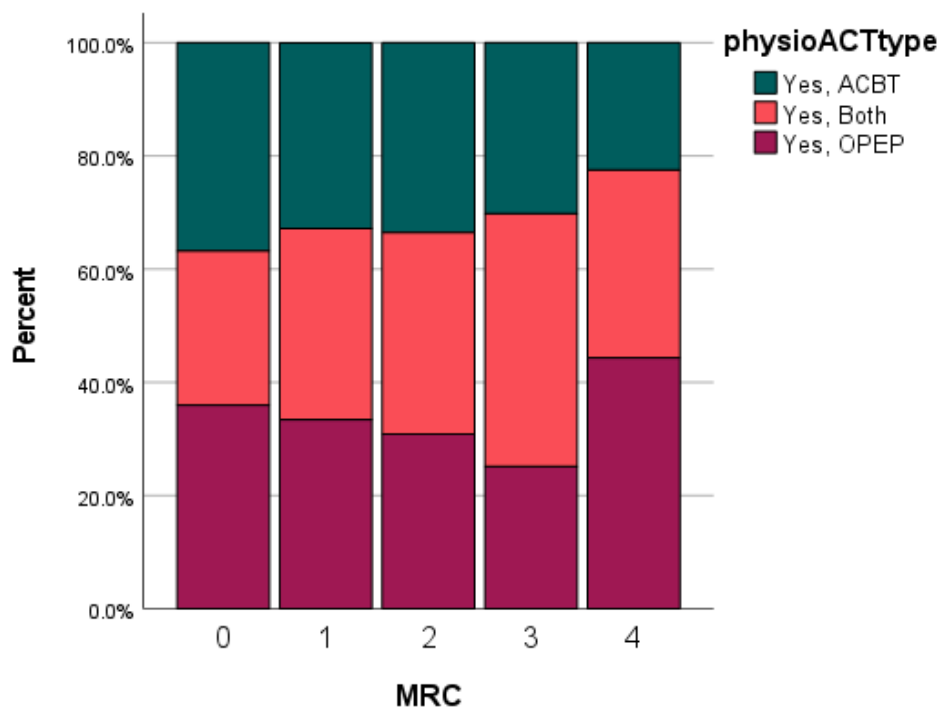


Figure 2.14 Association between clinical factors and the specific ACT (mMRC)

2.4.2 Aim Two

Identify associations between the use of ACT and model patient risk factors.

Null-Hypothesis (2)

There is no significant association between patient risk factors and the use of ACT.

Null hypothesis rejected.

The use of ACT was strongly associated with severity, as shown in Table 2.6, measured using the number of exacerbations ($p < 0.001$) see Figure 2.15, BSI ($p < 0.001$) see Figure 2.16, mMRC ($p < 0.001$) see Figure 2.17, PsA see Figure 2.18, asthma ($p < 0.001$) see Figure 2.19, FEV₁ ($p < 0.001$), see Figure 2.20, and gender ($p = 0.01$) see Figure 2.21.

Table 2.6. The association between Individual factors and the use of ACT.

Clinical Factor	Comparison	P	OR	Nagelkerke psuedo-R2
Exacerbation rate	Each additional event	<0.001	1.149 [1.097,1.204]	3.9%
BSI	Each additional unit	<0.001	1.104 [1.068,1.141]	3.2%
mMRC	Each additional level	<0.001	1.339 [1.206,1.487]	2.8%
PsA	Presence vs absence	<0.001	1.810 [1.430,2.292]	2.3%
Asthma	Presence vs absence	<0.001	1.811 [1.437,2.282]	2.2%
FEV ¹	Per additional unit	<0.001	0.992 [0.988,0.997]	1.3%
Gender	Male vs female	0.010	0.749 [0.602,0.932]	0.6%
HADs Anxiety	Each additional unit	0.086	-	-
Sputum	Purulence vs Mucoid	0.117	-	-
HADs Depression	Each additional unit	0.133	-	-
Age	Per additional year	0.456	-	-
COPD	Presence vs absence	0.525	-	-

*Variables listed in order of statistical significance Where $p > 0.05$ then odds ratios not supplied and neither is R2, for clarity.

Despite the high level of statistical significance in the associations between these factors and the use of ACT, the effect size itself was rarely very large (as we can see from the pseudo-R² values in Table 2.6).

The strongest clinical factor associated with ACT use was found with the number of exacerbations; however, this still only explains around 4% of the variation in ACT use.

For example, in the case of gender, the rates of ACT use are 72% and 66% for females and males respectively. Similarly, the presence of PsA or asthma did not result in a large increase in ACT usage, rising from 65% to 77% (for each variable).

Higher rates of breathless on mMRC dyspnoea scale are (broadly) associated with increased use of ACT, with rates rising from 62% at level 0 up to around 80% at level three and four (see Figure 2.17).

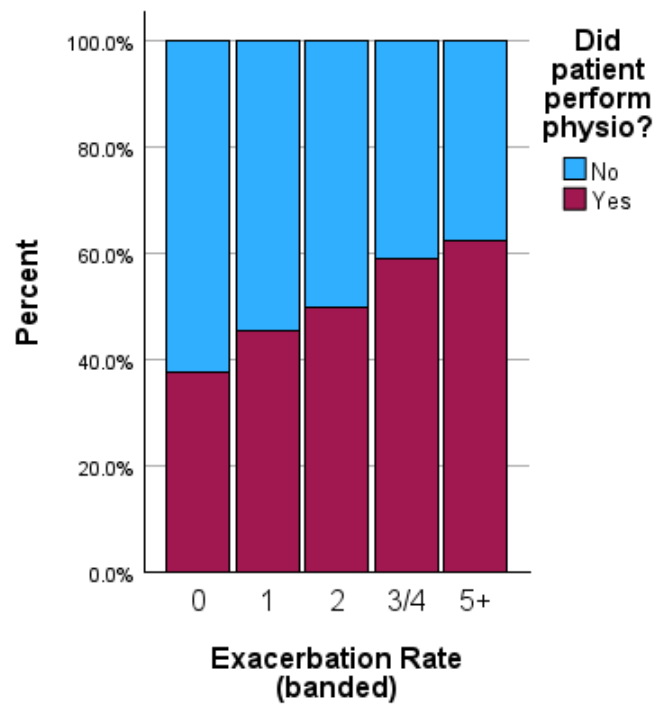


Figure 2.15. Association between severity and the use of ACT (Exacerbation Rate)

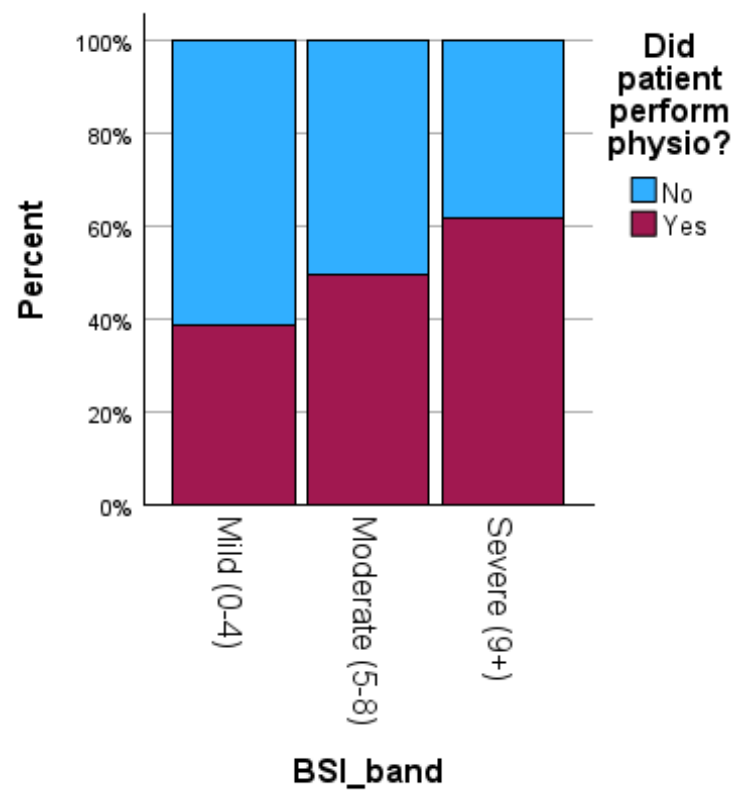


Figure 2.16 Association between severity and the use of ACT (BSI)

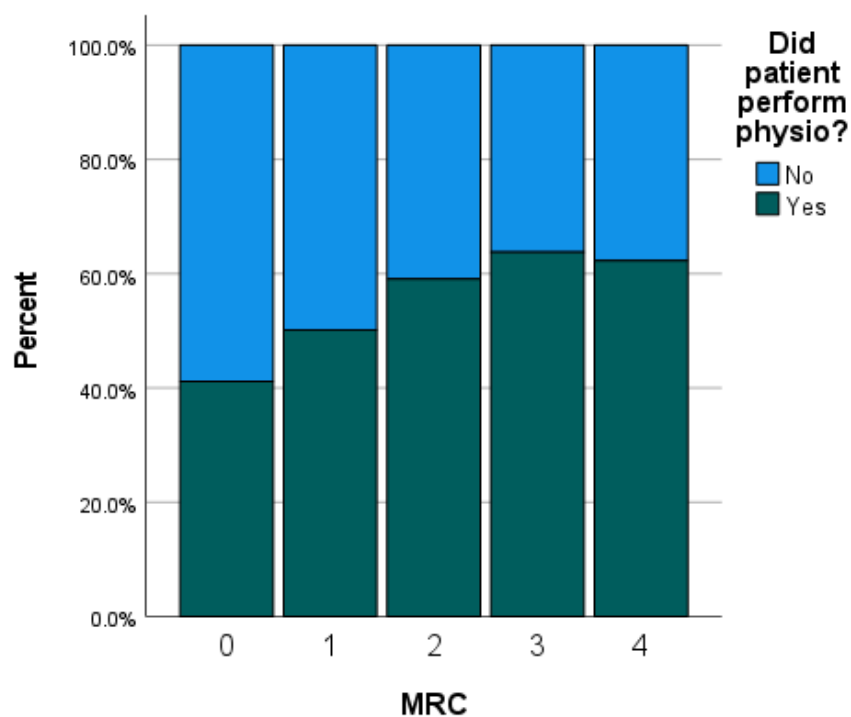


Figure 2.17 Association between severity and the use of ACT (mMRC)

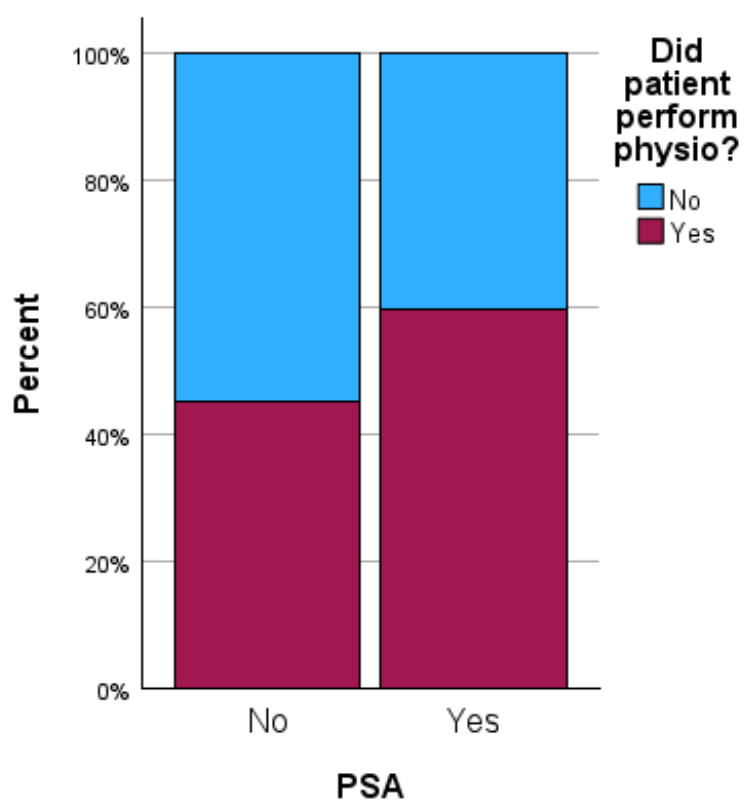


Figure 2.18 Association between severity and the use of ACT (PsA)

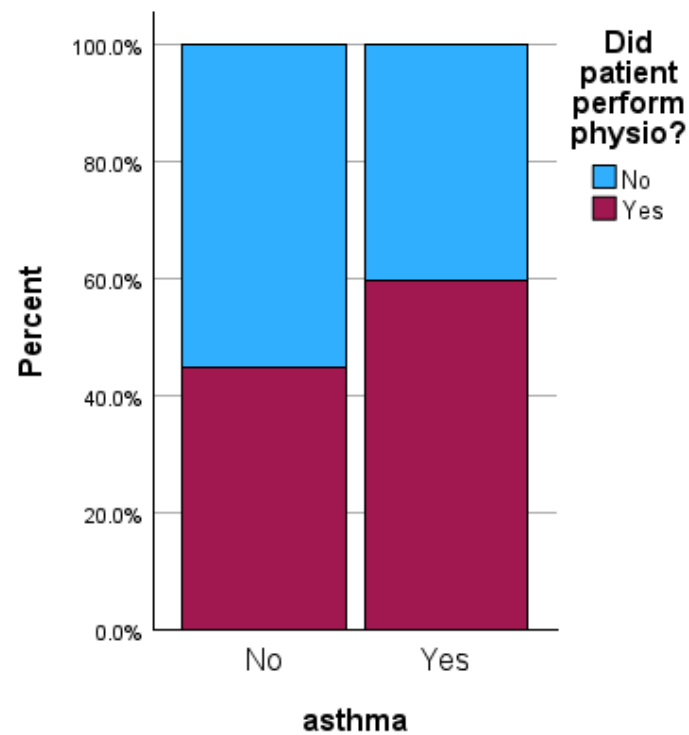


Figure 2.19 Association between severity and the use of ACT (Asthma)

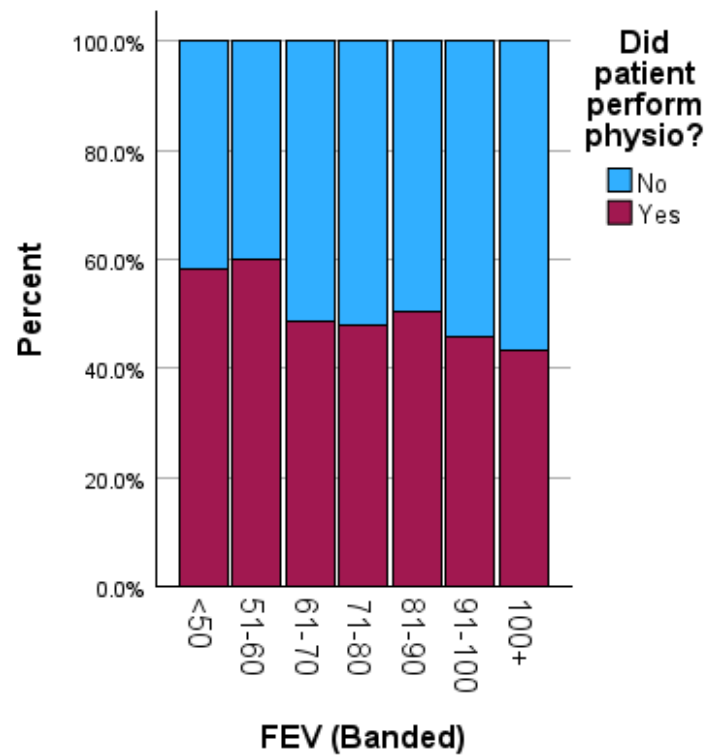


Figure 2.20 Association between severity and the use of ACT (FEV₁)

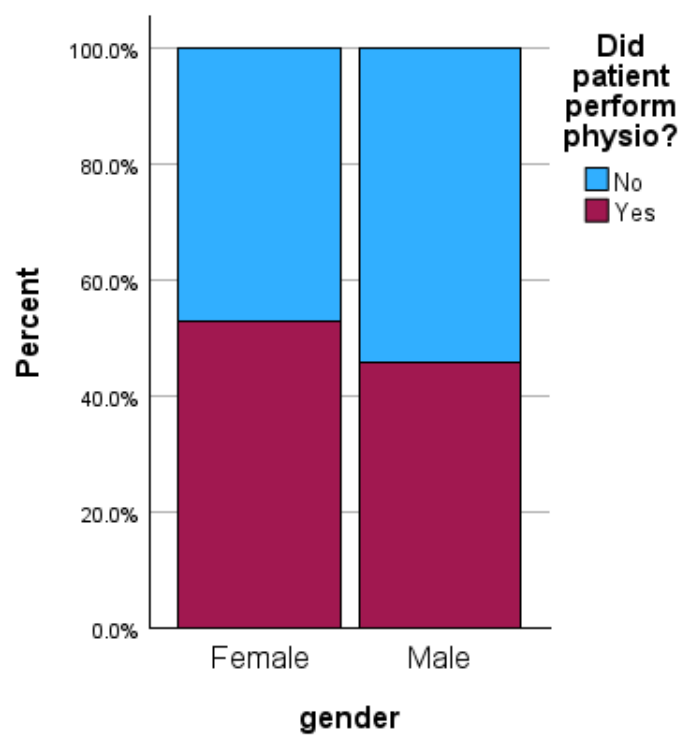


Figure 2.21 Association between severity and the use of ACT (Gender)

The eight dimensions of QoL are all closely related, with a level of internal consistency rated as 'Good' to 'Excellent' (Cronbach's Alpha 0.898). As such, all (except Emotion) are strongly associated with the use of ACT, ($p < 0.001$). As can be seen in Table 2.7.

Table 2.7 The association between the dimensions of QoL and the use of ACT

Variable	p-value	Effect Size OR	Nagelkerke psuedo-R2
Physical	<0.001	0.994 [0.991,0.998]	1.1%
Role	<0.001	0.990 [0.985,0.994]	2.2%
Vitality	<0.001	0.991 [0.986,0.996]	1.4%
Emotion	0.160	N/A	N/A
Social	<0.001	0.989 [985,0.994]	2.3%
Treatment	<0.001	0.975 [0.968,0.981]	8.2%
Health	<0.001	0.988 [0.983,0.992]	2.5%
Respiratory	<0.001	0.985 [0.980,0.990]	3.2%

If all these QoL dimensions are combined into a single model (predicting the use of ACT) using forward and backward stepwise methods both approaches return the same, simplified model. In this combined model only two variables are retained, EmotionQ ($p=0.024$) and TreatmentQ ($p<0.001$). This is interesting since EmotionQ did not initially appear significantly associated with ACT use. In each case, the association we observe acts in the same direction, with higher QoL scores being associated with lower rates of ACT use (or vice versa).

In simple terms, when trying to describe a set of factors that would indicate ACT use, we found that better health related QoL in the emotion and treatment domains of the QoL-B. This implies people who do less ACT have less emotional and treatment burden in relation to their bronchiectasis. However, when this was not the case when we looked at the domains in isolation, emotional burden did not register as significantly associated.

However, since all QoL variables are significantly (positively) correlated with each other there is considerable potential for confounding effects. Furthermore, we needed to assess the contribution made by these variables in the presence of the factors already identified in previous research on disease severity (BSI, exacerbation rate, mMRC, PsA, asthma, FEV, gender, age) and sputum purulence (Aliberti et al., 2024; McDonnell et al., 2016).

To discern the specific contribution of the QoL metrics, they were considered alongside the other variables. The results for this are found below (see Table 2.8). Stepwise methods were used to obtain this model with forward and backward algorithms returning the same final model.

The main objective in building a Stepwise model was to determine whether the QoL indicators remained associated with the use of ACT even in the presence of other, possibly correlated, predictors.

Table 2.8 A combined model for the use of ACT built using stepwise methods.

Variable		p-value	Effect Size OR
Exacerbation Rate	Continuous	0.003	1.100 [1.032,1.171]
Asthma	Categorical	<0.001	1.687 [1.249,2.280]
EmotionQ	Continuous	0.005	1.010 [1.003,1.0107]
TreatmentQ	Continuous	<0.001	0.973 [0.965,0.980]
Gender	Categorical	0.013	0.686 [0.508,0.924]

2.5 DISCUSSION

Summary of Main Findings

The demographics of the cohort broadly match those of the population with bronchiectasis in the UK. The respondents were predominantly female (62%,) with a mean age of 67 years, which matches well with the prior observation that around 60-62% of diagnoses are female (Snell et al., 2019; Spinou et al., 2024) 29% of people in Bronch-UK had 'severe disease' at the time of recruitment; this may be higher than the background population as a result of recruitment bias, which occurs from those attending secondary care.

The reported rate of ACT usage of 70% is higher than previously reported, which is encouraging given the guidelines' recommendations. However, a significant group of 30% still do not perform regular ACT. The data provided no reason why almost one in three do not perform regular ACT, which may be related to access to physiotherapy training, patient choice, or both.

The use of ACT is more prevalent in those with higher disease severity as measured by BSI (exacerbation rate, mMRC, FEV1 and microbiological status). This has been shown in a similar study in the United States Bronchiectasis and NTM Registry and the EMBARC data (Basavaraj et al., 2020; Spinou et al., 2024). One reason for this may be that people with bronchiectasis only feel the need to use ACT as their symptom burden or disease severity increases rather than using ACT as a preventative strategy to slow or prevent disease progression (Basavaraj et al., 2020; McCullough, Tunney, et al., 2015). Interestingly, sputum purulence was not significantly associated with the increased use of ACT. A recent paper by Aliberti et al. (2024) suggests that this may be important as this simple clinical marker is linked with increased rates of exacerbations and could also be used to encourage the use of ACT. It is unlikely that ACT leads to worse disease.

Interestingly asthma was a comorbidity in 38% of the cohort and was identified as a clinical factor associated with increased use of OPEP. There is no clear clinical reason for this however it may be linked to the increased healthcare utilisation of this

cohort, and a greater chance that they would be referred to a respiratory physiotherapist for review. Alternatively, this could be as a result of increased clinical nervousness of this cohort resulting in stepping up the clinical pathway quicker and therefore provision of a device to augment ACT. Further work is needed to identify the reason for this finding.

In the model lower use of ACT was associated with higher TreatmentQ and EmotionQ scores in the QoL-b domains. This is interesting, as studies previously showed that patients with increased treatment burden were less likely to perform ACT (Herrero-Cortina et al., 2023), demonstrating some differences between real-world data and empirical research. However, the findings may give a mixed picture due to the low pseudo-R² value for each of the domains that indicates that only a small amount of the variation in the data can be explained by each individual domain.

We then aimed to describe the most common ACT use in the UK and identify associations between the use of specific ACT modalities and disease severity, QoL and additional clinical factors. The use of different modalities of ACT in the literature varies depending on the geographical location, healthcare education and how healthcare is provided (McLeese et al., 2023). British national guidelines recommend a stepwise model using non-adjunct techniques, such as ACBT, first, then progressing to using an adjunct, such as OPEP, depending on several clinical and human factors (A. T. Hill et al., 2022). Our study showed that ACBT was the most used ACT (53%), followed by the use of an OPEP device (14%), consistent with these prevailing guidelines. Interestingly, 24% of patients (n = 262) used both ACBT and OPEP, demonstrating that these techniques are applied simultaneously more often than switching from ACBT to OPEP in isolation. This is likely related to intra-patient variation in symptoms and the complicated nature of an ACT regime.

Spinou et al. (2024) reported 34% of the EMBARC using two modalities and 29% using more than three. Our findings in the UK data are much lower than this at 24% using ACBT and OPEP. Although these are not directly comparable as we did not identify other combinations in our data, there are a few considerations that could explain this discrepancy. Firstly, the different healthcare systems across Europe may

support the combined use of multiple modalities whereas the BTS stepwise approach (Hill et al., 2019) suggest titrating from one to the other. Secondly, the populations are different with the EMBARC data collecting data across the patient pathway whereas the Bronch-UK data is from specialist centres, where the access to respiratory physio may be different. This may change with current research underway to develop collaborative decision-making tools.

Comparison of Findings with Literature.

While most (70%) people in the Bronch-UK data said they performed ACT. Data reported by (McLeese et al., 2023) in Northern Ireland was 86%, Europe at different time points reported 53% (Spinou et al., 2024) and 48% (Spinou et al., 2020) whilst Australia 50% (A. L. Lee et al., 2021) and USA 59% (Basavaraj et al., 2020).

The most common ACT used individually was ACBT (53%) and OPEP alone (14%), with 24% using both. This compares to 28% in Europe, UK 42.9% (Spinou et al., 2024) and 64% in Northern Ireland (Spinou et al., 2024) and 64% in Australia (A. L. Lee et al., 2021). The European data demonstrates the variance across countries, with the UK-only data maybe indicating the likelihood of being taught ACBT if you attend a secondary care setting. OPEP usage was reported as 52% in Australia by (A. L. Lee et al., 2021). This is much higher than that found in this study; however, the results may be distorted as this study is from a single site-specific clinical practice. We are unable to compare OPEP directly to the European data; however, the total use of devices in the UK only data form Spinou et al. (2024) was 12.3%, again alluding to differences in the populations.

The link between severity and ACT use is well documented. Spinou et al. (2024) reported associations with higher mean BSI ($p<0.0001$), PsA ($p<0.0001$), 3+ exacerbations ($p<0.0001$) and all domains of QoL-B except Physical and Emotional. This is similar to the findings in the current study; however, they did not report effect size or attempt to create models to predict the use of ACT.

Discuss and Challenge the Results of Others.

Spinou et al. (2024), McLeese et al. (2023), and the current study reports different results on the usage of ACT, analysing different subsets of the same data. EMBARC data includes the Bronch-UK data, and the data used by McLeese et al. (2023) was a smaller individual nation subset of the Bronch-UK data. Each study provides a unique and interesting data analysis, and the reader should consider the different contexts of each data set. EMBARC provides data from across the European continent and includes data collected from primary and secondary care from many different health systems. Bronch-UK, as previously described, is data from 15 secondary care centres across the nations of the UK (DeSoyza et al., 2021). McLeese et al. (2023) separates the data collected from EMBARC and Bronch-UK in Northern Ireland.

The different data sets provide a picture of the different settings and reporting rates of use of ACT, which further explore the associations. Both recognise the role that severity plays in the use of ACT, with Spinou et al. (2024) focusing on the geographic differences and McLeese et al. (2023) exploring the possibility of linking data sets with questionnaires. The current study presents UK secondary care data and further explores the associations. Conversely, the data used by (Basavaraj et al., 2020) in the USA and A. L. Lee et al. (2021) in Australia are separate data sets from different healthcare systems.

Clinical Importance

Airways clearance is a crucial component recommended in consensus guidelines for managing bronchiectasis (Chalmers et al., 2018; Herrero-Cortina et al., 2023; Ramsey et al., 2020). However, performing ACT can be challenging and is often integrated into a complex and burdensome treatment regime for patients. It is, therefore, important that clinicians understand the drivers and influences different clinical factors, including disease severity and QoL, could have on the use of these non-pharmacological treatments.

Previous studies have shown that use of ACT in bronchiectasis can improve clinical symptoms and QoL (Murray et al., 2009). Describing the associations between BSI, QoL, and additional clinical factors on the use of ACTs could lead to improved

educational material or targeted adherence interventions for people with bronchiectasis to allow an informed choice of which ACT may be best suited to them (McCullough, Ryan, et al., 2015).

Our study found that using multiple ACT simultaneously is common in bronchiectasis. This could support the move from the current guideline “Stepwise” model and align with a shared decision-making approach for treatments where a lack of empirical evidence for one superior treatment can put the healthcare professionals (HCP) in clinical equipoise regarding what to prescribe (Alderwick & Dixon, 2019; DeSoyza et al., 2022). Evidence shows shared decision-making improves adherence to treatment and outcomes in asthma (Wilson et al., 2010) and could be used to support patient adherence to ACTs in bronchiectasis.

As described in the sections above the variance in data reported across the research from different healthcare systems and populations gives an opportunity to understand the drivers in different healthcare systems. As this was the first presentation of this data in the UK it sets a baseline for us to measure future data against. This will be useful as we measure the changes in ACT delivery and the implementation of guidelines, decision making tools and policy that will shape the future delivery of ACT.

Strengths and Weaknesses of Study

A limitation of the data is that ACT is self-reported and could be influenced by selection, recall and reporting bias.

A significant proportion of patients (n = 480 or 30%) who say they do not perform “regular” ACTs may actually perform ACTs when they are symptomatic or in “irregular” patterns, which may still influence their clinical outcomes. Additionally, this data only represents baseline data captured on initial patient visits. These patients may have been reviewed by a respiratory physiotherapist afterwards, which may have altered our findings.

The statistical approach this study can be considered in two parts with descriptive methods used to achieve aim one and a model building approach to achieve aim two. Use of the model building approach was chosen to try and identify a set of

characteristics that could identify a subgroup within the data. We were able to reject the null hypothesis. However, there are limitations in this approach as building models requires statistical skill, clinical judgment and data with limited overlap and confounding factors. Due to the high overlap and confounding factors in the data our findings should be treated with caution. The search for ways to identify these cohorts has led to the development of tools like the BSI, an alternative approach would have been to rely on this however this was not possible due to the lack of radiological data in the data set.

The findings of the Bronch-UK data support the choice to not exclude people with a comorbidity of bronchiectasis from TIPTOP. 16% of the cohort also reported comorbid COPD and although a disease specific cohort for RCT's makes for greater rigor in research design it does not represent real world conditions. Excluding this cohort would have lowered our pool of patients, to approach. Also, in clinical practice it's recognised that an even larger subset of patients with COPD and sputum retention may have undiagnosed bronchiectasis.

Way Forward

True to clinical practice, patients' self-reported adherence to ACTs and their fidelity to following techniques appropriately would benefit from objective validation. Electronic OPEP devices (the Connected-Aerobika) would provide daily usage of patterns, and even ACBT could be objectively recorded, e.g. with sound recording uploads or chest movement detectors.

The nature of the Bronch-UK data allowed us to report the rates of use of ACT at that moment in their clinical journey. Things are likely to change over time as disease states change, new evidence and guidelines accrue, or clinical services develop (e.g., PsA eradication, bronchiectasis networks, etc.). As we worked toward publication of this data it was agreed by the working group that further data would be needed to create a clearer picture prior to submission to a journal. Bronch-UK continues to collect follow up data and analysis of this will allow a richer description of patient journeys and also allow any anomalies in data collection and entry to be accounted for. Another possible novel collaboration of this further analysis could be

the use of the rich primary care data that is available in Wales through the SAIL database. This would add a valuable insight into the earlier stages of the bronchiectasis patient journey.

Observational studies are not able to provide causality; they only provide associations. A better understanding from interventional trials (preferably large RCTs) would better inform the choice, duration and regularity of ACTs; Larger studies can also inform a personalised approach with individualised management plans and care packages based on treatable traits and clinical phenotypes as opposed to generic statements. As symptoms and disease severity increase, patients appear to engage with some form of ACTs more- compared to those with fewer symptoms and lower disease severity.

What is unclear and requires further research is when airway clearance best serves a patient's individual need to move from "as needed" usage based on clinical symptoms or factors to regular usage. Identification of the most appropriate algorithm or decision-making tool to inform ACT prescription is required to support adherence to these essential disease management treatments.

The analysis presented in Chapter 2 provides contextual insights into the patterns and predictors of ACT use in routine clinical practice across the UK. Findings from the Bronch-UK dataset demonstrates that both ACBT and OPEP are widely prescribed, often concurrently, and that the choice of technique is not strongly influenced by demographic or clinical characteristics, with the exception of disease severity. These results highlighted the need for more robust evidence to guide technique selection, particularly in conditions like COPD where practice varies and the evidence base remains limited. Chapter 3 addresses this gap through the TIPTOP pilot randomised controlled trial, which compared ACBT and OPEP in patients hospitalised with acute exacerbations of COPD. The TIPTOP study is novel in its focus on real-world delivery during acute care and its inclusion of patient-reported outcomes beyond the acute phase. It represents an important step towards understanding the comparative impact of these commonly used techniques, and builds on the observational data in Chapter 2 by testing these approaches in a controlled yet clinically representative setting.

3 STUDY: EXPECTORATION OF SPUTUM TECHNIQUES REAL WORLD DATA IN COPD (TIPTOP)

“Don’t smoke. I did. Wish I never had. Live long and prosper”

(Leonard-Nimoy, 2015)

3.1 INTRODUCTION

Expectoration of sputum techniques real world data in COPD (TIPTOP): Is a pilot randomised control trial (RCT) study directly comparing two currently used standard treatments, ACBT versus OPEP. We recruited patients who were experiencing an AECOPD. The study aims to add to the body of literature and be the first to report findings in both Aerobika compared to ACBT in an acute cohort.

3.1.1 COPD Definition

COPD is a complex heterogenous lung condition characterised by symptoms of chronic cough, dyspnoea, sputum production and exacerbation. It is a persistent, often progressive, common, preventable, but treatable lung disease (GOLD, 2024a).

COPD occurs due to abnormalities of the airways and alveoli, causing airflow obstruction (Bartolome Celli et al., 2022; GOLD, 2024a). Interestingly, this definition was updated in the GOLD (2023) report due to an improved understanding of the causes and effects. A newly proposed taxonomy allows the diagnosis of different populations with earlier pathological changes (Agustí et al., 2022; Bartolome Celli et al., 2022; Stolz et al., 2022), see Figure 3.1 and Figure 3.2. Agustí et al. (2022) highlight that COPD could be considered a syndrome and may not have a single cause with cumulative gene-environment interactions over an individual lifetime leading to the clinical symptoms of COPD.

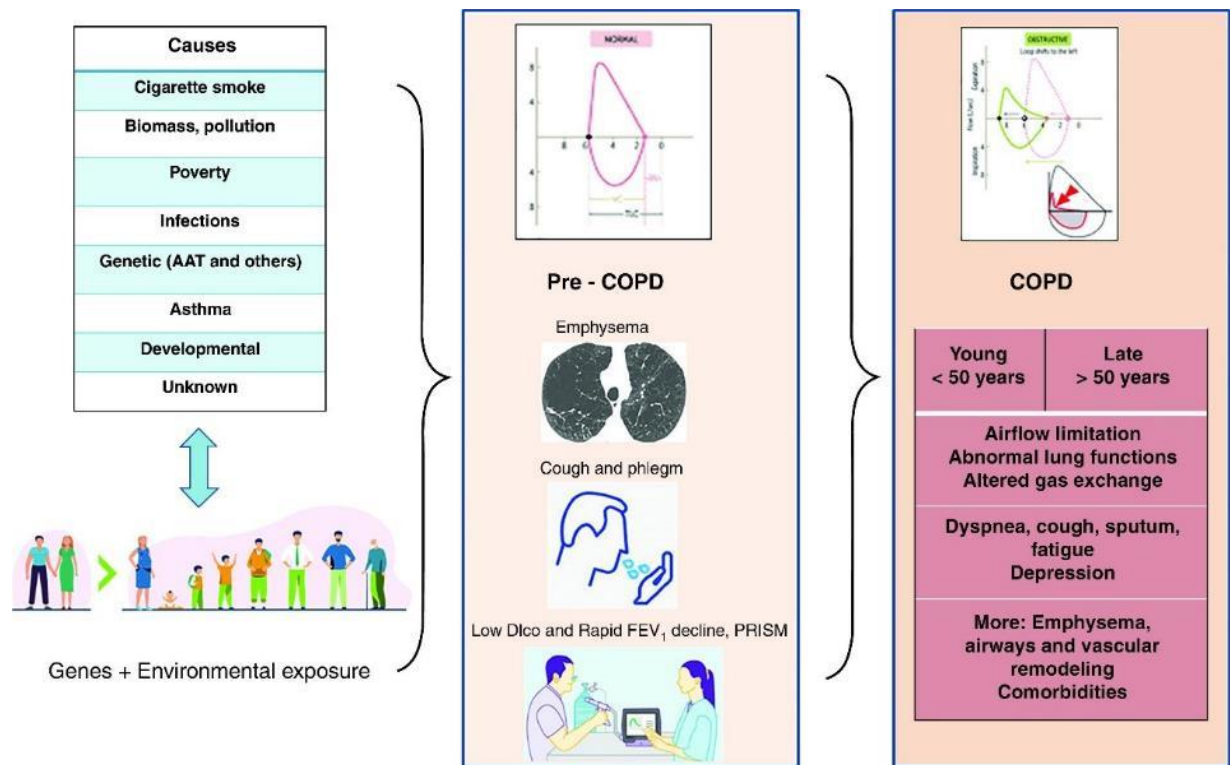


Figure 3.1 Causes and Progression of COPD

(Bartolome Celli et al., 2022).

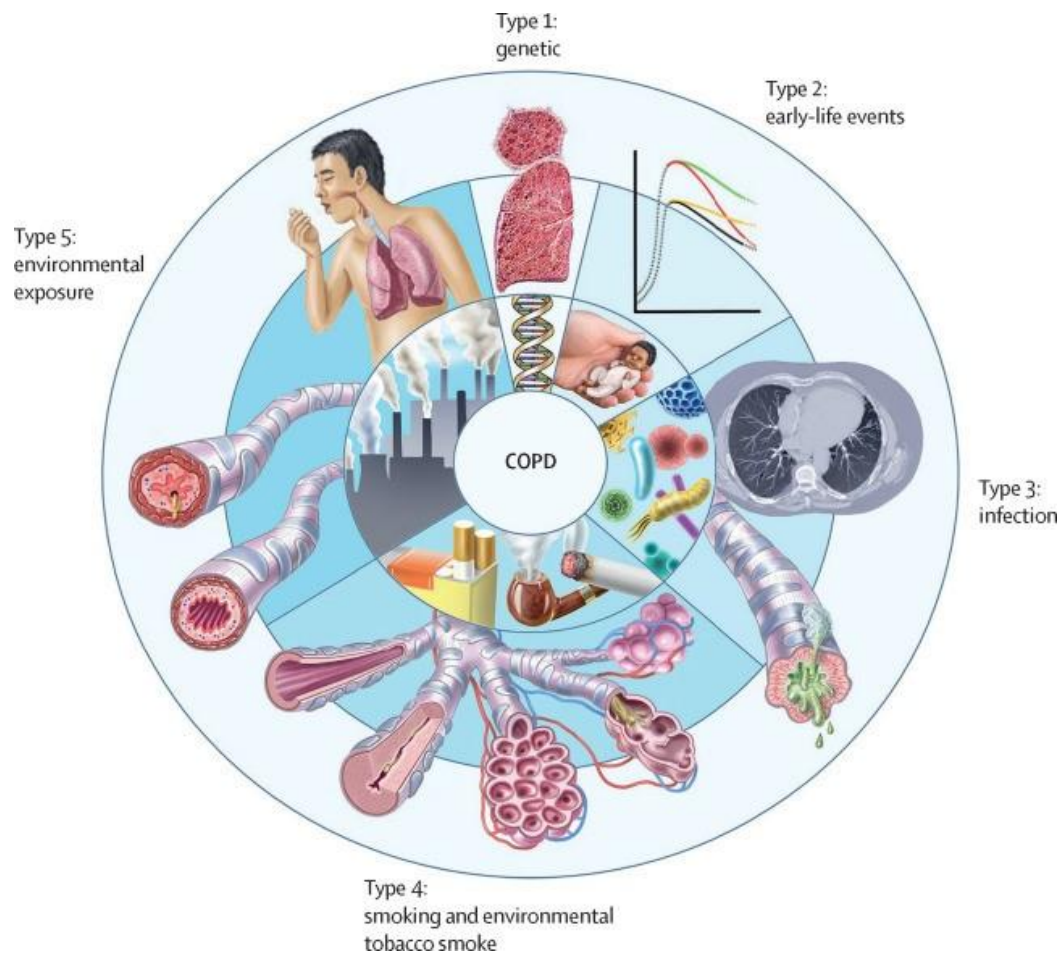


Figure 3.2 Classification of COPD according to risk factors.

(Stolz et al., 2022).

3.1.2 Incidence and prevalence

According to the World Health Organization (WHO), in 2020, approximately 384 million people worldwide were estimated to have COPD. The burden of COPD varies across different regions, as can be seen in Figure 3.3 by Blanco et al. (2019), the prevalence tends to be higher, primarily due to higher rates of smoking and exposure to indoor and outdoor air pollution (WHO, 2023).

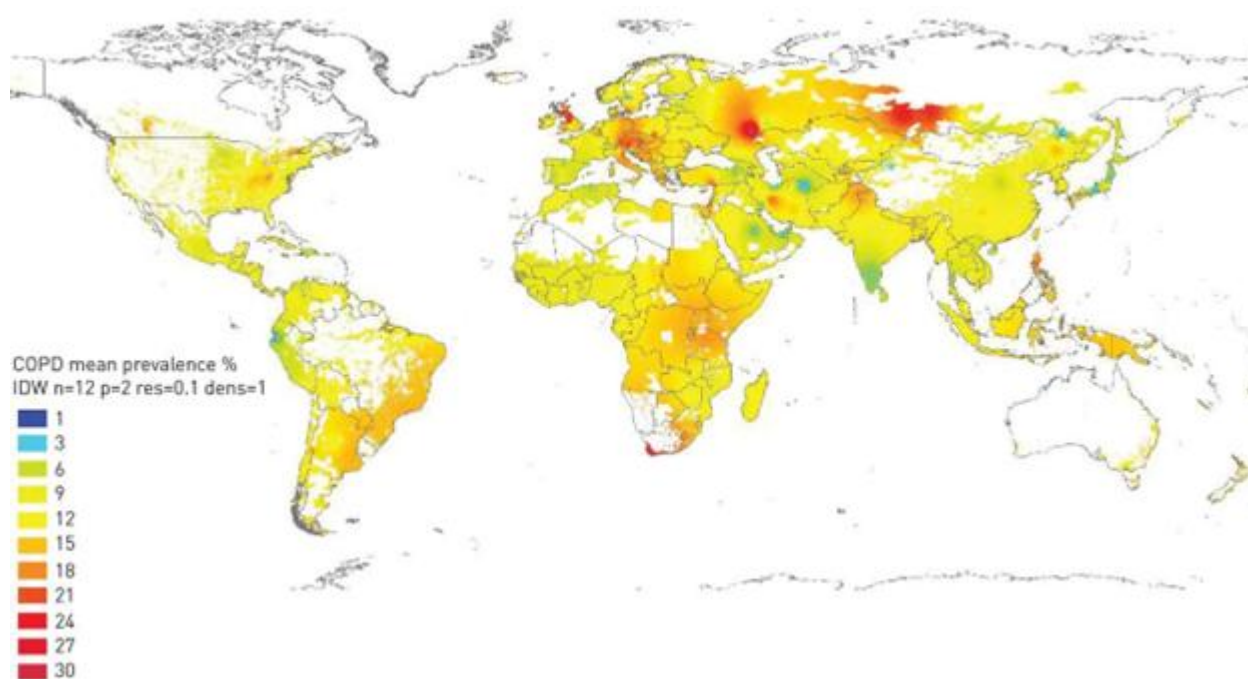


Figure 3.3 Inverse distance weighted (IDW) interpolation map of chronic obstructive pulmonary disease (COPD) prevalence in the world.

(Blanco et al., 2019).

COPD is a leading cause of morbidity and mortality globally and is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. Nearly 90% of COPD deaths in those under 70 years of age occur in low- and middle-income countries (WHO, 2023).

It is estimated that 1.2 million people in the UK have a diagnosis of COPD. This has increased by 27% in the last 10 years. In 2012 roughly 10% more males than females were diagnosed with COPD in the UK (BLF, 2023). In the UK, COPD is more common in areas of heavy industry and higher socioeconomic deprivation (Williams et al., 2022). Figure 3.4 shows the variation in percentages of patients with COPD on general practitioners (GP) registers by clinical commissioning groups (CCG) (Public-Health-England, 2018).

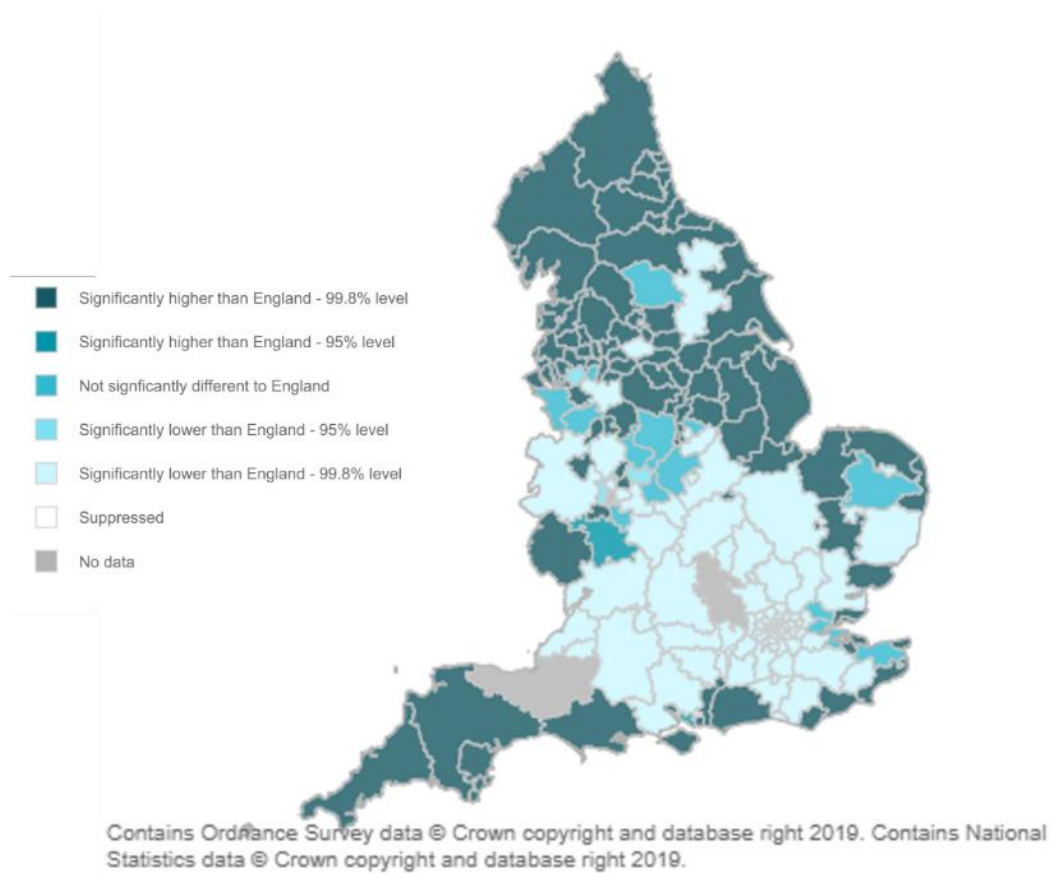


Figure 3.4 2nd Atlas of variation for respiratory disease in England, map 7c variation in COPD.
(Public-Health-England, 2018)

Rates of hospital admissions were higher in Wales than in the other nations of the UK and death rates were also higher (BLF, 2023). Those living in the most disadvantaged areas of Wales are five times more likely to die from COPD with the direct cost of treating asthma and COPD to the National Health Service (NHS) in Wales estimated at £290 million (Asthma-Lung-UK, 2024). Lung conditions including COPD have the biggest impact in urban areas across Wales with the most deprived health boards having higher admissions and death rates, as can be seen Figure 3.5. A lower ranking means more admissions/deaths.

Health Board ranking

Based on respiratory admission + death rates

- Top 2
- Middle 3
- Bottom 2

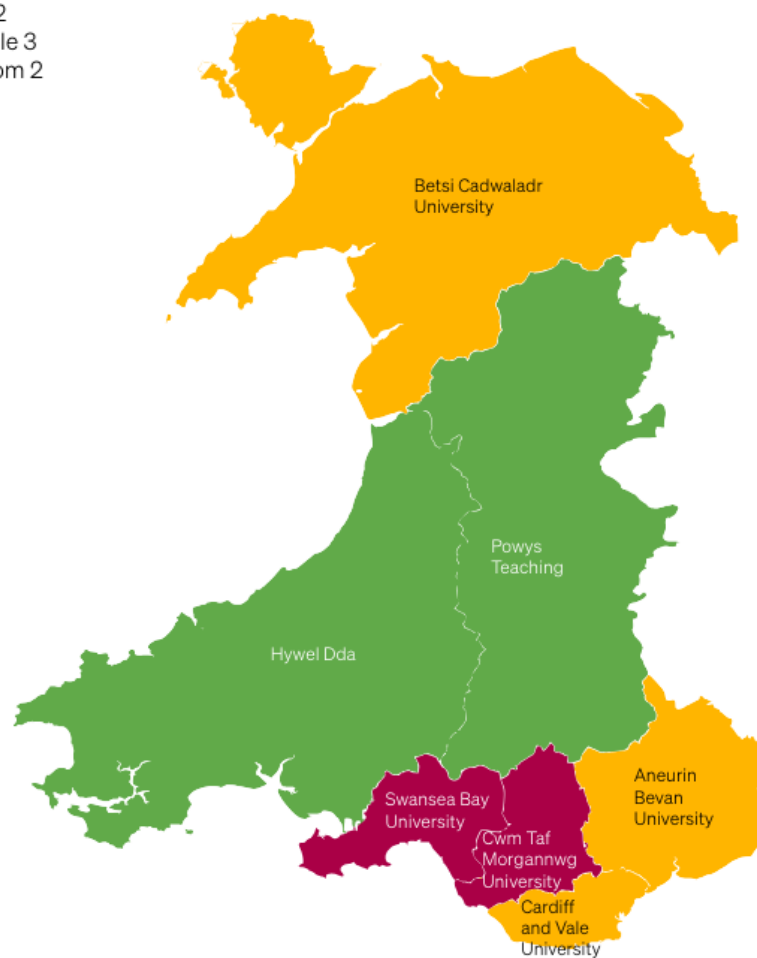


Figure 3.5 Respiratory admissions and death rates, Wales 2020/21
(Asthma-Lung-UK, 2024)

3.2 COPD AETIOLOGY

The previously mentioned taxonomy of COPD outlined by (B. Celli et al., 2022; Stolz et al., 2022) has been presented in (GOLD, 2024a) outlining the categorisation of the aetiology of COPD. The following section is split into subheadings that follow the taxonomy in Figure 3.6.

Proposed Taxonomy (Etiotypes) for COPD	
Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including <i>in utero</i> or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Figure 3.6 Taxonomy of COPD.
(GOLD, 2024b)

Genetically determined COPD (COPD-G)

Genetically determined COPD is a complex interplay of genetic factors and environmental factors (Avci et al., 2022; Li et al., 2017). Alpha-1 antitrypsin deficiency (AATD) is an autosomal, co-dominant inherited condition, 1 in 3000 in the UK (Blanco et al., 2017). The deficiency or dysfunction of the alpha-1 antitrypsin results in lung tissue damage and emphysema. AATD can lead to early-onset COPD (Toumpanakis & Usmani, 2023). DNA methylation is commonly linked to gene repression that regulates critical pathways in COPD (Adcock et al., 2011; Machin et al., 2017).

COPD due to abnormal lung development (COPD-D)

Prematurity and the later development of COPD have been established (Bose et al., 2023). Prematurity, particularly when coupled with poor in-utero growth, maternal smoking, nutritional depletion and low birth weight, is linked with impaired lung growth, reduced alveolar development, impaired immune defence and small airways relative to lung sizes (Bose et al., 2023; Smith et al., 2018).

Biomass and pollution exposure COPD (COPD-P)

Prolonged exposure to biomass fuel smoke, such as wood, animal dung, and crop residues used for cooking and heating in poorly ventilated conditions, is a significant cause of COPD-P in lower-income populations such as those in Africa. (Pathak et al., 2020).

Chronic exposure to outdoor air pollutants, such as particulate matter (PM), sulphur dioxide (SO₂), nitrogen oxides (NO_x), and ozone (O₃), contribute to the development and exacerbations of COPD (Squillacioti et al., 2024). Urbanisation and industrial activities have led to increased exposure to these pollutants, particularly in developing and densely populated regions (Landrigan et al., 2018). Raising awareness about the health risks of pollution is vital in addressing COPD-P (Feng et al., 2024).

Cigarette smoking COPD (COPD-C)

COPD-C from chronic exposure to cigarette smoke, which contains noxious particles and gases (Borgerding & Klus, 2005), is the leading cause of COPD, accounting for

approximately 80% of cases in the UK (NICE, 2018). This compares to 70% of cases in high-income countries and 30-40% in low, and middle-income countries (GBD Collaborators et al., 2015).

Passive exposure to second-hand smoke or exposure to other tobacco products is now linked to COPD (Diver et al., 2018). There are concerns about the use of electronic cigarettes with links being drawn between electronic cigarettes and lung injury (Osei et al., 2020; Park et al., 2022; J. B. Wang et al., 2018).

Environmental COPD (COPD-E)

COPD-E is caused by environmental factors other than cigarette smoke. These include air pollutants (both indoor and outdoor), occupational dusts, chemicals, and biomass smoke (KC et al., 2018). Estimates suggest that COPD due to occupational dust may make up 14% of the population (Murgia & Gambelunghe, 2022).

Exposures to specific inorganic dusts have been associated with COPD (Rodrigues et al., 2021). Recognised occupational exposures include silica, asbestos, and coal (Hoy & Chambers, 2020; Laney & Weissman, 2014; Sen, 2014). Organic dust from grains, mould, animal dander, flour dust, wood dust and textile dust (Peng et al., 2020)., welding fumes, from stainless steel and other metals, can contribute to the development of respiratory conditions (Riccelli et al., 2020).

COPD due to infections (COPD-I)

Repeated respiratory infections, particularly during childhood, can cause lung damage and increase the risk of developing COPD later in life. Infections like pneumonia and bronchitis can lead to chronic inflammation and scarring of the airways (Sethi, 2010).

COPD and Asthma (COPD-A)

Poorly controlled asthma can contribute to the development of COPD (GOLD, 2024a). Adults with asthma are twelve times more likely to develop COPD (Agustí et al., 2023). However, similarities in the spirometry patterns of COPD and asthma make a differential diagnosis difficult in childhood and adolescence. This is further complicated by the recognition of COPD-D (Agustí & Hogg, 2019).

3.3 PATHOPHYSIOLOGICAL PROCESS

COPD pathophysiological mechanisms result in persistent and irreversible lung damage (Rovina et al., 2013). Inflammatory reactions in the airways and lung parenchyma lead to small airway fibrosis and airway remodelling. Inflammation is a key driver of the COPD disease process, drawing macrophages, neutrophils and lymphocytes into the lungs (Comer et al., 2013; Kanazawa et al., 2012), see Figure 3.7.

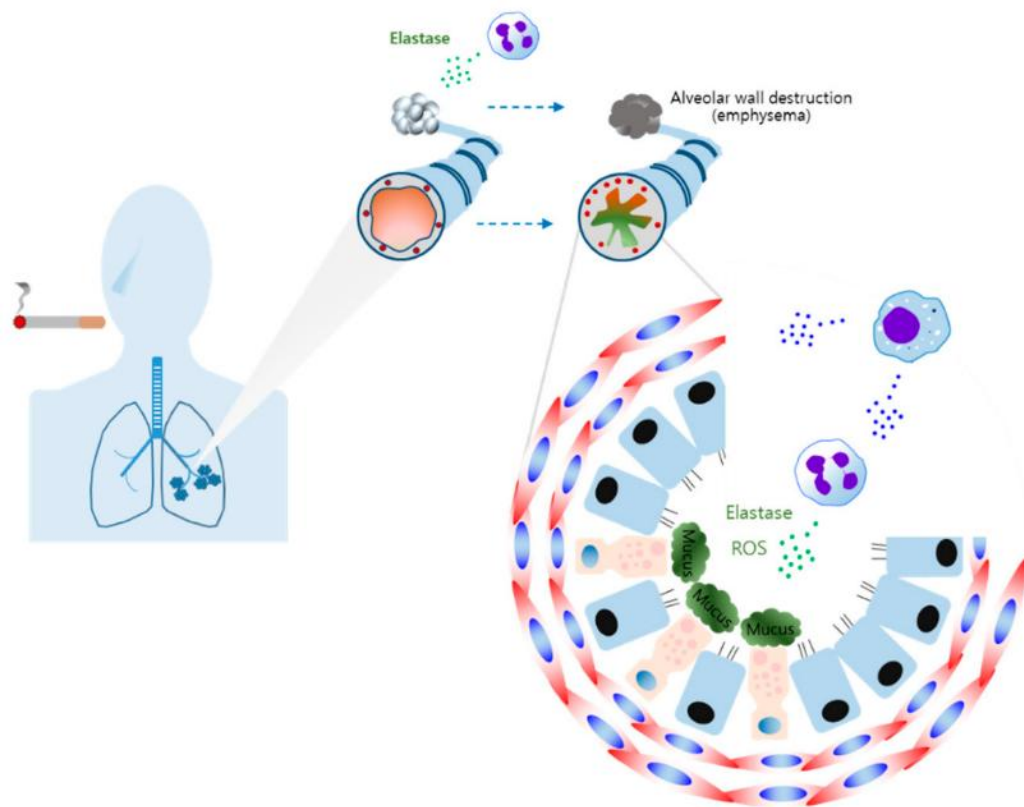


Figure 3.7 Monocyte and neutrophil recruitment in the pathogenesis of COPD.

(J.-W. Lee et al., 2021)

Higher numbers of neutrophils correlate with disease severity (Rovina et al., 2013) with neutrophils secreting proteases, including neutrophil elastase and proteinase-3, that contribute to alveolar destruction and enhanced mucus production (Barnes et al., 2003). Activated macrophages release inflammatory mediators involved in inflammation in COPD (J.-W. Lee et al., 2021; Yamasaki & Eeden, 2018). Alveolar macrophages secrete enzymes promoting neutrophil recruitment and fibrotic remodelling. Inflammatory proteins increase in activity during exacerbations (Y. Wang et al., 2018).

All these cellular processes release reactive oxygen species (ROS), contributing to oxidative stress and driving pathology in COPD (Barnes, 2022). Cellular processes, including leaky mitochondrial respiration and inflammatory responses to viruses and bacteria, release ROS (Barnes, 2009; Cloonan et al., 2020). ROS has also been linked with increasing resistance to corticosteroids, accelerating lung ageing, and promoting an autoimmune response (Barnes, 2022), see Figure 3.8.

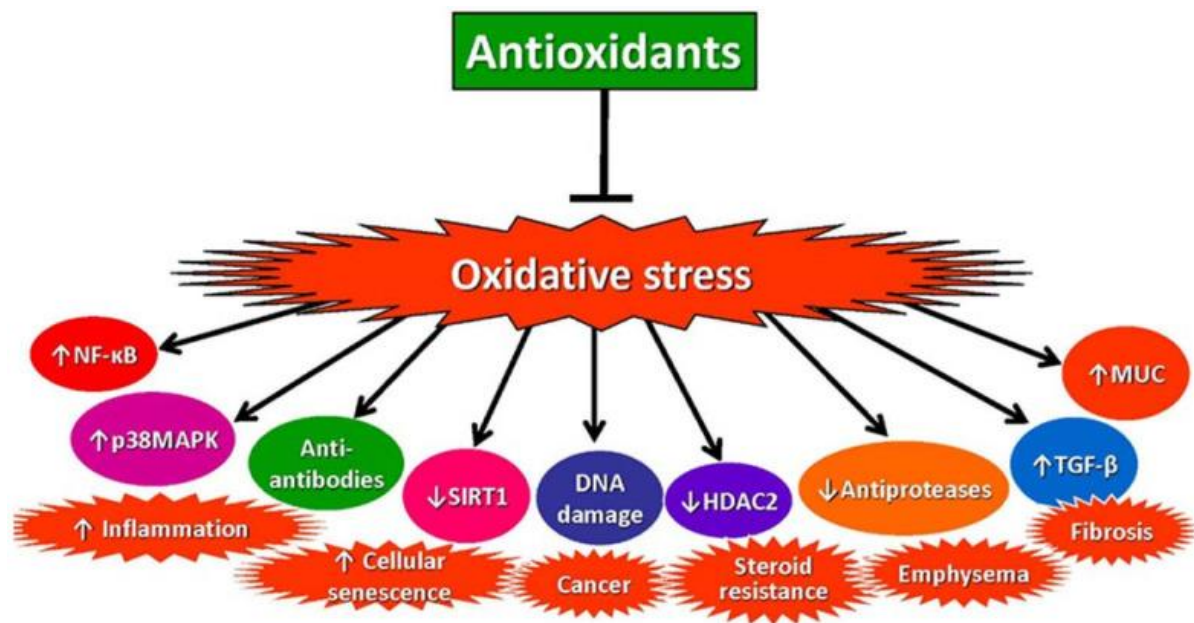


Figure 3.8 Increased oxidative stress drives the pathology of COPD through several mechanisms.

(Barnes, 2022)

Oxidative stress affects mucociliary clearance as the presence of ROS by stimulating mucus secretion through the expression of mucin MUC5AC, a contributing factor in COPD airway narrowing (Cazzola & Molimard, 2010). In particular, smoking has been shown to dysregulate CFTR function, resulting in poor mucociliary clearance and altering the rheology of sputum (Raju et al., 2016).

It has been proposed that the rheology of sputum in COPD contributes to the clinical manifestation of the condition (Nettle et al., 2018). Chisholm et al. (2019) discovered that a tighter mesh observed in COPD sputum was associated with disease severity and lung function. The investigation also noted a reduced rate of bacterial motility, indicating that this might increase the risk of exacerbations.

Increased viscoelasticity makes secretions difficult to clear (McIlwaine et al., 2017) and may account for the widespread mucus plugging seen in some patients with severe COPD (Diaz et al., 2023; Nettle et al., 2018; Yuan et al., 2015).

3.4 DIAGNOSIS

COPD should be considered in people over 35 years presenting with symptoms such as breathlessness, chronic cough, frequent sputum production and recurrent chest infections, with identified risk factors (NICE, 2023; Pleasants et al., 2016). The GOLD (2024a) criteria are central to the clinical diagnosis and management of COPD and recommend a comprehensive approach that includes assessment of symptoms using tools like the CAT or mMRC questionnaire, risk evaluation of exacerbations, and spirometry to confirm airflow obstruction (see Figure 3.9) in the presence of non-fully reversible airflow limitation measured by spirometry.

Spirometry quantitatively assesses lung function by measuring the volume and speed of air exhaled. The FEV₁ and FVC are vital metrics, with the FEV₁/FVC ratio serving as a key diagnostic criterion. A ratio below 0.70 post-bronchodilator administration confirms airflow obstruction, indicative of COPD (Hoesterey et al., 2019), however, repeated measures have been found to be more accurate than one-off assessments (Andreeva et al., 2017). Spirometry not only facilitates early diagnosis but also allows for the staging of disease severity, as can be seen in Table 3.1 adapted from (GOLD, 2023).

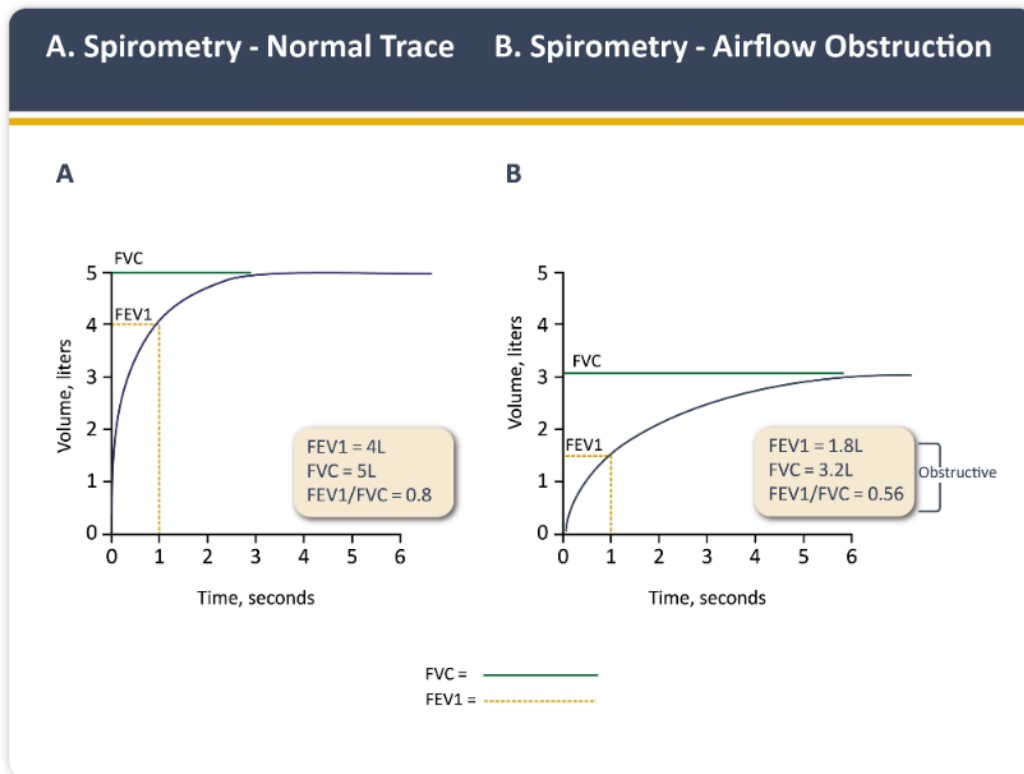


Figure 3.9 Airflow Obstruction spirometry trace.

(GOLD, 2024b)

Table 3.1 Post bronchodilator spirometry grades of severity.

	Severity of Disease	In COPD (FEV ₁ /FVC <0.7)
GOLD 1	Mild	FEV ₁ ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV ₁ <80% predicted
GOLD 3	Severe	30% ≤ FEV ₁ <50% predicted
GOLD 4	Very Severe	FEV ₁ <30% predicted

However, the availability of this resource has proven to be patchy at best with an audit run by the Royal College of Physicians reported 60% of patients did not have a recorded spirometry prior to hospitalisation with an exacerbation of COPD (Johns et al., 2014; Wise, 2019). Delivery of spirometry was made worse by the COVID-19 pandemic and services have been rebuilding since (Doe et al., 2023). The NHS (England) long-term plan (Alderwick & Dixon, 2019) prioritised the improvement of spirometry.

Understanding the symptoms that make up the lived experience of patients is also important giving an insight into the level of burden presented by symptoms and be used to target treatments and measure success. Identification of phenotype is useful to guide clinical management (Miravittles & Ribera, 2017). Differential diagnosis should also be considered as comorbidities can mimic and/or aggravate an acute exacerbation and time should be taken to consider the possibility of them as a differential diagnosis, see Figure 3.10, (Celli et al., 2023).

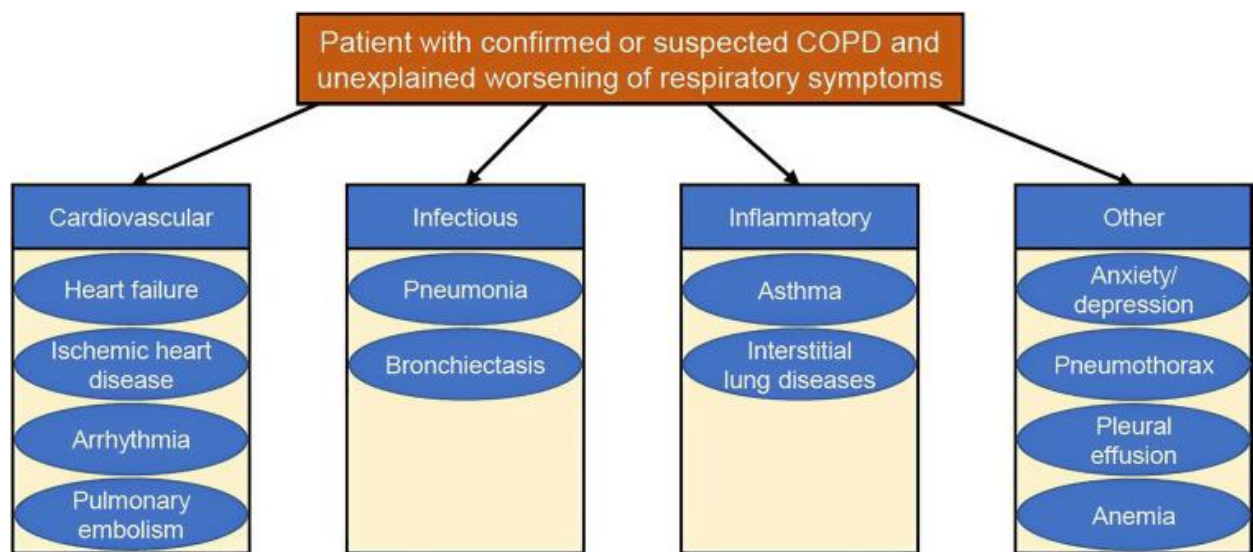


Figure 3.10 Differential diagnosis that may mimic or contribute to an exacerbation of COPD.

(Celli et al., 2023).

3.5 PHENOTYPES

COPD can be defined by clinical phenotypes or characteristics that allow the grouping of patients based on observable characteristics, including symptoms and disease manifestations. Phenotypes include chronic bronchitis (CB), emphysema, and frequent exacerbators. It should be recognised that phenotypes are not exclusive and may overlap leading to the complex spectrum of COPD (Nikolaou et al., 2020).

Patients with a CB phenotype have worse health status and a worse CAT score, experience more frequent exacerbations, receive more pharmacological treatment and have higher mortality than other phenotypes (Cosio et al., 2016). CB is characterized by inflammation and irritation of the bronchial airways, resulting in increased mucus production and a chronic cough. Mucus plugs have been shown to cause a significant increase in risk of mortality in COPD (Mettler. et al., 2024).

A proposed definition of CB is cough and sputum production for at least three - months per year for three consecutive years, in the absence of another cause that can explain it (Bartolome Celli et al., 2022). The prevalence of CB in COPD patients is estimated to be 27% to 35%, with males, younger age, higher pack-years of smoking, severe airflow obstruction, and increased occupational exposures showing higher rates (Agustí et al., 2023).

Research into the treatment of CB is ongoing, focusing on smoking cessation, long-acting muscarinic antagonists (LAMA), oral mucolytics, antioxidants and ACT including OPEP therapy (GOLD, 2023). This study is limited to patients with CB for this reason.

Emphysema, on the other hand, involves the destruction of alveoli, leading to decreased lung elasticity and impaired gas exchange. The process of abnormal permanent dilation of airspaces through activated macrophages releasing inflammatory mediators, as previously described (Y. Wang et al., 2018).

Individuals with emphysema often present with dyspnoea, wheeze, reduced exercise tolerance and impaired FEV₁ (Yousuf et al., 2021). Many patients have features of CB and emphysema. Chronic mucous hypersecretion is a part of the CB phenotype, and we feel this trait is more relevant for ACT, hence the focus of this study.

Frequent exacerbator phenotype in COPD is characterised by individuals experiencing two or more exacerbations per year and is recognised as leading to poor clinical outcomes. Wedzicha et al. (2013) described this group as having higher inflammatory markers, greater susceptibility to viral infections, more comorbidities and increased cardiovascular risk. QoL measured using CAT in this group (>2 exacerbations) was 19.5 compared to 16.8 with <2 exacerbations (Mackay et al., 2012). Le Rouzic et al. (2018) found that this group experienced a faster decline in FEV₁, QoL, functional status and increased mortality risk. Blood markers, including neutrophils and eosinophils (>300 cells/ μ l), have been shown by (Wu et al., 2021; Zhang et al., 2023) to be independent risk factors for frequent exacerbators, see Figure 3.11 that shows a comparison of Kaplan–Meier curves for time to readmissions within one year of discharge comparing FEV₁ and eosinophil count. The graphs shows that the lower the chance of readmission, the higher your FEV₁ and the lower your eosinophil count. COPD overlap phenotype describes patients who exhibit characteristics of both COPD and asthma. Hosseini et al. (2019) estimated that 30% of people with COPD and 27% of people with asthma could be characterised as asthma-COPD overlap (ACO).

The pathophysiologic processes of asthma and COPD both result in airway remodelling. Asthma involves the infiltration and increased activity of eosinophils and mast cells prior to airway remodelling. Whereas COPD involves neutrophils and macrophages in small airway remodelling and fibrosis (Dey et al., 2022).

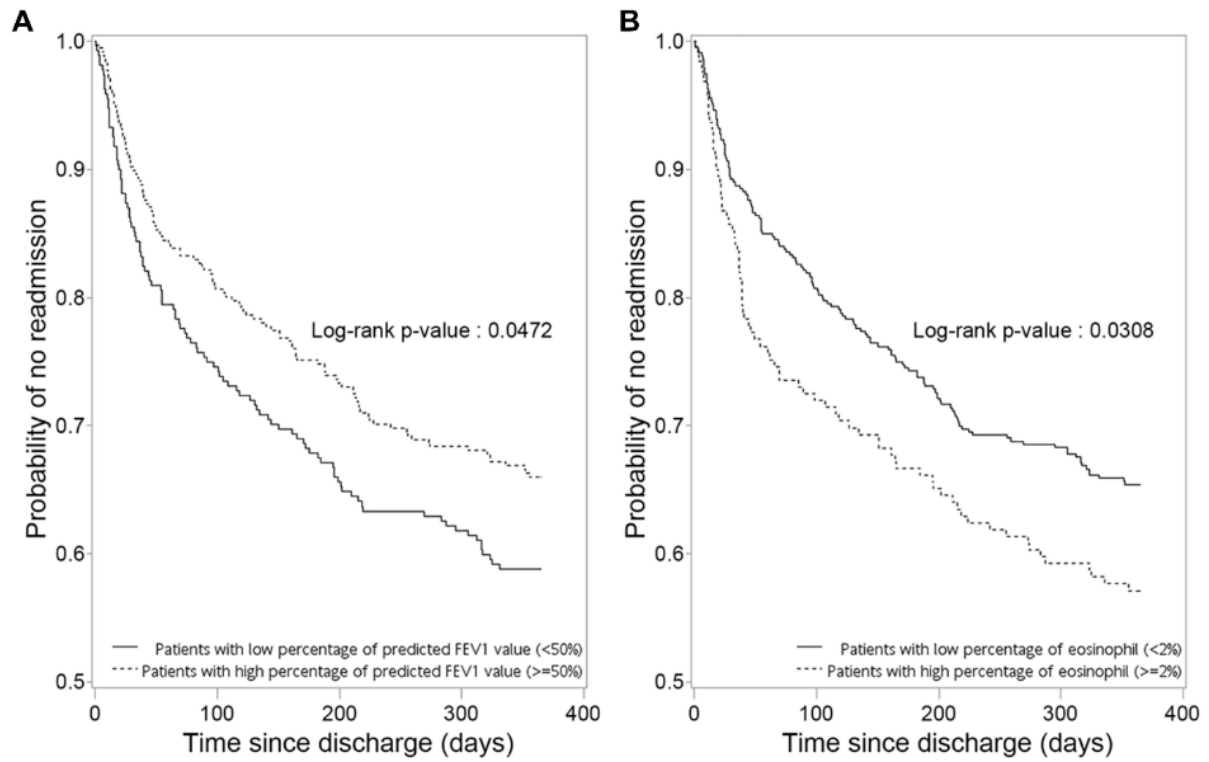


Figure 3.11 Increased probability of no readmission against FEV1 and eosinophil.

(Wu et al., 2021)

3.6 EXACERBATIONS

Exacerbations are acute periods of worsening symptoms above normal day-to-day variation, leading to increased treatment and often emergency hospital admissions placing a significant burden on the health care system and are associated with a worse QoL and poorer long-term prognosis (Celli et al., 2023). COPD causes over 30,000 deaths in the UK annually and is the second highest cause of hospital admission (NICE, 2018). Figure 3.12 shows the causes and resulting pathobiology of AECOPD which leads to acute inflammation and a host pathophysiological change.

Diaz et al. (2023) identified people from a genetic epidemiology database of COPD enrolling them to receive a CT scan (n=4363). The results showed the presence of mucus plugging in the medium to large airways (2-10mm) in >0 segments in 41% of participants, with the greater the number of segments affected the higher the rate of mortality over the 9.5-year follow-up period. Those with >3 lobes obstructed had an adjusted hazard ratio of death of 1.24 (95%CI, 1.10-1.41) (Diaz et al., 2023).

Ouaalaya et al. (2020), in a retrospective and prospective cohort study of 932 people with COPD, found that frequent exacerbator phenotype (>2 a year) were more likely to have chronic sputum ($p<0.00001$). A multivariate analysis of the prospective cohort showed an odds ratio of 1.6 (95%CI 1.07-2.39). This was mirrored in the three-year follow-up, also making it into the top four factors associated (presence or absence) with frequent exacerbations alongside anxiety, LABA, and influenza vaccination. Therefore, therapies that target chronic sputum, such as ACT, may influence exacerbation rates and, consequently mortality (Fortis et al., 2022).

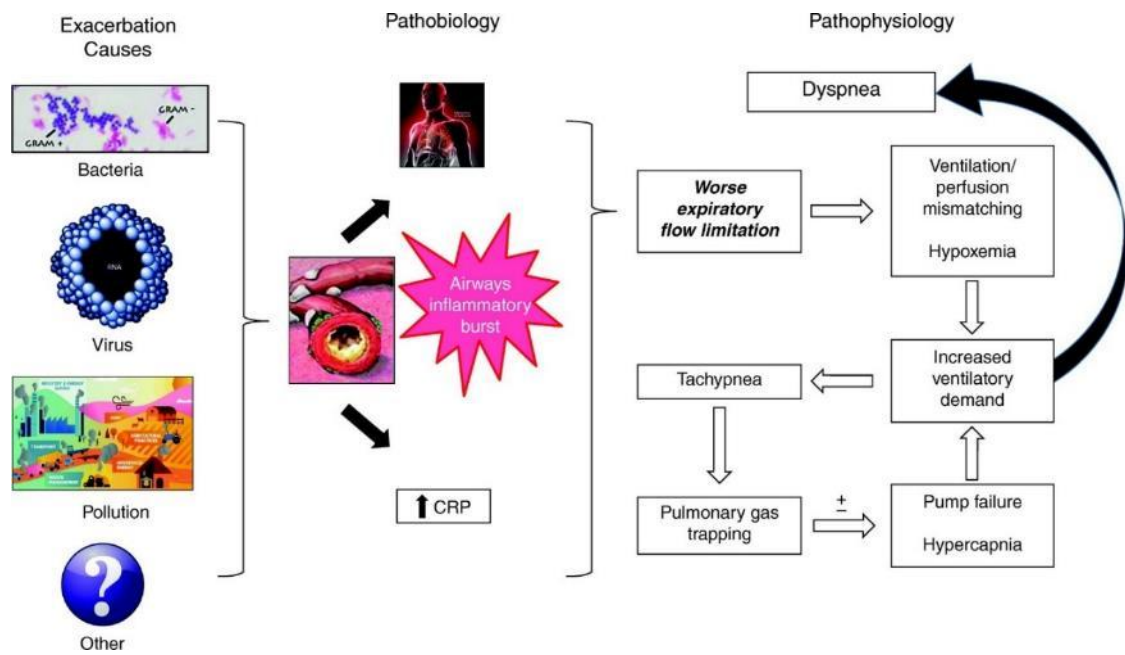


Figure 3.12 Causes, Pathology and Physiology of Exacerbations in COPD.

(Celli et al., 2021)

GOLD (2023) in recognition of the need to recognise the importance of exacerbation in the clinical journey of COPD has updated the ABCD assessment tool to ABE combining C and D as can be seen in Figure 3.13.

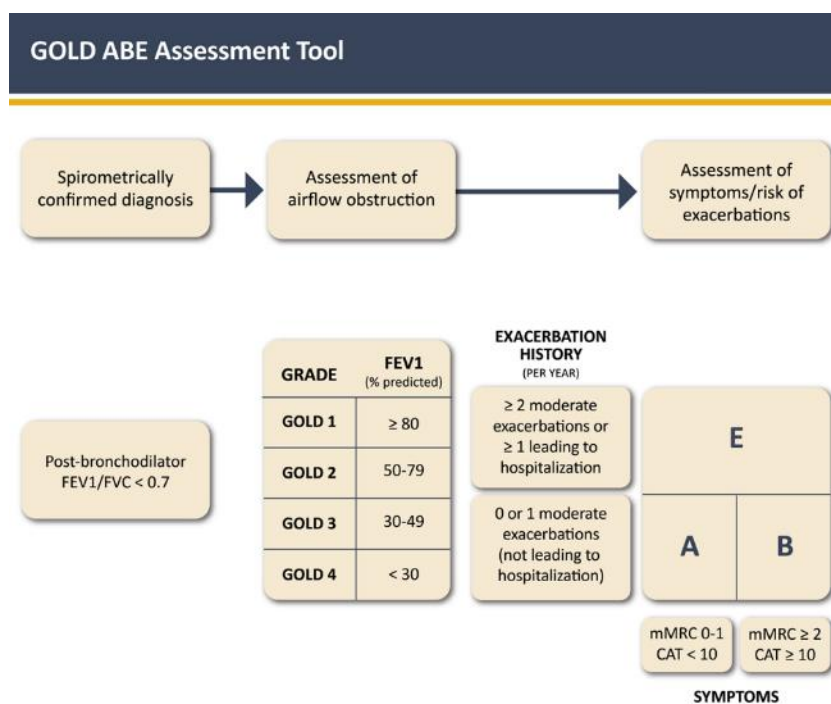


Figure 3.13 ABE assessment tool for exacerbations.
(GOLD, 2024b)

3.7 PHARMACOLOGICAL TREATMENTS

Pharmacological treatments are critical in managing COPD as they help to relieve symptoms, prevent and control exacerbations, improve health status, and increase exercise tolerance. Medications, including bronchodilators and corticosteroids, target the airway inflammation and obstruction characteristic of COPD and are tailored to the individual. Figure 3.14 outlines the initial pharmacological treatment in the GOLD (2023) guidelines.

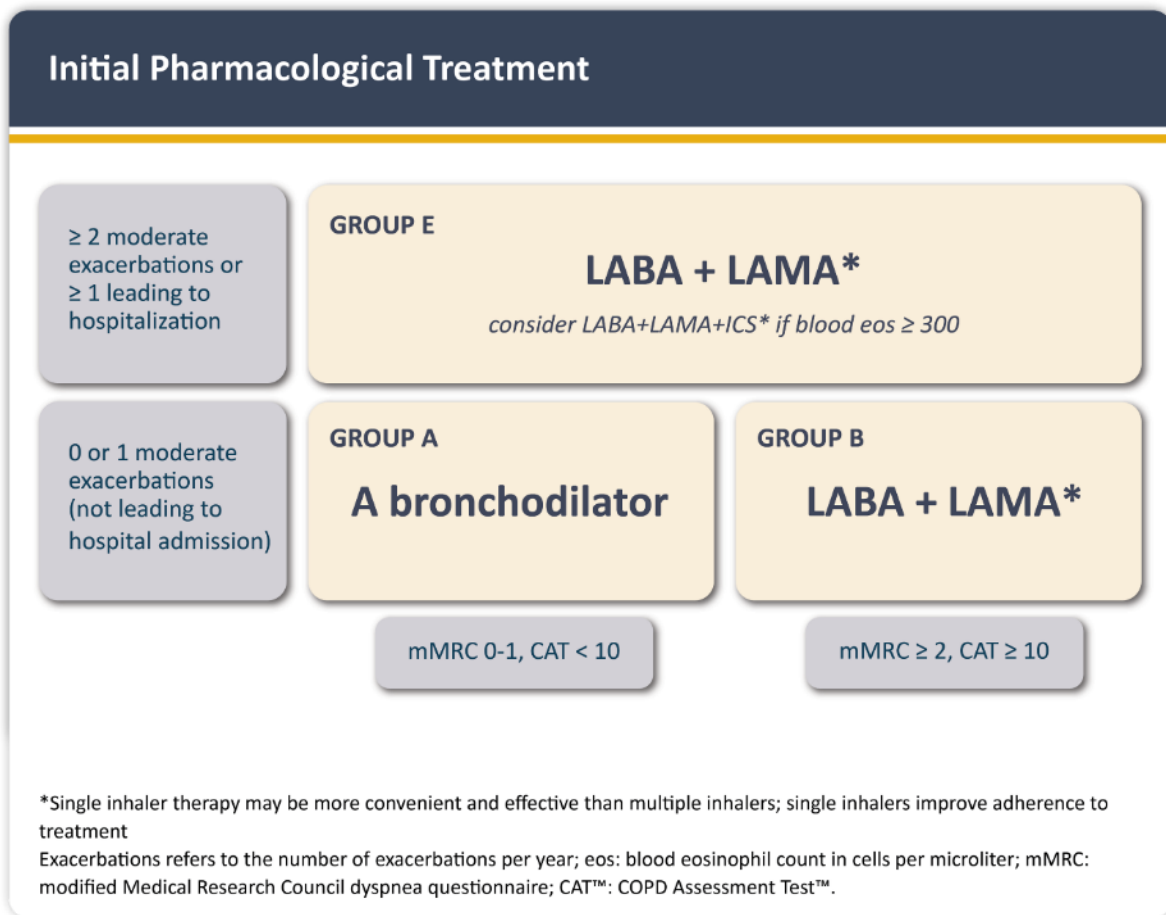


Figure 3.14 Initial Pharmacological Treatments.

(GOLD, 2024b)

Bronchodilators in COPD (SABA/LABA)

Bronchodilators are used to manage acute exacerbations and can be broken down into two subgroups: beta₂-agonists and antimuscarinics. They can be short-acting (SABA), requiring frequent use, or long-acting (LABA), taken as part of a daily routine, with long-acting formulas shown as superior (Cazzola et al., 1994; Vincken et al., 2002). Smooth muscle in the airways is affected, resulting in improvements in FEV₁ and FVC and a reduction in dynamic hyperinflation, leading to an increase in exercise tolerance and a reduction in breathlessness. Beta-agonist receptors can be found in many organs of the body, as shown in Figure 3.15

Beta₂ receptors are located on the airway smooth muscle cell wall, and the presence of the beta-agonist starts a cascade of events (Cazzola & Molimard, 2010). Beta-agonists have additional benefits in the airway, including preventing the release of mast cell mediators, affecting inflammation, reducing microvascular leakage linked to airway oedema, and increasing mucus secretion, allowing the clearance of pathogens (Barnes, 1994).

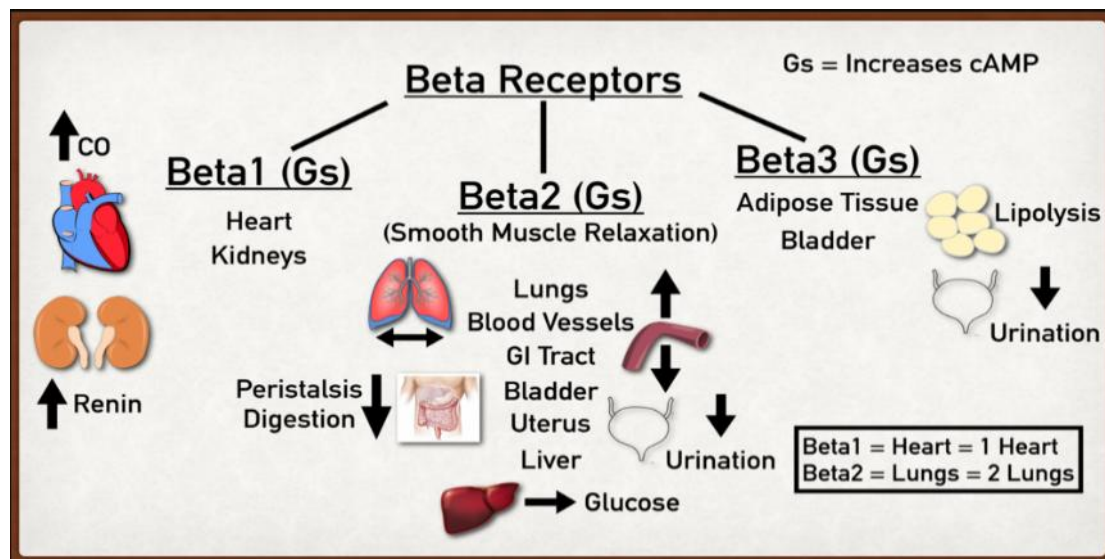


Figure 3.15 The distribution of beta receptors in the body.

(i.pinimg.com, 2023)

Antimuscarinic or muscarinic antagonists are also known as anti-cholinergic bronchodilators. The cellular action of antimuscarinic bronchodilators affects smooth muscle tone and mucus secretion in the lung. This shows the location of the receptors in the parasympathetic ganglia in the thoracic cavity. Vagal nerve activity plays a key part in bronchoconstriction and mucous gland secretion; interrupting this process reduces bronchoconstriction and mucus secretion (Cazzola & Molimard, 2010).

The M receptors responsible for the mediation of bronchoconstriction and mucus secretion act via a negative feedback loop to inhibit bronchoconstriction (Matera et al., 2020). This is superior to beta₂-agonists at reducing exacerbations but has no impact on long-term decline in lung function or mortality (Cheyne et al., 2015).

Long-acting antimuscarinics LAMA

LAMA remain bound to receptors for longer (Scullion, 2007). Inhaled preparations of the long-acting antimuscarinics are Tiotropium (2003), Aclidinium and Glycopyrronium bromide (2012) in COPD, both drugs had a similar safety profile (Karabis et al., 2013; Tashkin et al., 2008).

Dual versus single bronchodilators LABA/LAMA

GOLD (2024a) now recommends LABA/LAMA combinations as first-line rather than LAMA only. A Cochrane meta-analysis concluded that a dual therapy inhaler containing both LABA and LAMA is superior to either a single component or combination of an inhaled corticosteroid (ICS) and LABA in reducing moderate to severe exacerbations in a high-risk population (Oba et al., 2018). In current UK and Wales guidelines, dual long-acting bronchodilators are recommended for breathless people with COPD before single long-acting formulations.

Inhaled Corticosteroids (ICS) and COPD

ICS have important anti-inflammatory properties in respiratory disease (Williams, 2018). This might partly explain why combining an ICS with an LABA has synergistic rather than additive effects (see Figure 3.16 and Table 3.2). Yang et al. (2012) found no evidence of mortality risk reduction but a risk reduction for exacerbations and rate of decline in HRQoL (SGRQ). The risk of pneumonia was increased when using an

ICS. The authors concluded that using an ICS had some potential benefits, but these needed to be weighed against the risks. While the risk of ICS-increasing pneumonia is widely accepted, care should be taken in interpreting studies as selection bias may play an important part in outcomes within and between studies, accounting for differences in mortality risk and incidence (Suissa, 2019).

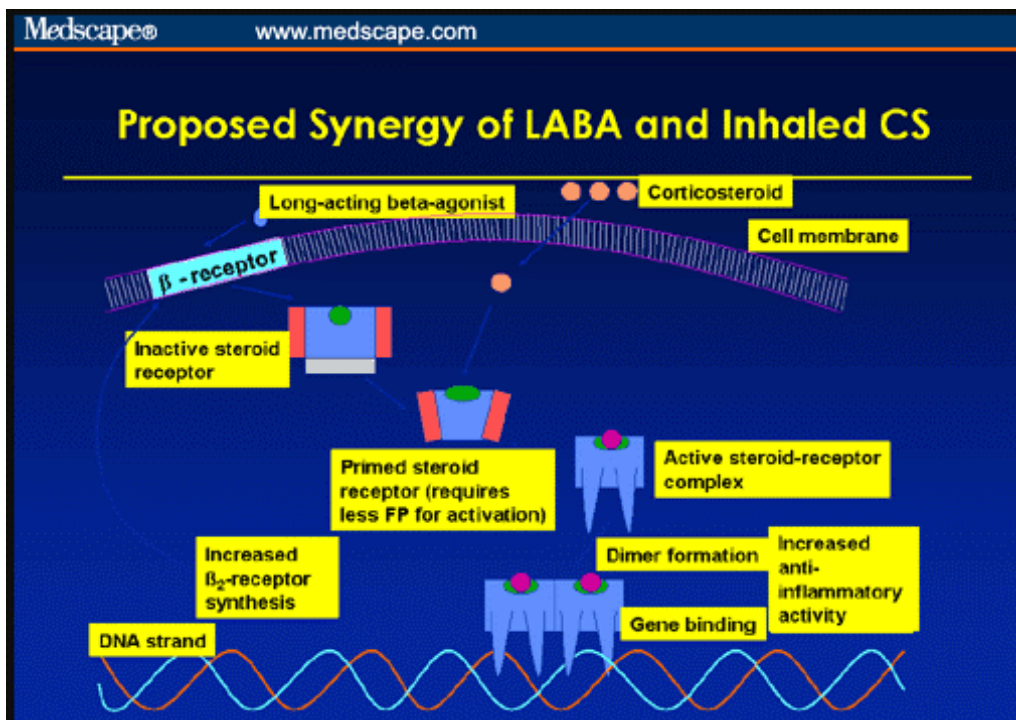


Figure 3.16 Proposed synergistic effect of LABA and inhaled corticosteroids.

(<http://img.medscapestatic.com/>, 2023)

Triple therapy inhalers – combinations of ICS+LABA+LAMA

Triple inhaled ICS, LABA, and LAMA therapies delivered in a single device offer simplified treatment regimens and a decreased treatment burden. A series of trials have been carried out to provide evidence to support the use of triple therapy inhalers TRILOGY (Singh et al., 2016), FULFIL (Bourbeau et al., 2021), TRIBUTE (Papi et al., 2018), IMPACT (Lipson et al., 2018), and ETHOS (Rabe et al., 2020) are summarised in Table 3.3.

IMPACT and ETHOS reported significantly higher pneumonia levels and a decrease in all-cause mortality in the arms containing ICS. However, mortality benefits of single inhaler triple therapy (SITT) in both the Rabe et al. (2020) ETHOS and Lipson et al. (2018) IMPACT studies were only apparent in the first three months of data and could be a result of ICS withdrawal at randomisation (Suissa, 2021; Suissa et al., 2022b). Care should be taken not to draw comparisons between studies, as the study populations were not comparable in terms of COPD severity. Participants were highly selected with any significant co-morbidities excluded and do not represent real-world patients (Halpin et al., 2016).

Two real-world studies, including an observational study by Buhl et al. (2018), reported the results of a 12-month study comparing multiple inhaler treatments to LABA/LAMA combinations. The LABA/LAMA combined inhaler group had fewer exacerbations than the multiple inhaler treatments group and had the greatest improvements in QoL scores as measured by CAT.

Suissa et al. (2022a) saw that the rate of moderate or severe exacerbations in the SITT group was more significant than the LABA/LAMA group. However, there was a benefit of SITT vs LABA/LAMA on exacerbations in those with ≥ 2 exacerbations in the previous 12 months.

Both studies identified the increased risk of pneumonia and positive effects on all-cause mortality. These studies support guideline treatment of ICS use as well as dual bronchodilator in frequent exacerbators, asthmatics, or a higher eosinophil count > 300 cells/ μ L (GOLD, 2024a).

Table 3.3 Study Summary Triple therapy inhalers – combinations of ICS+LABA+LAMA

Study Name	Intervention	Participants	Primary outcome (PO)	Population	Length of study	Results of PO	Significance of PO
TRILOGY	(SITT) ICS/LABA/LAMA Vs ICS/LABA	1368	FEV ₁ and TDI	COPD FEV ₁ 36.2-39.6% GOLD D	52 weeks 26 week (PO)	0.081 L (95% CI 0.052-0.109;	FEV p<0.001 TDI p=0.160
FULFIL	(SITT) ICS/LABA/LAMA Vs ICS/LABA	1810	FEV ₁ and SGRQ	COPD High symptom burden, frequent exacerbator	24 Weeks	FEV ₁ and SGRQ (6.6 point)	Both p<0.001
TRIBUTE	(SITT) ICS/LABA/LAMA Vs LABA/LAMA	1532	Exacerbation rate	COPD FEV ₁ <50%, ≥ 1 exacerbation in 12 months	52 Weeks	Reduction in exacerbation rate (SITT)	p=0.043
IMPACT	(SITT) ICS/LABA/LAMA Vs LABA/LAMA Vs ICS/LABA	10355	Exacerbation rate	COPD FEV ₁ <50%, ≥ 1 exacerbation in 12 months	52 Weeks	Reduction in exacerbation rate (SITT)	p<0.001
ETHOS	(SITT) ICS/LABA/LAMA Vs LABA/LAMA Vs ICS/LABA	8509	Exacerbation rate	COPD FEV ₁ 25-65% ≥ 1 exacerbation in 12 months	52 Weeks	Reduction in exacerbation rate (SITT)	p<0.001

*SITT = Single Inhaler Triple Therapy

Phosphodiesterase-4 (PDE4) inhibitors in COPD

PDE4 inhibits the metabolism of cAMP by intracellular enzymes, resulting in a rise in Protein Kinase A, which stimulates increased protein phosphorylation, inhibiting pro-inflammatory cells and inflammatory mediators, inhibiting fibrosis (Rabe, 2011). The benefits appear to be strongest in a chronic bronchitis phenotype on optimal inhaled therapy in those who have moderate or severe exacerbations (Janjua et al., 2020).

Prophylactic macrolides

Macrolides not only have antibacterial properties but also anti-inflammatory properties (Jaffé & Bush, 2001). In a large RCT, 1142 participants with confirmed COPD having exacerbated in the previous year or if exacerbation-free on continuous long-term oxygen therapy (LTOT) were recruited when stable (Albert et al., 2011). They received Azithromycin 250mgs daily versus placebo for one year, with those on Azithromycin having a significantly greater time to first exacerbation (see Figure 3.17), 266 versus 174 days ($p < 0.001$), as well as a significantly smaller number of exacerbations per patient per year, 1.48 compared to 1.83 ($p = 0.01$).

Side effects included reduced hearing in the azithromycin group, 27% versus 21% ($p = 0.04$) in one year. Although both groups were well matched, one weakness of the study would be the lack of data analysis identifying subgroups in different disease severities and on different permutations of guideline inhaled therapies of ICS, LABA and LAMA (Albert et al., 2011). Also, patients with a risk of prolongation of PR/QT should have an ECG prior to the commencement of azithromycin, as this is a recognised side effect of azithromycin (Khan et al., 2019).

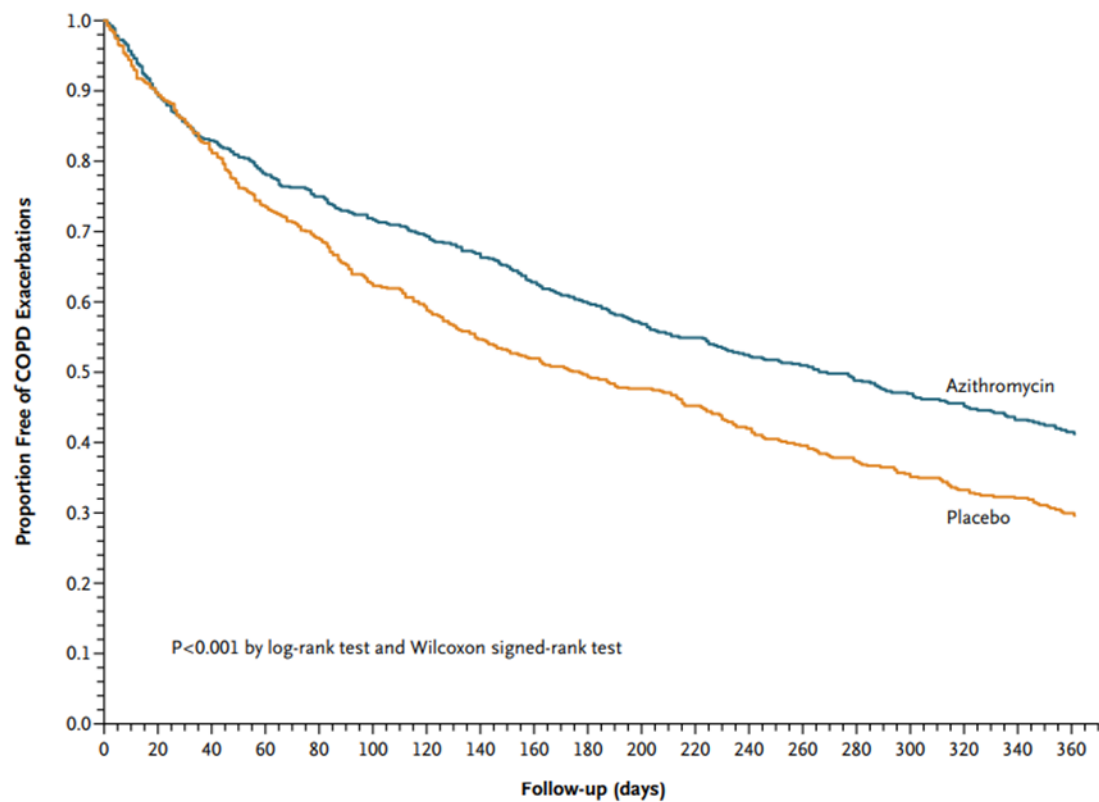


Figure 3.17 Proportion of participants free from acute exacerbations of COPD for 1 year.

Reproduced with permission from (Albert et al., 2011), Copyright Massachusetts Medical Society.

The increasing awareness of antibiotic stewardship has raised concerns about a significantly higher level of macrolide resistance in those taking azithromycin (81% Vs 41%, $p < 0.001$) (Albert et al., 2011). The Health Research Authority (HRA) and the National Institute for Health and Care Research (NIHR) have a statement on the appropriateness of long-term antibiotics in COPD, with a view to identifying non-responders and considering how to withdraw them.

Vaccinations

Current national and international guidelines advocate offering those with a diagnosis of COPD pneumococcal vaccination and annual influenza vaccination (GOLD, 2024a; NICE, 2018)

Population data demonstrates significant benefits from the influenza vaccine. Nichol et al. (1994) reported a 9% reduction in hospitalisations due to community-acquired pneumonia (CAP) or influenza ($p < 0.002$) and a 12% reduction in admissions for acute and chronic respiratory conditions ($p < 0.01$). All-cause mortality was reduced by 15% over three flu seasons ($p < 0.001$). However, only 10% of the 25,000 suffered from a chronic lung condition, therefore limiting comparability to people with COPD.

Kopsaftis et al. (2018) conducted a Cochrane review and meta-analysis and reported that the number of exacerbations in the vaccinated group reduced ($p = 0.006$).

Walters et al. (2017) reported that pneumococcal vaccination provides significant protection against CAP in COPD.

Long-term domiciliary oxygen therapy (LTOT)

The use of LTOT for those clinically stable COPD patients prescribed optimal pharmacotherapy who had chronic severe hypoxaemia ($\text{PaO}_2 < 8 \text{ kPa}$), using oxygen for greater than 15 hours per day has been shown to prolong survival but there is no effect on dyspnoea nor quality of life (Cranston et al., 2005; Hardinge et al., 2015).

3.8 NON-PHARM TREATMENTS

Smoking cessation

The Welsh government has demonstrated a commitment to reducing smoking prevalence through its tobacco control delivery plan 2022-2024, setting out to be smoke-free by 2030, which aligns with the UK's ambition to create a smoke-free generation (Government, 2022), with the UK government pledging to ensure children turning 14 in 2021 will not be legally able to buy tobacco products (DHSC, 2024). This plan emphasises the importance of comprehensive smoking cessation services, public education on the risks of smoking, and legislation to limit smoking in public spaces (DHSC, 2024). Figure 3.18 shows the adult smoking prevalence by nation in the UK and Figure 3.19 shows the mortality rate by deprivation in Wales, demonstrating the disparity across socioeconomic divisions.

UK smoking prevalence, age-standardised percentage, persons aged 18+, UK constituent countries, 2018

Produced by Public Health Wales Observatory, using APS (ONS)

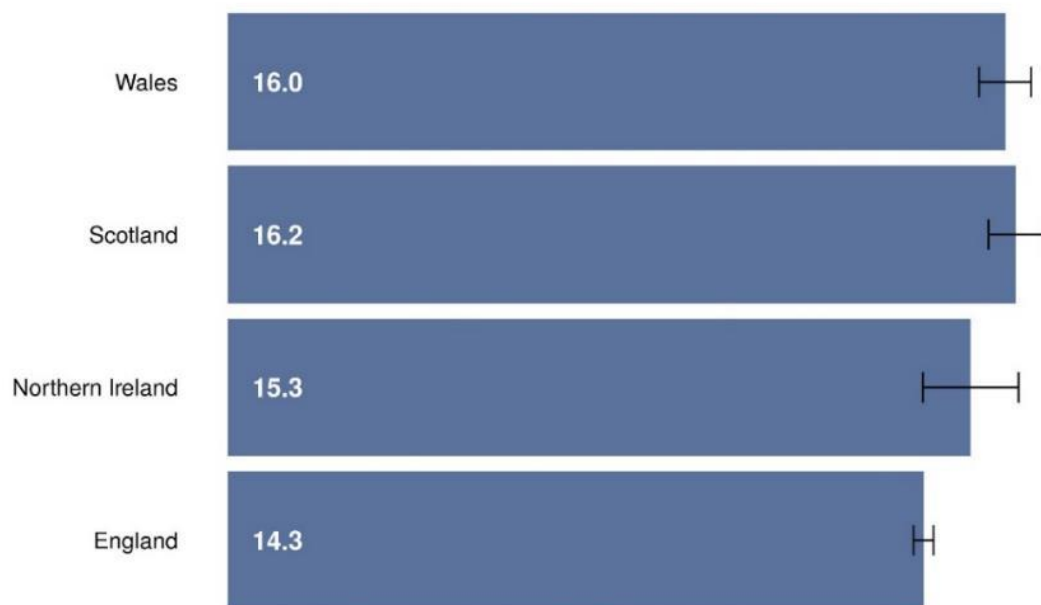


Figure 3.18 Smoking prevalence in the UK
(PHW, 2018)

Smoking-attributable mortality, EASR per 100,000, males and females aged 35+, Wales by deprivation fifth, 2008-2010 to 2016-2018

Produced by Public Health Wales Observatory, using PHM & MYE (ONS) and NSW & WIMD (WG)

— 95% confidence interval

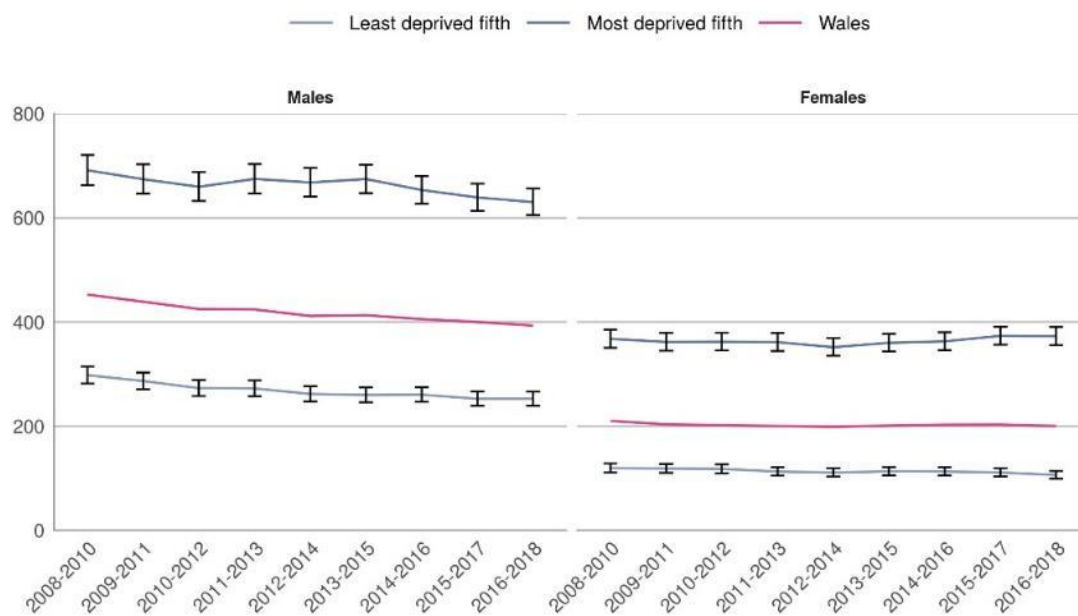


Figure 3.19 Smoking attributed mortality in Wales by deprivation.

(PHW, 2020)

Research showed a reduction in non-smoking adults being exposed to second-hand smoke from 42% to 29% between 2007 and 2015 (ASH, 2018). Furthermore, new legislation introduced in 2021 banned smoking in cars with children present and expanded the ban to include hospital grounds, school grounds, and playgrounds to protect the public from second-hand smoke and to de-normalize smoking behaviour in vulnerable groups. This legislative approach is complemented by educational campaigns, like “*No if’s no Butts*”, aimed at raising awareness of illegal tobacco products (ASH, 2022). All these initiatives should reduce the future prevalence of COPD as well as other tobacco-related diseases.

The integration of e-cigarettes as a cessation aid is also a notable aspect of the smoking cessation landscape in Wales, with public health bodies recognising their role in helping smokers quit. However, there is an emphasis on ensuring that e-cigarette use is targeted towards smokers seeking to quit, with measures in place to prevent uptake among non-smokers, particularly young people (ASH, 2024).

Pulmonary rehabilitation

GOLD (2024a) recommends PR with the highest level of evidence (A) in patient groups B and E. This is unusual for a non-pharmacological treatment and demonstrates the large body of research, further to the evidence described in Chapter 2. Early research in COPD, from (Griffiths et al., 2000) recruited 200 participants from sites in England and Wales in an RCT with the intervention arm being six weeks (18 visits) of MDT rehabilitation. The results showed a decrease in the length of hospital stay at the next hospital admission with the PR group, 10.4 (9.7) and the control group 21.0 (20.7) days ($p=0.022$). Shuttle walk distance at one year was improved by 28.1m (CI 10.9-45.3) ($p=0.002$). QoL measures taken included SGRQ, which saw the total score decrease by >4 (MCID) $p=0.01$.

A meta-analysis of PR programs initiated within four weeks of discharge by Rysø et al. (2018) showed lower mortality (Incidence Rate Ratio, IRR = 0.58 95% CI: 0.35 to 0.98), fewer hospital admissions (IRR = 0.47 95% CI: 0.29 to 0.75) and reduced hospital days (IRR = 0.47 95% CI: 0.29 to 0.75).

PR has been shown to reduce symptoms of depression and anxiety in COPD patients, likely due to increased social interaction, support, and improved physical

health (Gordon et al., 2019; Pumar et al., 2014). In a study evaluating the cost-effectiveness of physical activity, a key component of PR, Ramos et al. (2019) found that in the UK COPD population, it could lower mortality by 6%, decrease hospital admissions by 2%, and offer a quality-adjusted life years cost savings.

Evidence strongly supports the use of pulmonary rehabilitation in managing COPD for its benefits. Strategies to improve long-term benefits, enhance patient engagement, and increase accessibility are critical for the wider implementation of PR. McCarthy et al. (2015) concluded that the evidence is adequate to support the use of PR and that there is no longer a need for RCTs to support its use and research should focus on promoting equality of access.

Surgery (LVRS/transplant)

Lung volume reduction surgery (LVRS) and transplant are non-pharmacological treatments that are often used in chronic lung disease (Benzo, 2011; Gordon et al., 2018). There is limited evidence due to the absence of RCT with observational data allowing conclusions on the benefits of these radical interventions (GOLD, 2023). Structural changes can significantly improve FEV₁ and improve the mechanics of the respiratory muscles and chest wall (Everaerts et al., 2023) however, higher mortality has been noted in those with <20% FEV₁, and therefore patient selection is key (Fishman et al., 2001).

The size of the lung transplant waiting list is greater than the number of available organs in the UK (Benzo, 2011). Kourliouros et al. (2018) reported that between 2004 and 2014, 2213 patients were listed for transplant, COPD at 28.4%, pulmonary fibrosis (PF) at 26.2%, cystic fibrosis (CF) at 25.4% and other lung pathologies at 20.1%. The mean survival of transplant recipients in 2020 was 6.2 years worldwide, improving to 8.3 years after one year of survival. The premorbid state of COPD patients leads to a worse prognosis, with recognition given that not all patients with severe COPD benefit from lung transplants (Mark et al., 2020).

Airways Clearance

Airways clearance appears to be an important adjunctive treatment in those with a chronic bronchitis phenotype of COPD who struggle with mucus hypersecretion, but the evidence is not strong. There is a small body of evidence and an even smaller pool of well-designed studies RCTs that compare different types of ACT against medication alone or against each other. This section will build on 1.3.3.2, OPEP with evidence on the use of Aerobika and study design that is pertinent to this study.

Recommendations for ACT as a guideline therapy in COPD have been recognised for many years in the UK, with NICE (2018) guidelines stating:

“If people have excessive sputum, they should be taught how to use positive expiratory pressure devices or active cycle of breathing techniques”.

Despite a paucity of evidence, NICE (2018) regards both OPEP, including Aerobika, and ACBT, previously described in 1.3.2.1, as standard care in COPD and excessive secretions. In clinical practice in Wales, ACBT forms the first-line treatment option, with OPEP offered as second-line due to availability and healthcare provision models. There is a lack of evidence to support this decision-making.

Further afield GOLD (2023) was the first iteration of the annually released global strategy document to recognise the importance of managing excess secretions using ACT, stating:

“Mucus clearance treatments that promote mechanical movement through the airway such as oscillating positive expiratory pressure therapy may improve mucus mobilization”.

However, GOLD (2023) included the caveat that there are limited studies in COPD and that the body of research results are inconsistent.

Whilst COPD guidelines in Australia and New Zealand recommend suitable ACT for those with excess sputum be delivered as a personalised approach (Yang, 2023).

The guidelines contain little guidance on the use of ACT adjuncts in COPD, as can be seen above; this is due to and has led to the absence of long-term clinical trial data. Prescription rates of devices do not match the population size of those with a chronic bronchitis phenotype, alluding to an unmet need that indicates the need for further research into the use of OPEP in COPD (Barker et al., 2017). However, the

number of studies reported in the last four-years or currently planned by the research community suggests that this is currently a hot topic.

The value and use of Aerobika have been described in several studies, including Bracey et al. (2019) in a national audit in the UK, reporting that of the 176 participants recruited with COPD to a one-month trial of the device, 92% found it acceptable to use and wished to continue with the therapy. A subset of this cohort (82%) completed CAT at zero and one-month time points, with 60% demonstrating a decrease greater than the two-point minimal clinically important difference (MCID) for CAT. However, no data was given on the reason for starting therapy or if this was due to an AECOPD.

Studies have also looked at retrospective data reporting exacerbations and resource use. Khoudigian-Sinani et al. (2017) analysed the cost-effectiveness of an Aerobika in the USA in the 30 days post exacerbation. Evaluating re-exacerbation using data from a health utilisation dataset that included data on the provision of Aerobika. Khoudigian-Sinani et al. (2017) concluded that the use of the device was associated with a 6% decrease in exacerbations and there for a >\$500 saving. Thanh et al. (2019), in a similar paper in Canada, looking at data over one-year, corroborated the healthcare savings and estimated an additional 0.4 quality-adjusted life years associated with the provision of Aerobika. Although a compelling argument, this paper uses complex modelling that is aligned with the USA and Canadian health care and would be difficult to extrapolate to the UK.

Burudpakdee et al. (2017), in a retrospective Canadian database analysis, enrolled 405 participants into two crossmatch groups over a two-year period and found that the provision of Aerobika devices was associated with a 19% re-exacerbation rate, compared with a 28% re-exacerbation rate in those receiving standard care ($p=0.01$). They also suggested that Aerobika may be a cost-effective way of reducing emergency department visits and costs associated with unplanned admissions.

Prospective studies looking at the implementation of Aerobika include. Tse et al. (2020), in a broader study in the USA, followed users of Aerobika ($n=619$) and Acapella ($n=1857$) for one-year post-discharge. Aerobika users were significantly less likely to exacerbate within one month (12% versus 17% $p=0.01$) or one year (40% versus 45% $p=0.01$). However, both Tse et al. (2020) and Burudpakdee et al.

(2017) are retrospective studies; the data used to make these assumptions may lack clinical detail and be prone to reporting and selection bias.

Trials utilising CAT as a primary outcome include Suggett (2016) and Bansal et al. (2023). Suggett (2016), in an eight-week field study, followed 26 patients collecting data at zero, four and eight-weeks of Aerobika use, concluded a clinically and statistically significant drop in CAT score ($p=0.01$). Bansal et al. (2023) in a similar study in India over six-weeks with 40 patients, demonstrated a change from 20 points to 12 in CAT ($p<0.001$) and an 82.5% responder rate. However, a lack of a control group and a small sample size limits the interpretability of both these studies, but they do show that CAT is sensitive to the change delivered by OPEP.

Kim et al. (2023), using data from a Korean registry, conducted a single-arm interventional study using the subjects as their own control. The primary outcome was the number of exacerbations, followed by secondary outcomes of the bronchiectasis health questionnaire and sputum volume. Seventeen participants were given Aerobika and followed up at one, three and six-months finding a significant decrease in exacerbations ($p,0.001$). However, caution should be taken when interoperating these results due to small numbers and a possible bias to the way the retrospective data was collected.

Svenningsen et al. (2016), in a study of COPD crossover design, recruited 14 self-identified sputum producers and 13 non-sputum producers, randomising them to use Aerobika for four-weeks or standard care. Evaluation was performed using SGRQ, FEV₁, FVC, a six-minute walk test, and MRI with hyperpolarised gas to identify changes in ventilation. Regular use of Aerobika improved ventilation, as can be seen in Figure 3.20, as measured by ventilation defect percentage ($p=0.009$), sputum mobilisation ($p=0.03$), SGRQ ($p=0.01$), FVC ($p=0.01$), and six-minute walk test ($p=0.04$).

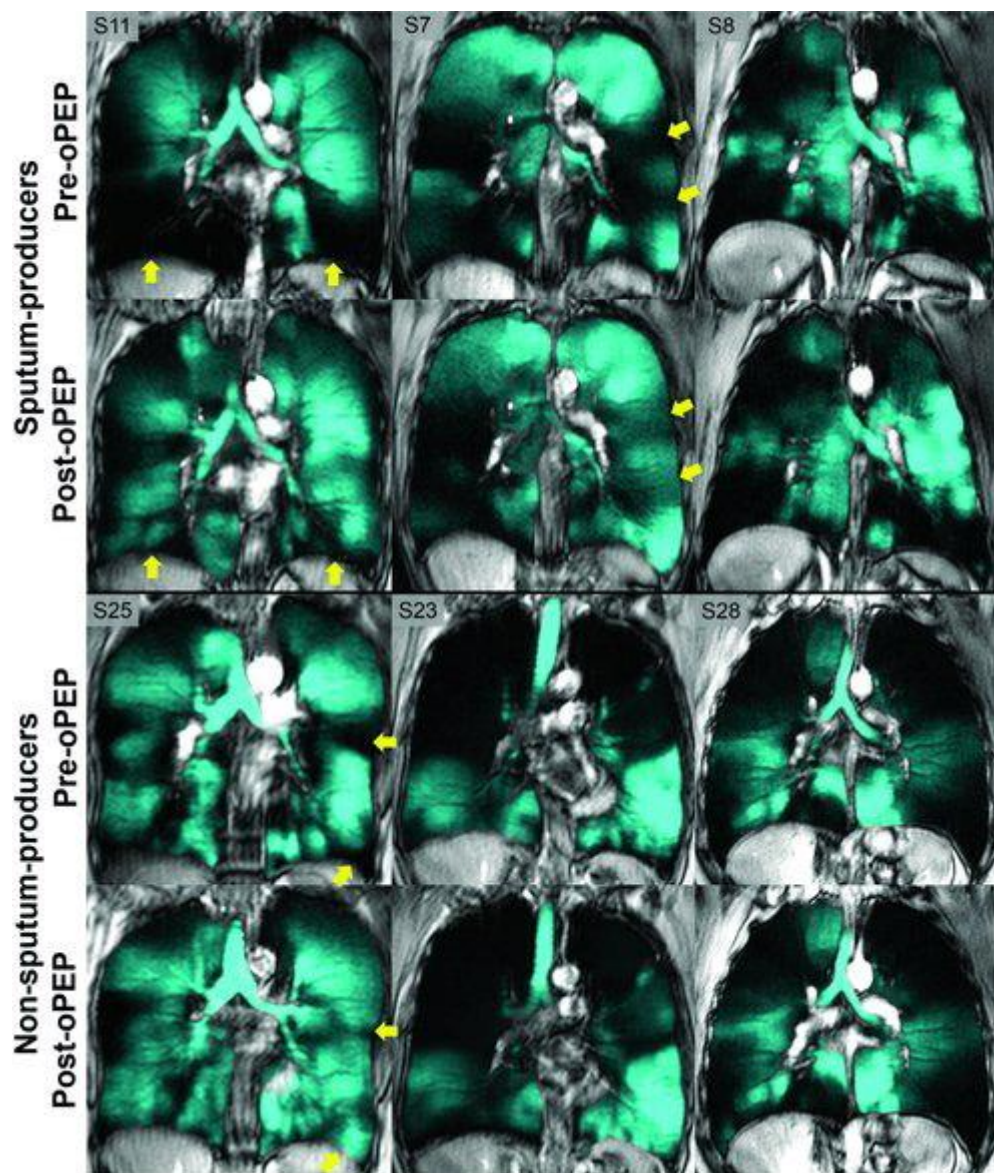


Figure 3.20 MRI ventilation in representative sputum and non-sputum producers.
(Svenningsen et al., 2016)

Although this study had a small sample size and lacked blinding, Svenningsen et al. (2016) conclude that this gives physiological evidence that Aerobika is valuable in the CB phenotype of COPD.

In a four week trial of AD v Aerobika in bronchiectasis, Livnat et al. (2021) evaluated LCI and sputum volume. 49 participants completed the study, with 24/25 being randomised to Aerobika (men age 66.3 $\pm$ 12.8 years). They found no difference between groups in LCI, but expectorated sputum decreased in the Aerobika group ($p=0.04$). However, patient-reported treatment burden increased in both groups, but Aerobika was better tolerated ($p=0.04$). This work highlights the need for robust evidence to support the implementation of any ACT and to measure and ensure there is no unnecessarily high treatment burden.

Sahardin (2021) in a Malaysian single-arm interventional study, Impulse oscillometry (IOS) was used as the primary outcome, and secondary outcomes reported the impact of Aerobika on CAT score and exacerbation rate in COPD. IOS measures small airways resistance by comparing oscillation frequency differences during a relaxed breathing manoeuvre. The study compared clinical data and events in the 24 weeks prior to enrolment to 24 weeks of Aerobika twice daily for 10 minutes. Data was analysed on 53 participants with a mean age of 71.55 ($\pm$ 6.33) years and a high proportion of males (96.7) FEV₁/FVC ratio 52.31 (IQR 44.67-61.67) and mean CAT 19.43 ($\pm$ 7.1). The demographics of this cohort demonstrate that they have severe symptoms of COPD and that this is an unusual split of gender. IOS results showed a significant improvement in small airways resistance at 24 weeks ($p<0.001$) and CAT scores decreasing to nine (SD7-14) $p>0.002$. This study showed a large, 10-point decrease in CAT score during the study; it was unclear if the subjects were stable at the time of recruitment.

Long-term and Comparable studies

S. M Alghamdi et al. (2023) conducted an RCT comparing the NICE (2018) guideline therapies of OPEP (Acapella, not Aerobika) versus Usual care, which was considered as ACBT. The O-COPD trial recruited 122 UK participants in 2021 with stable COPD and followed them over time. Primary outcomes were LCQ between groups at three-months. Secondary outcomes included the CAT plus sputum frequency scale. Demographics of the cohort were 60% males, 17% current

smokers, mean age 62_(+/-10) years, and 80% of participants reporting >3 AECOPD requiring antibiotics or steroids in the previous year. Primary outcome analysis of 103 data sets showed a significant difference in LCQ between groups at three-months ($p=0.03$ 95%CI 0.71-2.03) with a mean difference of 1.03, in favour of the intervention group. However, this difference is below the considered MCID for LCQ of 1.3 (Nguyen et al., 2022), and no significant difference in CAT score or other measures was seen. There were more AECOPDs (classified as adverse events, not secondary outcomes) in the control arm of 54% to 32% in the OPEP arm ($p=0.029$) and a slightly lower dropout rate of 9% in the OPEP arm versus 11% in the control arm, but this was not significant. This trial suggests OPEP is a useful non-pharmacological adjunct for stable COPD with a chronic bronchitis phenotype, but the differences between groups over three months are small.

Milan et al. (2019) looked at the effects of PEP and OPEP versus standard care in a study composed of two parts. The first study randomised 91 participants in the USA who were admitted to hospital during AECOPD and who were productive of sputum to a randomised comparison of PEP and OPEP (acapella choice). Mean (SD) age 64 (+/-11.6) 58 female, no comment was made on the severity of COPD or current lung function and the baseline age was lower in the PEP group ($p=0.08$). The primary outcome was Length of Admission (LoA). The results showed a mean (SD) of 5.2 days (+/-4.9) LoA in the OPEP group and 5.1 days (+/-2.7) in the PEP group, but no significant difference between groups. In the second part of the study, the 91 from the first study were matched with a retrospective cohort of 182 reporting mean (SD) LoA as 5.1 (+/-4) days in the treatment (OPEP/PEP) group and 6.6 (+/-5.1), concluding that OPEP or PEP were significantly better than standard care ($p=0.02$) (Milan et al., 2019). The study concluded that a significant benefit of ACT (PEP or OPEP) in reducing LoA in AECOPD with Milan et al. (2019) commenting that a larger trial would be needed to compare the two ACT modalities.

Phillips et al. (2023) published the methodology of a proposed RCT evaluating ACBT versus OPEP (Aerobika) versus walking and huffing in bronchiectasis. They follow patients for six-months after recruitment following an admission for AECOPD. With studies like this in the pipeline, the community's interest in evaluating ACT, including OPEP, in chronic respiratory health is growing.

3.9 AIMS AND OBJECTIVES

A pilot RCT including real-world evidence to assess the outcomes of ACBT versus OPEP (Aerobika) for people with AECOPD with a chronic bronchitis phenotype.

Primary Objectives

- To test the null hypothesis, there is no difference in LCQ between groups at three-months.

Secondary Objectives

- To test the null hypothesis, there is no difference in CAT between groups at three-months.
- To test the null hypothesis, there is no difference in numbers and duration of hospital admissions at one, six and 12-months.
- To compare numbers and duration of hospital admissions in the 12 months prior to starting the trial and 12 months after starting the trial within and between each group
- Time to first exacerbation between groups
- To compare the number of courses of oral antibiotics or steroids
- To compare reported healthcare contacts in both groups at one, three and 12 months
- To compare the proportions of participants achieving a change of $\geq \pm 1.3$ on the LCQ in the ACBT versus OPEP groups at one, three and six-months
- To compare the proportions of participants achieving a change of $\geq \pm 2$ on the CAT in the ACBT versus OPEP groups at one, three and six-months
- To note measures of cough severity (LCQ) and Quality of Life (QoL) (CAT and SF-36) within groups over time
- To note patient feedback on the tolerability and acceptability of Aerobika and ACBT (free text and Likert questions)
- To identify refusal, study completion and adherence

3.10 METHODS

3.10.1 Ethics and peer review

The study was conducted in compliance with the principles of the Declaration of Helsinki (World-Medical-Association, 2013) and the principles of Good Clinical Practice (GCP) in accordance with all applicable regulatory guidance, including but not limited to the UK Policy Framework for Health and Social Care 2023 (HRA, 2023). The protocol and related documents (and any subsequent amendments) were submitted for review to the relevant parties, Health Care Research Wales (HCRW) and the Regional Ethics Committee (REC). Annual progress reports and a final report after the study were submitted to Wales REC 4.

Ethical approval was sought from HCRW and REC for the protocol, informed consent forms, and other relevant documents, e.g., advertisements, and GP information letters. Rec reference: 21/WA/0144, Integrated Research Application System (IRAS) reference: 289817. All study documentation received ethical approval. A copy of the approval letter from the Health Research Authority (HRA) and HCRW can be found in Appendix 3.

The trial was registered with ClinicalTrials.gov, with the ID NCT05548036. Appendix 4 contains a copy of the agreed Participant Information Sheet-Informed Consent Form (PIS-ICF) V5.0, 6th April 2022.

Table 3.4 provides a summary of approvals and subsequent amendments.

Table 3.4 Amendments dates and summary

Date	Type	Protocol	Summary
20/5/2021	Initial Approval	V3.0 15/5/21	Original approval
6/7/2021	Non-Substantial	V3.0 15/5/21	Invite 2 nd recruiting site (Cardiff)
17/3/2022	Substantial	V4.0 3/3/22	Recruitment from Outpatients and community settings as well as Inpatients

The study underwent peer review at Swansea University and was reviewed by the Hywel Dda R&D Study Review Panel, which included a patient representative with COPD, to ensure scientific quality and rigour.

3.10.2 Participant Selection

Participants with confirmed COPD and a chronic bronchitis phenotype (daily sputum producer) who had experienced at least two exacerbations in the last year requiring oral antibiotics and or steroids or one or more unplanned hospital admissions due to an AECOPD over the last three years. Participants met the GOLD 2022-23 criteria 'C or D' to be considered at the time of protocol development. GOLD have since combined 'C' and 'D', now classified as E (GOLD, 2023).

3.10.3 Participant Identification and Approach

Patients were identified by their clinical care team, and their notes were pre-screened against the inclusion and exclusion criteria.

Recruitment strategies included following pathway A, as shown in Figure 3.21, or pathway B seen in Figure 3.22.

Pathway A Recruitment

The clinical care team approached patients directly when they were admitted to hospital and provided an invitation letter and PIS-ICF. If the patient was interested the clinical staff arranged a subsequent recruitment visit with a member of the research team.

Pathway B Recruitment

The clinical care team, e.g., COPD specialist nurses or allied health professionals (AHPs), approached participants through standard clinical contacts. This may have been in emergency departments, medical admissions units, community settings, virtual and phone or face-to-face clinics. Potential participants were given or sent, via post or email, an invitation letter on hospital-headed paper, which provides an overview of the study and a PIS-ICF. The clinical staff gained consent to contact the subject. A member of the research team contacted the participants to answer any

questions and invited them to a research visit in the hospital, where written consent was gained.

If the participant seemed interested in the study after being provided with an invitation letter and PIS-ICF but was discharged prior to consenting, the research team contacted the participant to seek consent, arrange the provision of a study pack, and provide an outpatient or home initial study visit.

3.10.4 Study Visits and Follow-Up

Following pathway A (Figure 3.21), the intervention was delivered during admission.

Following pathway B, (Figure 3.22), the delivery of the intervention required a single research visit to the hospital, where baseline data and OPEP teaching were performed. In some circumstances, a home visit or virtual appointment was considered, depending on the resources available and whether the participant preferred a clinic visit.

No other face-to-face follow-ups, other than routine clinical care, were needed. Data on hospital admissions, GP visits, and medications was checked from hospital records and online databases and also self-reported. Due to participant preference, follow-up OCM data was collected by phone in most instances. Each study contact lasted approximately one hour.

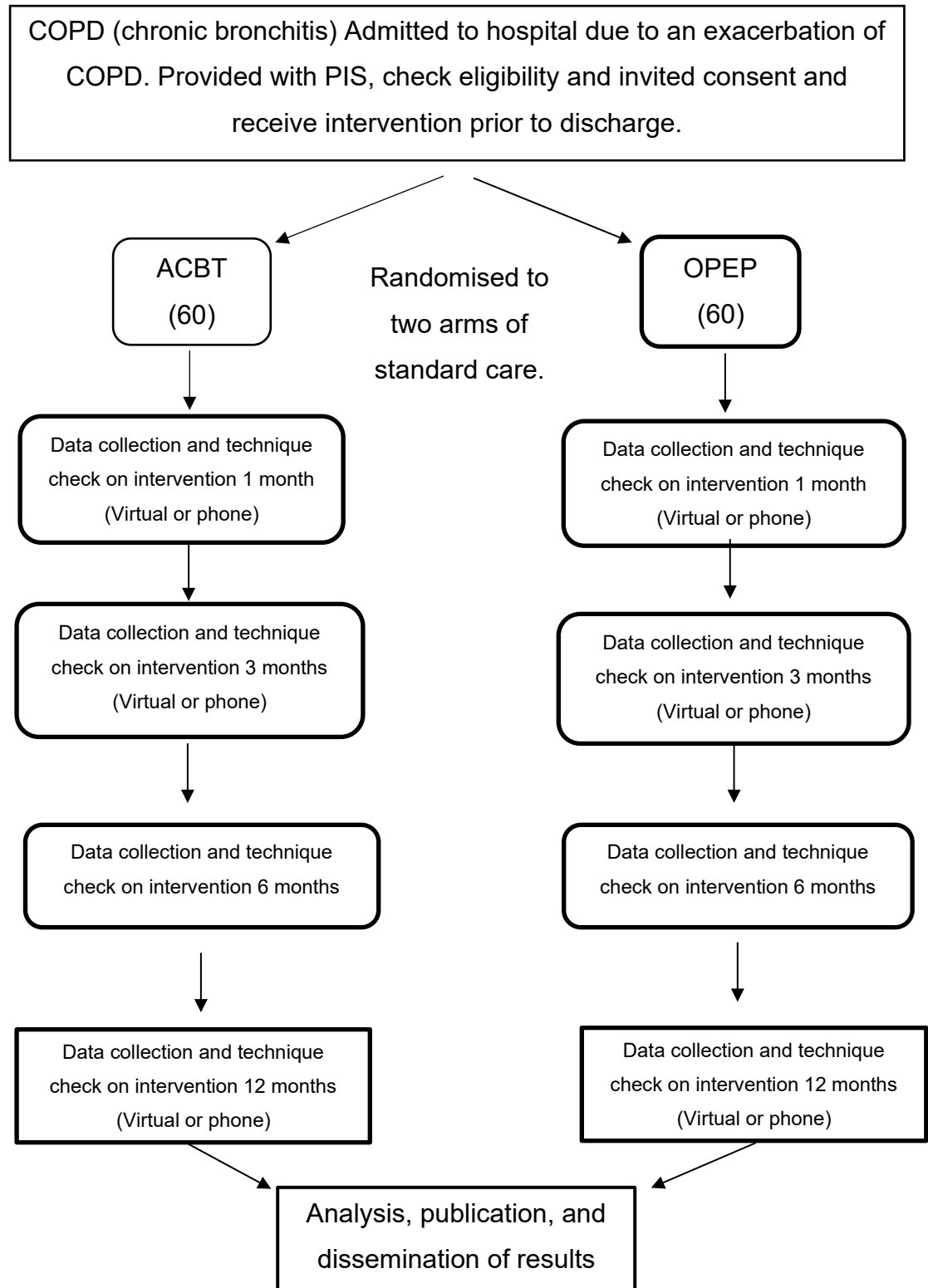


Figure 3.21. Pathway A (Admitted to Hospital)

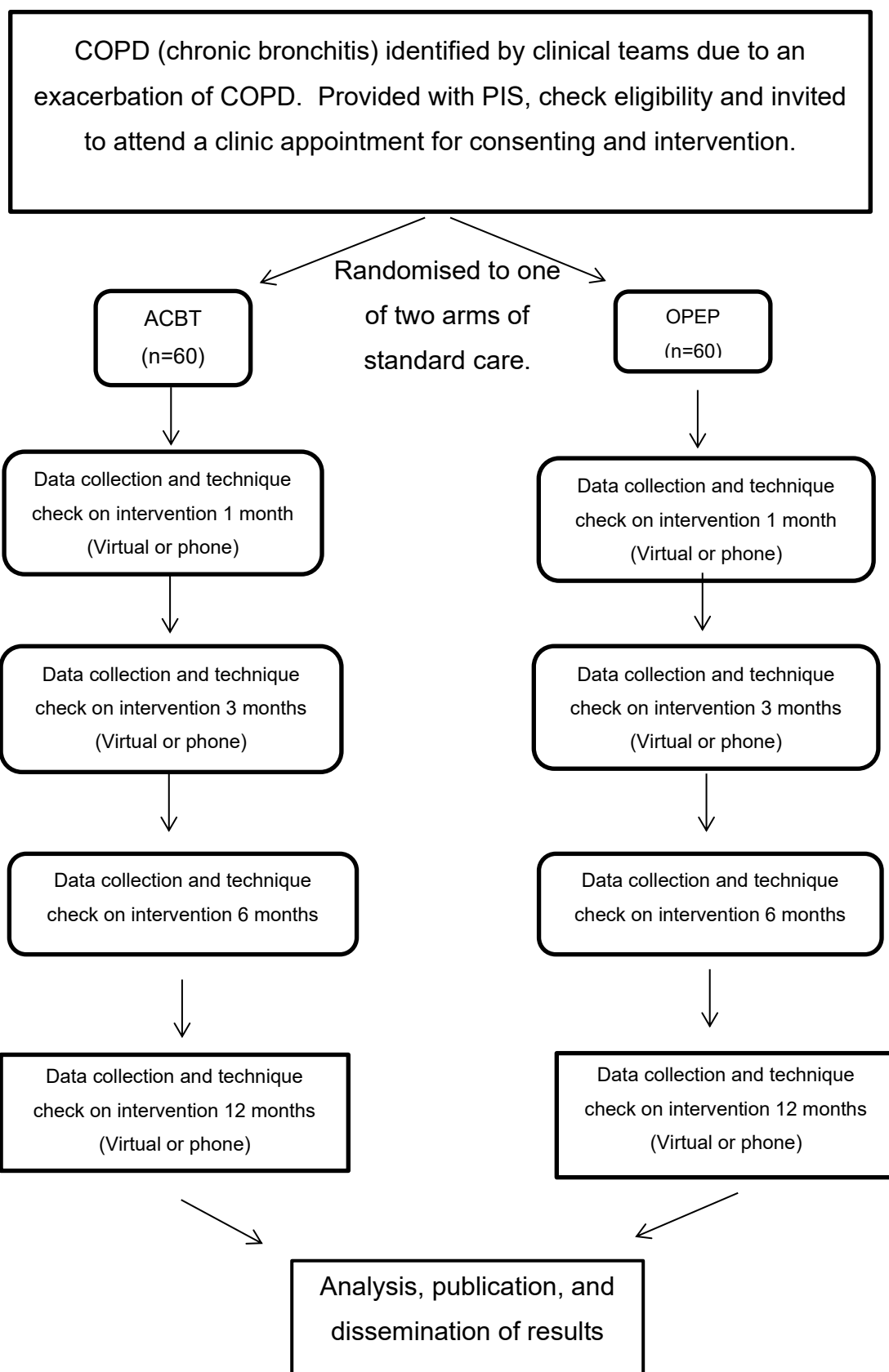


Figure 3.22. Pathway B (Outpatient identification)

3.10.5 Screening procedures

Once the potential participants were identified by the clinical team, the study team checked eligibility against the inclusion and exclusion criteria.

Participant Inclusion Criteria

- Admitted to hospital (current inpatient) or recent exacerbation treated in the community within 14 days with systemic steroids and/or antibiotics.
- Male or Female, aged 40-90 years
- A diagnosis of COPD
- Greater than 10 pack year history
- FEV₁ /FVC Ratio <0.70 at any time point in the last five-years
- Regular sputum production (most days for at least three-months)
- Prescribed optimal pharmacological treatment
- Able to provide informed consent
- CAT score >15

Participant Exclusion Criteria

- Contraindications to OPEP: The use of the device is not recommended in the presence of;
 - Patients unable to tolerate the increased work of breathing
 - Intracranial pressure (ICP) > 20 mm Hg
 - Hemodynamic instability (blood pressure instability)
 - Recent facial, oral, or skull surgery or trauma
 - Acute sinusitis, Epistaxis (bleeding nose)
 - Oesophageal surgery
 - Active haemoptysis
 - Untreated pneumothorax
 - Known or suspected tympanic membrane rupture or other middle ear pathology
- Unable to use OPEP (manual dexterity)
- Unstable cardiac conditions in the opinion of the clinical team

- Life expectancy of less than 12 months

3.10.6 Informed Consent

Written informed consent to enter the study was obtained from patients after explanation of the aims, methods, benefits, and potential hazards of the study through reading the PIS-ICF and having the opportunity to have their questions answered and before any study specific procedures are performed. The procedures performed in advance of written consent were those that would be performed as usual standard of care.

Participation in the study was entirely voluntary, allowing the participant to withdraw at any time and for any reason without affecting their future care or treatment. While they were not obliged to provide a reason, a reasonable effort was made to understand their decision, ensuring full respect for the participant's rights.

Two signed copies of the PIS-ICF and one photocopy were obtained. The signed versions were placed in the patient's case notes and the trial master file (TMF). The photocopy was given to the patient to keep, and references were made to the relevant sections for raising a concern, withdrawing from the study, and GDPR.

The consent form did state that for patients who withdraw consent for any reason, the anonymous data that had already been collected until withdrawal may still be used. A consort flow diagram showing the experience of the research team and the number of participants included at each stage of the process can be seen in Figure 3.24.

3.10.7 Interventions

The following descriptions were provided to the study team and supported by written materials for use during participant contacts.

Oscillating Positive Expiratory Pressure (OPEP) device (Aerobika)

OPEP is a technique aimed at loosening and mobilising secretions it can be achieved by using a device (Aerobika). The device provides pulses of resistance as you exhale acting to open airways and shake secretions, enabling expectoration using a huff and cough technique. Key factors to consider when completing a treatment session are body position, users should be seated, with good posture, in a comfortable position.

Instructions will be given to

- Inhale through the device taking a deeper breath than normal
- A short breath-hold of three seconds
- Exhale actively through the device taking care to keep your cheeks flat and firm, aiming for exhalation time to be three times longer than inhalation
- Aim for 15 breaths in each set prior to performing two huffs and a cough if necessary
- Aim for 5 sets as a minimum or until you complete two sets without expectorating
- Each treatment session should last at least 10 minutes
- Complete once in the morning and once in the evening if experiencing increased sputum load/ symptoms of productive cough
- Complete once a day during times of decreased sputum load / symptoms of productive cough.
- Continuation of your airways clearance regime should continue for the duration of the study

A structured teaching regime was provided to each participant by a specialist respiratory physiotherapist as part of the intervention. The physiotherapists had experience in OPEP and ACBT (both are used routinely in Hywel Dda and in many wards in Cardiff & Vale UHB); in addition, each physiotherapist underwent study specific training in the techniques by the PI and was provided with standardised study instructions and resources.

Active Cycle of Breathing Technique (ACBT)

ACBT is a method of breathing performed in a cycle, used to help loosen and clear secretions from within the lungs. It consists of three different phases.

Phase 1, Breathing control consist of gentle relaxed breathing using your diaphragm. This type of breathing is often useful when tired or breathless. Relaxed breathing is used to decrease airway tightness and improve breathing rate pattern.

Phase 2, Thoracic expansion exercises are deep breaths used to expand the lungs and thereby getting air behind secretions to aid motility. Instructions are given to breathe in slowly through your nose until the lungs feel full; hold the breath, for +/-3 seconds and then breath out gently through your mouth.

Phase 3, Forced expiratory technique, also known as a huff, helps to move secretions centrally so that an effective cough can be stimulated. Take a medium size breath in and then with your mouth open huff from the back of your throat like you are trying to steam up a mirror (see Figure 3.23).

Secretions can be cleared using this cycle alone and a cough should only be performed if secretions are expectorated easily.

- Each treatment session should last at least 10 minutes
- Complete once in the morning and once in the evening if experiencing increased sputum load
- Complete once a day during times of decreased sputum load.
- Continuation of your airways clearance regime should continue for the duration of the study

A structured teaching regime was provided by a specialist physiotherapist as part of the intervention. The physiotherapists have undergone study specific training in the technique and was provided with standardised study instructions and resources.

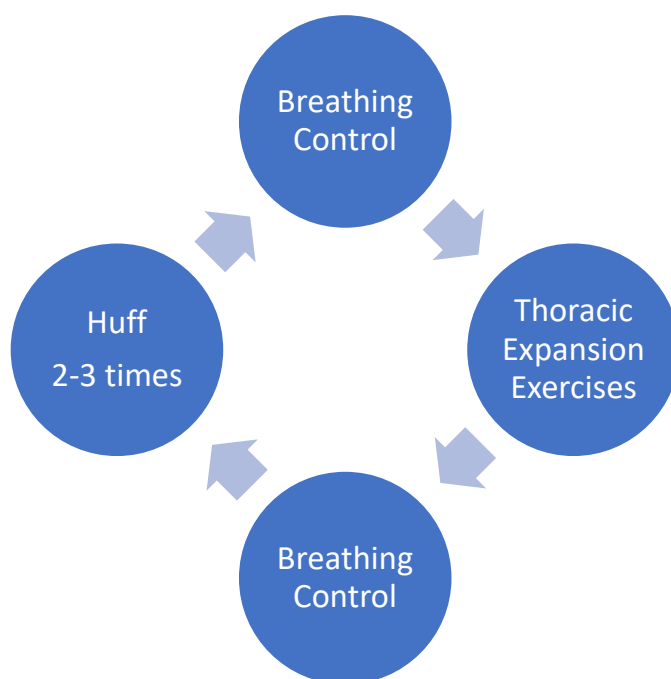


Figure 3.23 ACBT diagram

TIPTOP CONSORT Flow Diagram

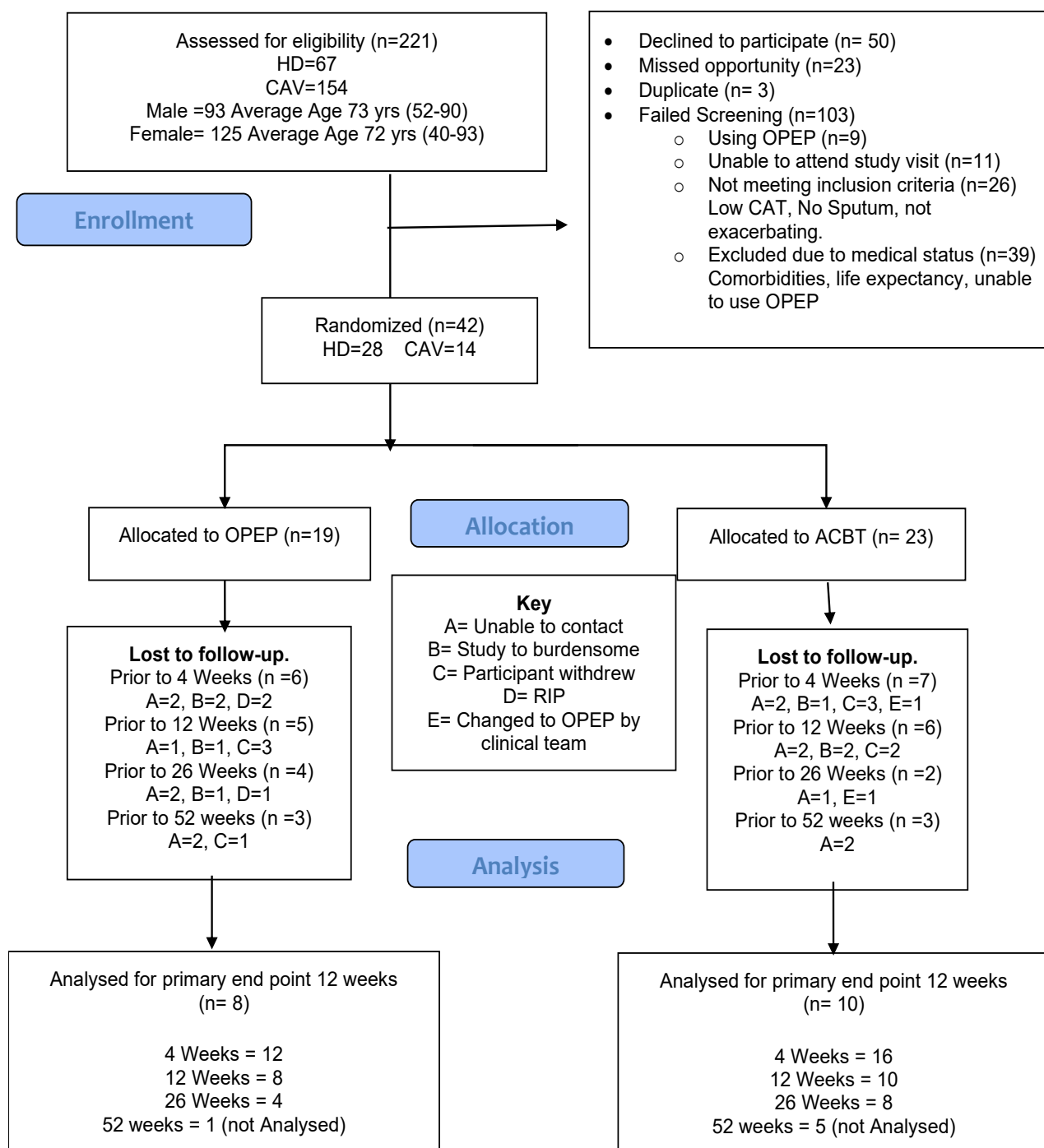


Figure 3.24 TIPTOP Consort flow Diagram

*HD (Hywel Dda UHB) CAV (Cardiff and Vale UHB)

3.10.8 Data collection

At baseline, participants completed several outcome measures as outlined below. Additional data was collected from participants about how many courses of antibiotics (Abx) they had taken in the last 12 months and how many hospital admissions they had made due to an AECOPD in the last 12 months. At each visit, participants were asked to report the number of Abx courses and hospital admissions for a chest infection since the last contact from the study team. This data was self-reported and not verified through clinical record searches.

Follow-up data was collected via the participants' preferred choice, predominantly over the phone. Participants were asked to complete the data before the call and then run through the numerical scoring to transfer the data to the study team. The author conducted all follow-ups. This method was chosen to keep the time of the study visit to a minimum and decrease the risk of inter-observer bias during data collection.

3.10.9 Outcome Measures

Leicester Cough Questionnaire (LCQ)

LCQ is a specific questionnaire designed to assess the impact of chronic cough on an individual's quality of life. It consists of a 19-part questionnaire with a Likert scale (1-7), allows analysis of physical, psychological, and social domains, and takes approximately three-minutes to complete (Berkhof et al., 2012).

Scores for the LCQ are calculated as a mean score from each domain and a sum of the three domains making up the total score, between 3 and 21 (Nguyen et al., 2022), with higher scores indicating better QoL; the physical domain focuses on cough frequency and severity of coughing episodes, sputum production, and the impact of cough on physical activities. The psychological domain explores emotional distress, embarrassment, and frustration associated with coughing. The social domain evaluates the impact of chronic cough on social activities, relationships, and the ability to participate in daily life (Birring, 2003).

The LCQ is commonly used in research studies and clinical practice to assess the severity and impact of chronic cough on an individual's well-being and to evaluate the effectiveness of cough treatments or interventions (McGarvey et al., 2022).

Turner and Birring (2023) report that completing it takes three-minutes. LCQ has been widely used as a primary and secondary endpoint in trials of medications to treat chronic cough and respiratory conditions, including COPD. Franks et al. (2020) identified studies that have used LCQ in studies of ACT, highlighting its sensitivity to these interventions. AbdelHalim et al. (2016) showed improvement in total LCQ score in a 14-day study comparing ACBT to conventional chest physiotherapy during respiratory exacerbations. Murray et al. (2009) found that three-months of twice-daily use of Acapella Choice improved all domains and total LCQ score. In a crossover study of one-week by Herrero-Cortina et al. (2016), LCQ scores improved with the use of AD or PEP, although this improvement did not reach clinical significance.

The MCID for LCQ total score was originally considered to be a change of 2.56 by the developers Birring (2003); subsequent research has suggested a range between 1.3 -2.3 points was noticeable to patients, and the measure has good specificity and sensitivity for predicting improvement in people with a chronic cough (Nguyen et al., 2022; Rebelo et al., 2020). Furthermore, Berkhof et al. (2012) concluded that LCQ is valid for use in those with a chronic bronchitis phenotype of COPD.

LCQ was chosen as the primary OCM for this study because it is a sensitive and valid measure of cough as a symptom that causes a level of burden. A copy of the LCQ can be found in Appendix 5.

COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) was developed specifically for use in COPD. It is a self-administered questionnaire consisting of eight questions assessing the impact of COPD on health status (Jones et al., 2009). It has been validated for use in individuals with COPD (Jones et al., 2009). CAT has been shown as sensitive and responsive to change following AECOPD (Jones et al., 2012). It has been shown to have good internal consistency (0.88-0.98), validity ($p > 0.05$) and responsiveness, with exacerbations increasing scores by 4-5 points. CAT also appears sensitive to changes post PR, decreasing scores by 2-3 points. The minimum clinically important

difference is now reduced and estimated to be 2 points (Gupta et al., 2014; Kon et al., 2014; Rebelo et al., 2020; Schultz et al., 2011). Permission was received from the Mapi research trust to use this OCM. A copy of CAT can be found in Appendix 6.

The eight items of the CAT cover the following domains:

- Cough: Assessing the severity and frequency of coughing.
- Phlegm: Evaluating the amount and burden caused by phlegm production.
- Chest Tightness:
- Breathlessness: Assessing the level of breathlessness during activities.
- Activity Limitation: Evaluating the impact of COPD on daily physical activities.
- Confidence to Leave Home: To engage in social activities.
- Sleep: The impact of COPD on sleep patterns.
- Energy Levels: The impact of COPD on overall energy.

Each item in CAT is scored between 0 and 5, added to provide a total score. The total score can be banded to indicate a level of impact on the responder (Jones et al., 2011).

Score 0-9: low impact of COPD, well-controlled symptoms, and minimal limitations in daily activities.

Score 10-20: moderate impact of COPD, moderate symptoms, and some limitations in daily activities.

Score 21-30: high impact of COPD, significant symptoms, and limitations in daily activities.

Score 31-40: Very high impact of COPD, severe symptoms, and substantial limitations in daily activities.

Quality of Life (QoL) SF-36

The SF-36 is a 36-item scale which measures eight domains of health status: physical functioning (10 items); physical role limitations (four items); bodily pain (two items); general health perceptions (five items); energy/vitality (four items); social functioning (two items); emotional role limitations (three items) and mental health (five items) (Ware & Sherbourne, 1992).

A scoring algorithm converts the raw scores into the eight dimensions listed above. The scores are transformed to range from zero, where the respondent has the worst possible health, to 100, where the respondent is in the best possible health (Burholt & Nash, 2011). It has been validated for use in individuals with COPD (Mahler & Mackowiak, 1995). SF-36 use in evaluating ACT is limited, but one study in bronchiectasis by Üzmezoğlu et al. (2018) reported a change in the physical domain of following twice-daily OPEP or ACBT over four-weeks. A copy of SF-36 can be found in Appendix 7.

Measure of Tolerability and Acceptability

A patient reported measure of adherence, tolerability and acceptability was used to gather data on these aspects of the treatment. The measure was aimed to act as a framework for an open conversation. The brief adherence rating scale was composed of three questions with a Likert scale between 1 and 10, with 1 being disagree and 10 agreeing. A free text section was included to allow the researcher to capture any additional comments. A copy of the measure of tolerability and acceptability can be found in Appendix 8

3.10.10 Statistical analysis

It was the intention to perform data analysis using the intention-to-treat principle, However, due to the large dropout rates prior to the primary end point and therefore statistical challenges of handling missing data a per-protocol analysis was completed; p values <0.05 were considered significant. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) IBM Chicago V29.1. Differences in the primary outcome measures (mean and total score) were tested using ANCOVA, adjusting for baseline scores. Differences in secondary outcome measures and subdomain scores of the CAT and LCQ were tested using ANCOVA, adjusting for baseline scores. If the data was not normally distributed, non-parametric tests were used to compare differences within or between groups, respectively the Wilcoxon or Mann Whitney U test.

Using Chi-squared tests, between-group comparisons of the proportions of patients with or without changes reaching the MCID of the questionnaires were performed. Careful attention to the homogeneity and completeness of the data was paid, and a test for normality was completed.

Sample size and power calculation: Based on previously published data by (Berkhof et al., 2012), we assumed a difference in LCQ between the control Group 13.6 ± 2.8 and the intervention Group 16 ± 3.0 at three-months. It was calculated that 21 patients per group were needed to detect a significant difference (alpha 0.05) with 80% power. A recruitment target of 60 per group allows for dropouts, readmissions, deaths and variable OPEP or ACBT usage.

3.10.11 Demographics

The demographics of enrolled participants are displayed in Table 3.5 and Table 3.6. The data is reported as mean and SD for convenience. It has been tested for normality, analysed with appropriate t-tests or Mann Whitney, and reported in the table footnote.

Table 3.5. Social demographics at base line.

Variable	OPEP (n=19)	ACBT (n=23)	P value=
Age years	66 (10.3)	69.7 (7.3)	0.17 (95% CI -9.3 to +1.7)
Gender (% male)	37 (n=7)	48 (11)	0.54
BMI* kg/m ²	28.8 (11.4)	28.3 (9.2)	0.95
Smoker % current	32% (n=6)	13% (n=3)	0.26
N ^o Comorbidities	2.4	2.0	0.50
Pack years	35.2 (22.8)	36.1 (25.0)	0.92 (95% CI -18 to +16)

Mean (SD) used for convenience but compared with *Mann-Whitney

Social demographic data was normally distributed except for BMI as highlighted with an Asterix. Groups were similar.

Table 3.6. Severity of disease at baseline.

Variable	OPEP (n=19)	ACBT (n=23)	P value=
FEV ₁ %p*	50 (20.3)	44 (18.7)	0.34
Gold E %	100 (n=19)	91 (n=21)	0.26 (Chi Sq)
mMRC*	3.4 (1.0)	3.5 (0.7)	0.78
NIV %	5 (n=1)	4 (n=1)	0.89
SF-36 Physical functioning*	12% (16%)	17% (23%)	0.37
CAT	31.0 (5.4)	32.6 (4.7)	0.32 (95% CI -1.6 to +4.8)
LCQ-Total	10.09 (4.03)	9.64 (2.90)	0.68 (95% CI -2.6 to +1.7)
GP visits	4.0 (5.0)	3.0 (4.0)	0.28
Admissions to Hospital*	1.9 (1.8)	1.3 (1.1)	0.42
Oral steroid courses	4.3 (4.0)	3.3 (2.8)	0.6
Oral Antibiotics*	4.3 (3.4)	3.7 (3.1)	0.57

Mean (SD) is shown for convenience and calculated with *Mann-Whitney. Groups were similar.

3.11 RESULTS

Primary Outcome:

The mean (SD) total LCQ at 12 weeks in the OPEP group was 13.91 (4.31) versus 14.55 (4.59) in the ACBT group, $p= 0.76$ 95% CI -3.9 to +5.1.

The null hypothesis cannot be rejected.

Secondary Outcome:

The mean (SD) CAT score at 12 weeks in the OPEP group was 27.3 (9.2) versus 29.6 (6.6) in the ACBT group $p=0.55$ 95% CI -6.0 to 10.7.

The null hypothesis cannot be rejected.

Table 3.7 shows the LCQ means and SD across time points 0, 4, 12, and 26 weeks and shows improvements in both ACBT and OPEP scores but no significant difference between groups; this is also displayed in Figure 3.25.

Table 3.7 Means and SD of LCQ at each time point.

Group mean (SD)	Week 0	Week 4	Week 12	Week 26
LCQ (ACBT) (n)	9.64 (2.90) (23)	13.68 (3.87) (16)	14.55 (4.59) (10)	15.11 (3.88) (8)
LCQ (OPEP) (n)	10.09 (4.03) (19)	13.13 (3.55) (13)	13.91 (4.31) (8)	15.31 (4.69) (4)
p Value	0.68	0.70	0.76	0.94
95% CI	-2.6 to +1.7	-2.3 to +3.4	-3.9 to +5.1	-5.8 to +5.5

LCQ were normally distributed. Kolmogorov Smirnov and Shapiro-Wilk both $p \geq 0.20$ throughout.

Groups compared with non-paired t-test.

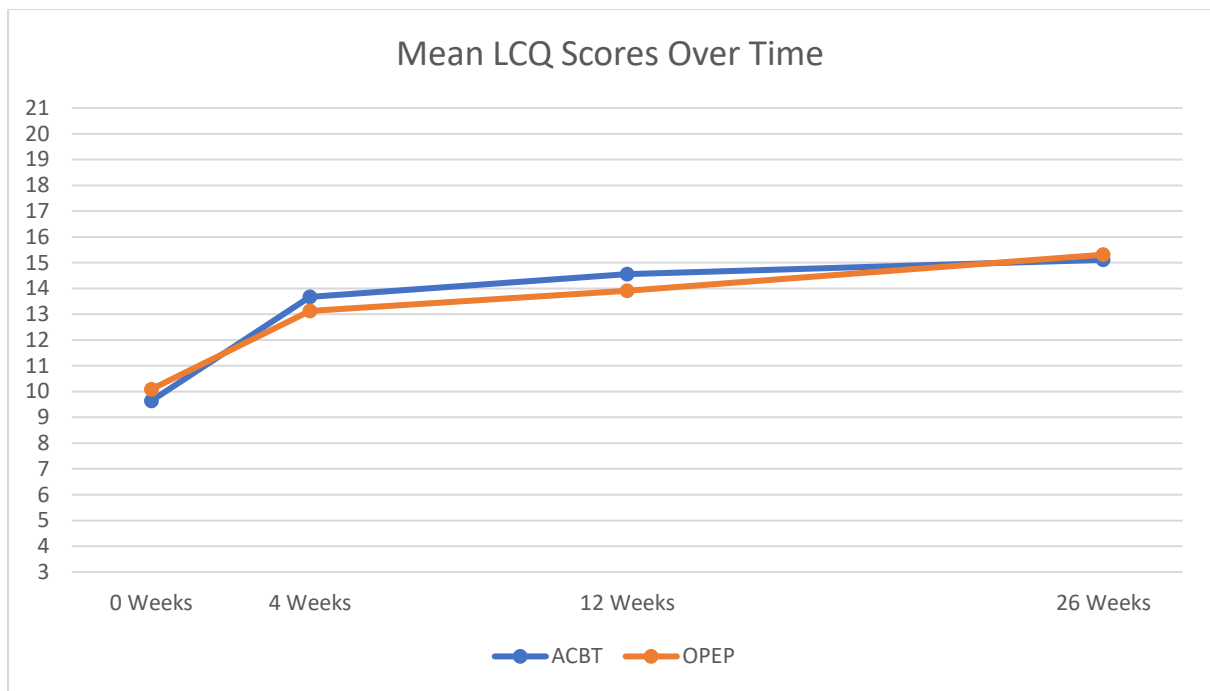


Figure 3.25 Graph of mean LCQ Scores over time

Post hoc analysis of the data showed the responder rates for LCQ in both OPEP and ACBT groups at 0-4 and 0-12 weeks, Table 3.8.

The score changes for individual respondents are shown in the OPEP group (Figure 3.26) and ACBT (Figure 3.27). MCID was set at 1.3 for this analysis.

Table 3.8 LCQ Responder rate percentages

		Responder Rates (%)	
Time Point	OCM	OPEP	ACBT
4 weeks	LCQ	69	56
12 weeks	LCQ	75	80

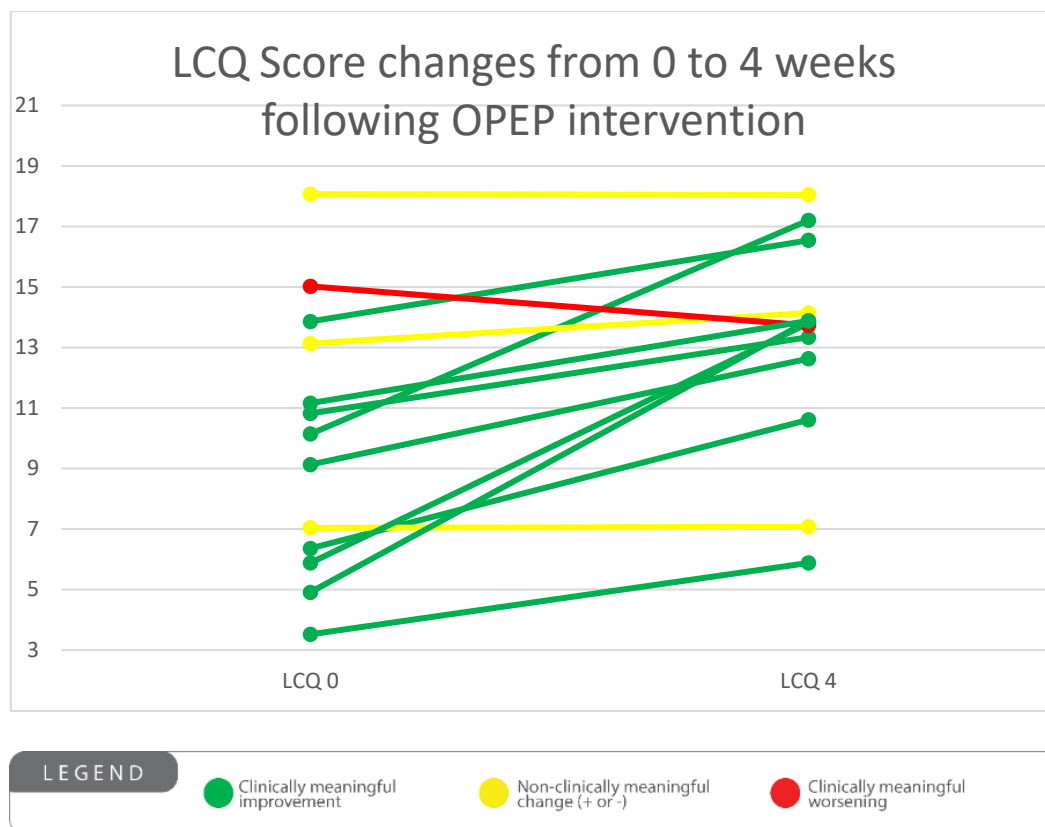


Figure 3.26 LCQ Score changes from 0 to 4 weeks following OPEP intervention

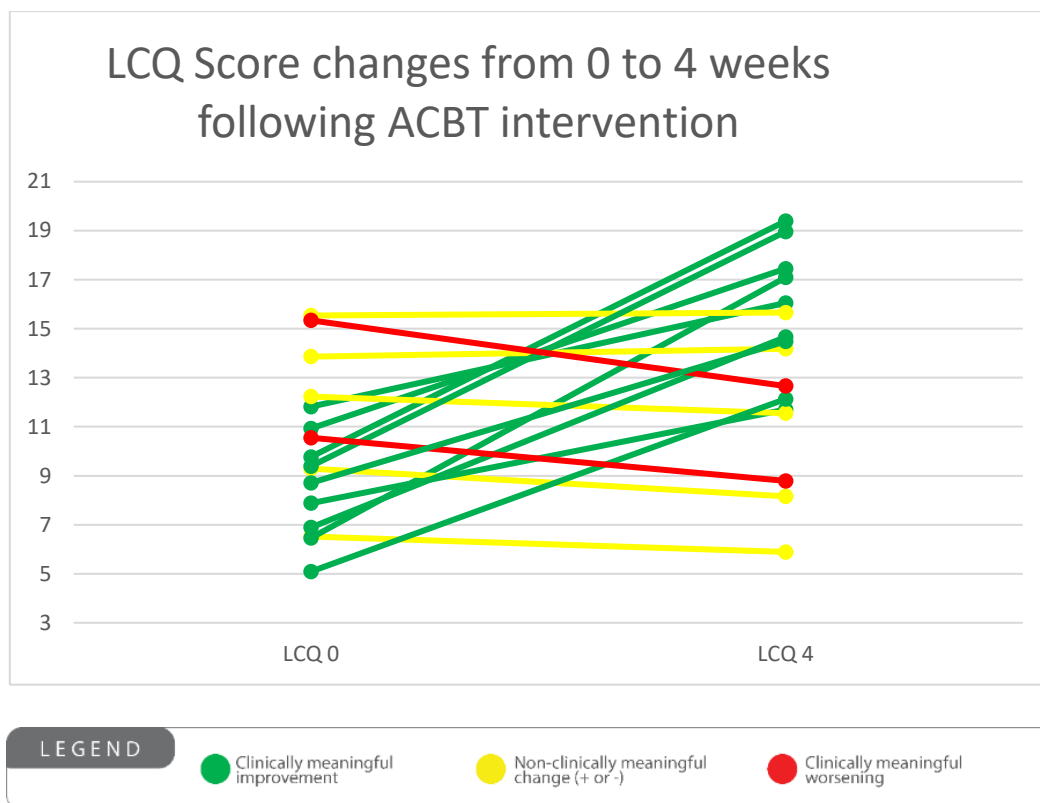


Figure 3.27 LCQ Score changes from 0 to 4 weeks following ACBT intervention

Table 3.9 shows the CAT means and SD across time points 0, 4, 12, and 26 weeks and shows improvements in both ACBT and OPEP scores but no significant difference between groups; this is also displayed in Figure 3.28.

Table 3.9 Means and SD of CAT at each time point.

Group mean (SD)	Week 0	Week 4	Week 12	Week 26
CAT (ACBT) (n)	32.6 (4.7) (23)	29.9 (6.9) (16)	29.6 (6.6) (10)	28.3 (6.5) (8)
CAT (OPEP) (n)	31.0 (5.4) (19)	28.5 (5.8) (12)	27.3 (9.2) (8)	27 (8.5) (4)
p Value	0.32	0.55	0.55	0.81
95% CI	-1.6 to +4.8	-3.5 to +6.4	-6.0 to +10.7	-11.3 to +13.8

Data Normally distributed Kolmogorov Smirnov and Shapiro-Wilk both $p > 0.20$ throughout. Groups compared with non-paired t-test.

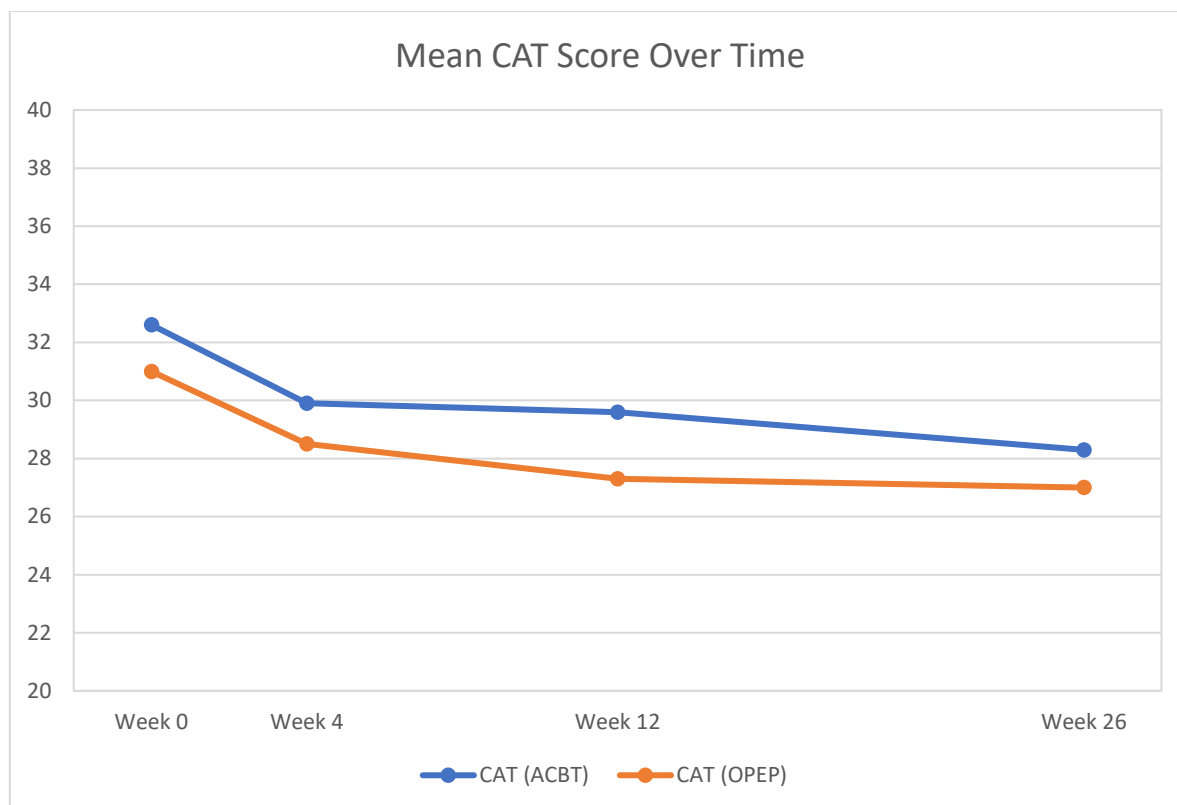


Figure 3.28 Graph mean CAT score over time.

Post hoc analysis of the data showed the responder rates for CAT in both OPEP and ACBT groups at 0-4 and 0-12 weeks, as can be seen in Table 3.10. The score changes for individual respondents are shown in the OPEP group (Figure 3.29) and ACBT (Figure 3.30). MCID for this analysis was 2.

Table 3.10 CAT Responder rate percentages

		Responder Rates (%)	
Time Point	OCM	OPEP	ACBT
4 weeks	CAT	58	25
12 weeks	CAT	63	33

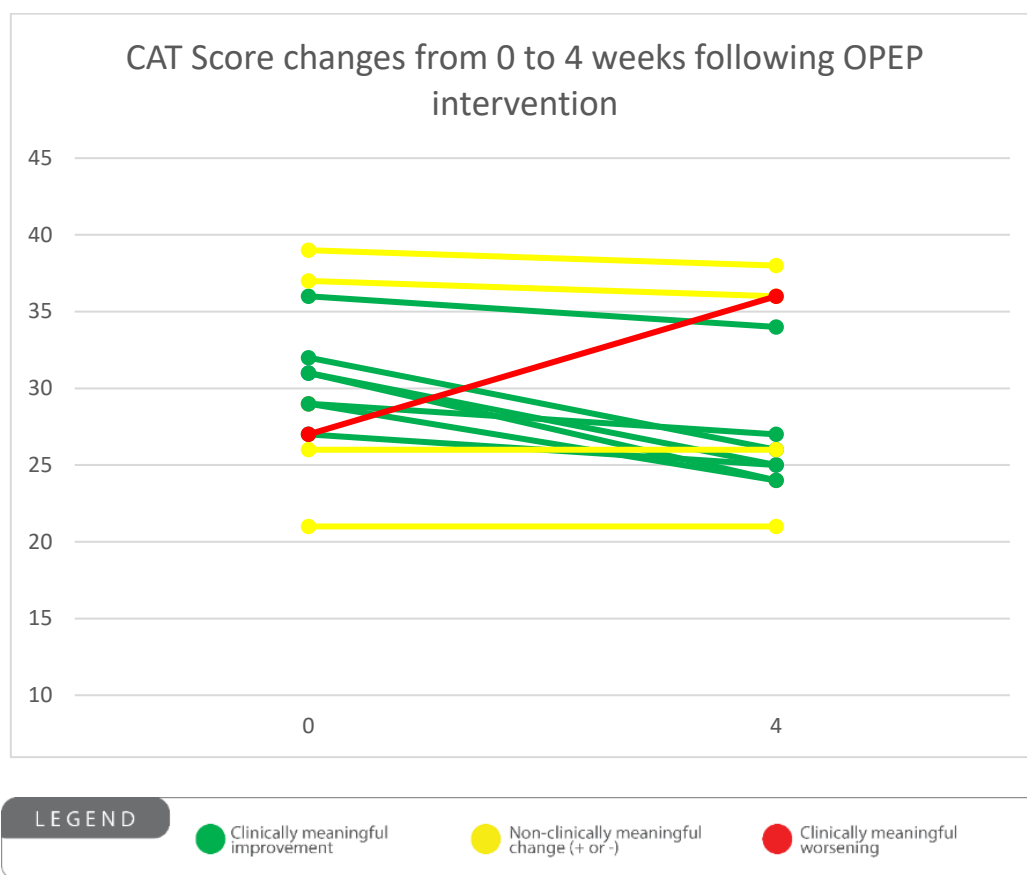


Figure 3.29 CAT Score changes from 0 to 4 weeks following OPEP intervention

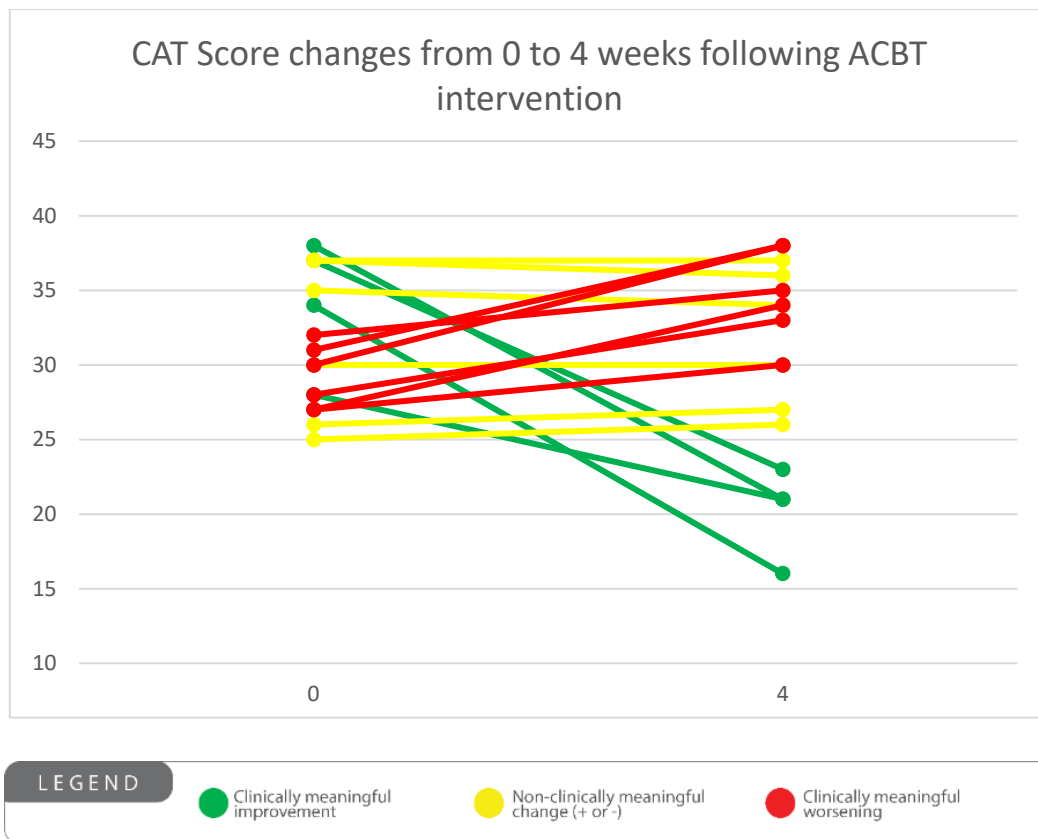


Figure 3.30 CAT Score changes from 0 to 4 weeks following ACBT intervention

Table 3.11 shows the use of antibiotics over time, with time point 0 representing courses used in the 12 months prior to recruitment. Figure 3.31 displays the mean number of courses used since the last study visit. Whilst Figure 3.32 shows cumulative number of courses used between recruitment and study visits.

Table 3.11. Means and SD of courses of oral Antibiotics (ABx).

Group mean (SD)	Week 0	Week 4	Week 12	Week 26
Oral ABx (ACBT) (n)	3.7 (3.1) (23)	0.56 (0.81) (16)	0.67 (1.0) (10)	1.13 (0.99) (8)
Oral ABx (OPEP) (n)	4.3 (3.4) (19)	0.08 (0.29) (13)	0.88 (1.13) (8)	1.5 (1.29) (8)
p Value	0.57	0.17	0.74	0.68

Data expressed as mean and SD but data was non parametric. Groups compared with Mann-Whitney.

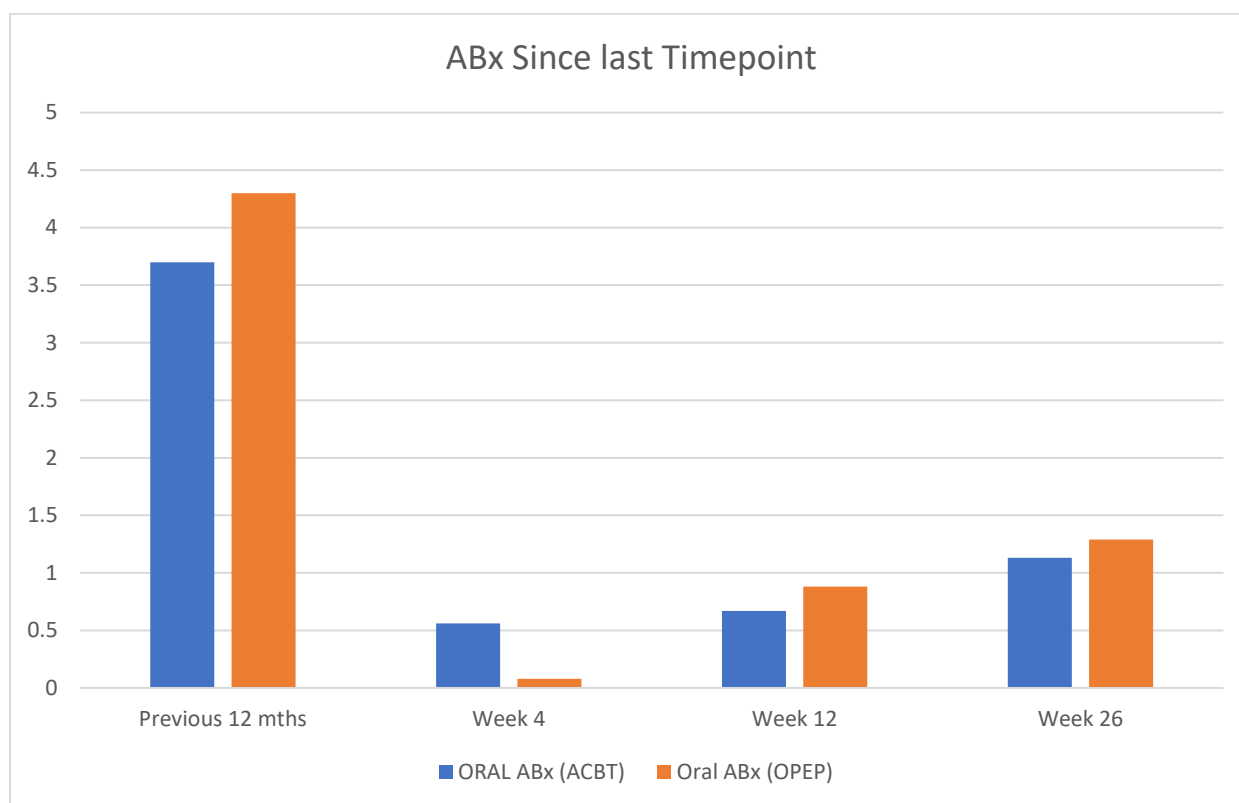


Figure 3.31 Graph self-reported courses of Antibiotics (Abx) since last review.

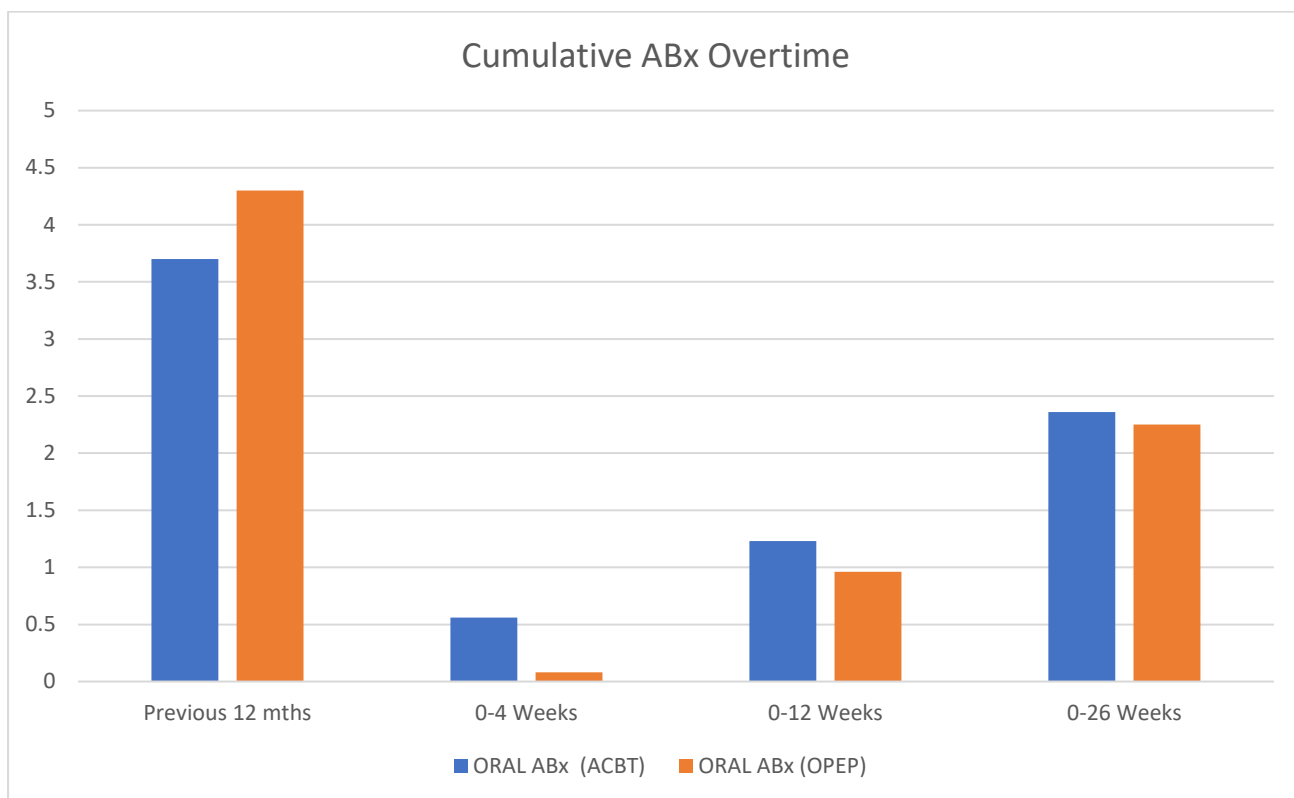


Figure 3.32 Graph self-reported courses of Antibiotics (Abx) Overtime.

Table 3.12 shows hospital admissions over time, with time point 0 representing admissions in the 12 months prior to recruitment. Figure 3.33 displays the mean number of admissions since the last study visit. Whilst Figure 3.34 shows cumulative admissions between recruitment and study visits.

Table 3.12 Means and SD of hospital admissions since last review.

Group	Week 0	Week 4	Week 12	Week 26
Admissions (ACBT) (n)	1.3 (1.1) (23)	0.13 (0.5) (16)	0.22 (0.44) (10)	0.0 (0.0) (8)
Admissions (OPEP) (n)	1.9 (1.8) (19)	0.0 (0.0) (13)	0.13 (0.35) (8)	0.75 (0.5) (4)
p Value	0.42	0.8	0.74	0.048

Data expressed as mean and SD but data was non-parametric. Groups compared with Mann-Whitney.

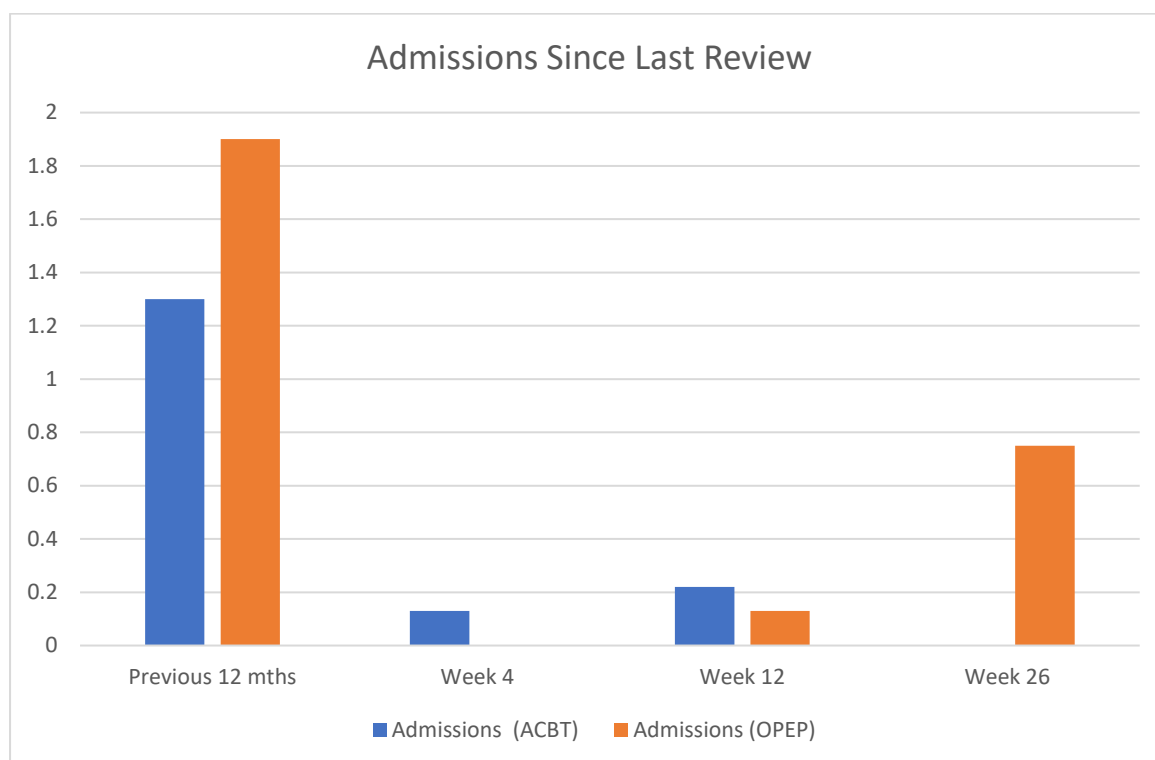


Figure 3.33 *Graph admissions since last review.*

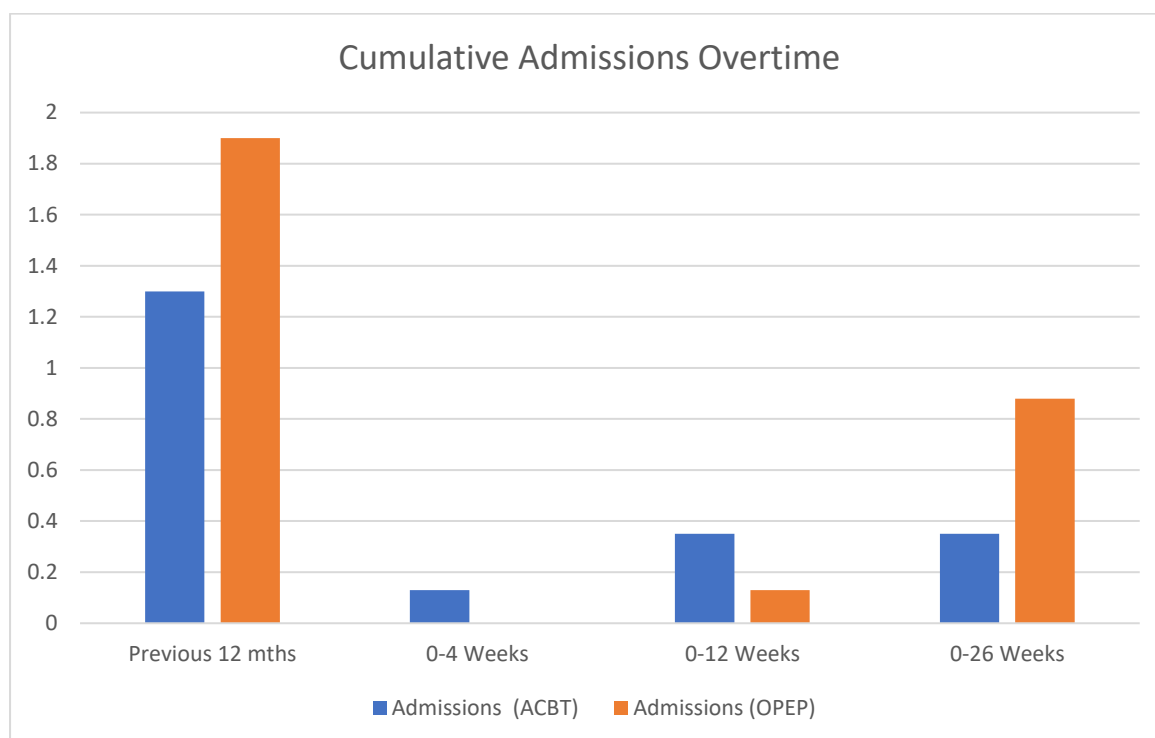


Figure 3.34. Graph cumulative admissions overtime.

Table 3.13 Serious Adverse Events (SAE)

SAE N ^o	ACBT	OPEP	Description	Outcome
1	Yes	-	Hospital admission due to comorbidity	Withdrawn from study
2	-	Yes	RIP	Not related to study
3	Yes		RIP	Not related to study

*All SAE reviewed by an independent clinician

TIPTOP did not record an AE during the trial; the exacerbation data is presented as an expected secondary outcome.

Acceptability and tolerability of intervention.

Participants were asked to score the following questions on a Likert scale (1-10), data from week 4 visit.

- I find doing my treatments difficult (1) easy (10)

Table 3.14 Tolerability of interventions

Intervention	Score >7	Mean (SD)
OPEP (n=13)	62%	7.5 (2.7)
ACBT (n=16)	50%	7.4 (3.1)

- I do not find doing my treatment useful (1) I find doing my treatments useful (10)

Table 3.15 Acceptability of intervention

Intervention	Score >7	Mean (SD)
OPEP (n=13)	77%	7.5 (4.2)
ACBT (n=16)	75%	7.8 (3.2)

3.12 DISCUSSION

Summary of Findings

The main finding of the TIPTOP study is that the use of ACBT or Aerobika was associated with a positive change to LCQ total scores post exacerbation with a clinically important increase (MCID >1.3) from base line at 4, 12, and 26-week time points post AECOPD. However, the primary outcome of difference between groups did not reach significance ($p=0.76$) (Bridges et al., 2023), suggesting equal improvements in both groups. This improvement could be attributed to the natural recovery of participants. Due to the lack of a true control group, it is not possible to isolate the individual effects of the interventions.

Analysis of CAT data also showed a similar pattern with an improvement over time but only achieving a clinically important difference (MCID >2) between baseline and four-weeks, with no significant difference between groups ($p=0.55$).

Post hoc analysis of the LCQ and CAT, using the MCID for each outcome, looking for patterns and trends showed the responder rates for each intervention with OPEP demonstrating responder rates at four-weeks of 69% (LCQ) and 58% (CAT) and ACBT 56% (LCQ) and 25% (CAT). With improvements levelling out and marginally flipping. 12 weeks for LCQ (OPEP =75% ACBT=80%) and remaining the same for CAT (OPEP =63% ACBT=33%) (Bridges et al., 2024). This flip of responder rates could be a result of the limited data available as a result of the per protocol analysis that introduces a higher risk of selection bias.

Other secondary outcomes of courses of oral antibiotics and hospital admissions, as a surrogate for exacerbations, showed a trend in improvement against the previous year with no difference between groups. However, a single significant result at 26 weeks ($p=0.048$) in the admission data can be seen; interpretation of this data is difficult due to the sample size and the reliance on self-reporting across the outcome.

Acceptability and tolerability of both interventions was good with 77% finding OPEP useful, and 75% finding ACBT useful. This shows that both interventions are practically useable and well-received by participants. However, the tolerability of both interventions was lower, OPEP 62% and ACBT 50%. This perhaps indicates the fact

that ACT needs to be effortful and purposeful and is not a pleasant activity to perform.

Comparison of Findings with Literature.

As previously described, all OPEP devices are not equal, with different performance and usage characteristics; TIPTOP is the first study to report a direct comparison between OPEP and ACBT using Aerobika in this population. Whilst both S. M Alghamdi et al. (2023) and Milan et al. (2019) used Acapella in similar studies in COPD, and Sahardin et al. (2023) carried out a single-arm interventional study using Aerobika. All but Sahardin et al. (2023) targeted the chronic bronchitis phenotype of COPD recognising the need for this clearly defined sub-group of patients that would benefit from the use of ACT (S. M Alghamdi et al., 2023; Bridges et al., 2023; Milan et al., 2019).

S. M Alghamdi et al. (2023) and TIPTOP shared a common primary outcome measure of the LCQ, recognising the burden that cough presents in this population. The LCQ scores in TIPTOP changed by +4.91 ACBT and +3.82 OPEP between baseline and primary endpoint (three-months), well above the MCID of 1.3. Whilst LCQ scores reported by S. M Alghamdi et al. (2023) changed by +1.54 in the OPEP group and +0.51 in the usual care (ACBT) group at three-months. Which are lower than TIPTOP but compare with the changes seen between 4-12 and 12-26 weeks.

The use of CAT is more common in the literature, measuring the impact of COPD on health status. S. M Alghamdi et al. (2023) did not move CAT scores in either group above the MCID (>2) from baseline. This difference may have been an indication of the stability of the cohort that S. M Alghamdi et al. (2023) were evaluating whilst patients in TIPTOP were experiencing an AECOPD which meant that a larger shift in CAT scores was seen as the participants were clinically less stable. Sahardin et al. (2023) reported the impact of Aerobika on CAT Score with a mean CAT 19.43 (+/- 7.1) prior to intervention, decreasing to 9 (SD7-14) $p > 0.002$ at 24 weeks. A large, 10-point decrease in CAT score was observed during the study. However, it was unclear if the subjects were stable at the time of recruitment. Although TIPTOP achieved greater than the MCID in both groups between 0-4 weeks further changes were smaller.

At the time of writing, no comparable studies reported responder rates in LCQ or CAT in the literature. Hospital admission data in TIPTOP did not allow us to draw any meaningful conclusions. In a non-interventional retrospective database study, Tse et al. (2020) compared readmission rates over 30 days and 12 months between Aerobika and Acapella and reported a significant difference in favour of Aerobika at both time points ($p=0.01$). Whilst not reporting admission rates, Milan et al. (2019) reported a mean(SD) LoA of 5.1(± 4) days in the treatment (OPEP/PEP) group and 6.6 (± 5.1) in a control group, concluding that OPEP or PEP was significantly better than standard care ($p=0.02$) (Milan et al., 2019).

Discuss and Challenge the Results of Others.

S. M Alghamdi et al. (2023), in an RCT using Acapella, recruited 122 stable COPD participants with 80% having <3 AECOPD in the last year from a UK population. TIPTOP recruited patients experiencing an AECOPD, with the mean number of courses of oral antibiotics in the previous year being 4.3 in the OPEP group. However, the FEV₁ was slightly higher (50%p) in TIPTOP and then in S. M Alghamdi et al. (2023) (38%). LCQ total scores were also closely matched at baseline. Baseline CAT scores were comparable between studies and coincidentally matched in study arms OPEP (31) and ACBT/usual care (33).

S. M Alghamdi et al. (2023) excluded anyone referred to a respiratory physiotherapist in the preceding year for difficulty with sputum. TIPTOP only excluded those currently using OPEP, recognising that this cohort needed a history of sputum production to meet the diagnostic criteria of the chronic bronchitis phenotype and may have sought input or been seen by a respiratory physiotherapist previously.

Although we expected high dropout rates, which was included in the power calculations, the rates of dropout at the primary endpoint was 57% ($n=24/42$) overall, 58% in the OPEP and 57% in the ACBT group, which was still higher than reported by S. M Alghamdi et al. (2023) ($n=19/122$, 16%). This may have been due to recruitment differences, with people in a stable state more likely to commit for the

duration of the study. A summary of S. M Alghamdi et al. (2023) can be found in Table 3.16.

Milan et al. (2019), in a two-part single-centre RCT and cohort study in the USA, recruited 91, 33% male, participants experiencing AECOPD, like TIPTOP, to an interventional study of OPEP (Acapella) and PEP. The primary outcome was LoA, with no data provided on the severity of the participants, limiting comparisons with TIPTOP demographics.

Milan et al. (2019) reported a 0% dropout rate and a high adherence rate to intervention; however, the study only measured the length of stay over a single five-day admission. Long-term adherence to ACT in research and clinical practice is a confounding factor in ascertaining its efficacy. Studies with longer follow up often report high dropout rates presenting a challenge in reaching endpoints, as experienced in TIPTOP. A summary of Milan et al. (2019) can be found in Table 3.16.

Sahardin et al. (2023), in a prospective single-arm trial of Aerobika, lacked a control for comparison, unlike TIPTOP, recruiting from a clinic setting in Malaysia. Baseline demographics of the study reported a very high male cohort of (98%) making the results difficult to extrapolate to a wider population. Whilst the severity data included FEV₁ (52.15, SD 15.65), CAT (low 8.3% Med 53.3%, high 30%, very high 8.3%), and mMRC (>3 was 43%). This compares well with TIPTOP. The primary outcomes of IOS are not comparable to any outcomes in TIPTOP. Sahardin et al. (2023) also reported a 12% dropout rate, which is much lower than we can report.

Interestingly, Sahardin et al. (2023) saw a dramatic improvement, 10 points, in CAT scores, five times the MCID, at 24-weeks which is greater than S. M Alghamdi et al. (2023) and TIPTOP by more than a factor of two. This seems very high and may indicate that the participants were experiencing an AECOPD at recruitment. However, this was not reported, and further judgment on this is difficult in the absence of a control group or comparison to standard care. A summary of Sahardin et al. (2023) can be found in Table 3.16.

Tse et al. (2020), in a retrospective database study in the USA, retrieved 2476 sets of hospital admission data for AECOPD comparing Aerobika and Acapella in a 1:3 matched ratio. Baseline demographics included age (72 years), gender 46% male,

which is a couple of years older than seen in TIPTOP with a comparable gender split. The primary outcome of exacerbation risk in 30 days and 12 months post initiation of OPEP device. TIPTOP gathered real-world data on exacerbation rate as a secondary outcome, but as previously reported, high dropout rates limited the interpretation of these results. However, like many other studies of this type, it only had a single outcome that reported limited details on the homogeneity of the sample. Tse et al. (2020) was a retrospective study, the data used to make these assumptions may lack clinical detail and be prone to reporting and selection bias. A summary of Tse et al. (2020) can be found in Table 3.16.

Table 3.16 Methodologies of recent studies for comparison

Author / Year	Population	Sample	Design	Endpoint	Intervention	Outcomes
S. M Alghamdi et al. (2023)	Stable COPD (Sputum), 80% >3 AECOPD, 62 years, 60% male. FEV ₁ 38%p (26-56)	n=122 Dropout 19/122 (16%)	Single centre, RCT	3mths	OPEP (Acapella) STD Care (inc ACBT)	LCQ (PO), CAT, FACIT*, sputum frequency scale. Objective cough and sleep. LCQ at 3/12 between groups <MCID (p=0.03)
Milan et al. (2019).	Inpatient 1/ AECOPD, 64 years 33%male, BMI 32.6. 2/ AECOPD matched to study 1.	1/ n=91 Dropout 0/91 2/ n=273	1/ RCT OPEP v PEP 2/ Cohort study 1 v standard care 1:2 matched	1/ LoA 2/ LoA	OPEP (Acapella) PEP Cohort	1/ LoA (PO**) no significant difference. 2/ LoA (PO**) 1.5 days less in the treatment group (p=0.02)
Sahardin et al. (2023)	72 years, 97% male, BMI 25, COPD (Clinic) GOLD A(60%), B(33%), E(33%).	n=60 Dropout 7/60 (12%)	Prospective single arm	12 and 24 weeks	OPEP (Aerobika)	IOS (PO), 6MWT, CAT, Exacerbations IOS improved at 12 and 24 weeks.
Tse et al. (2020)	AECOPD (Hospital) 72. years, 46% male. 12mth pre 45% Severe and 46% moderate exacerbation.	1/ n=619 2/ n=1857	Retrospective database study 1:3 matched	30 days and 12mths	1/ Aerobika 2/ Acapella	Severe exacerbation (30 days 1/ 12%, 2/ 17.4% p=0.001) (12mths 1/ 39.6%, 2/ 45.3% p=0.01). Moderate exacerbation.

Study previously described. Table of methodologies and significant results. *FACIT (Functional assessment of chronic illness therapy). **PO (Primary outcome).

Strengths and Weaknesses of Study.

The COPD guidelines NICE (2018) recognise the need for ACBT or OPEP, and the GOLD (2024a) guidelines suggest OPEP in those with muco-hypersecretion. However, there remains only a small body of evidence to inform practice, mainly in the chronic bronchitis phenotype and almost exclusively during stable state COPD. However, the implementation of ACT in AECOPD, when sputum is often worse, is limited. TIPTOP aimed to recruit exacerbators from this population, mirroring clinical practice. The methodological challenges of researching ACT are clear in the literature, and the current study, with designs chosen specifically to answer clear research questions that often create a unique set of challenges in refuting the null hypothesis.

Inclusion and exclusion criteria did not exclude those with co-morbid conditions such as asthma and/or bronchiectasis. As was seen in chapter 2 the Bronch-UK data of bronchiectasis patients contained 34% asthma and 16% COPD showing that these populations overlap. Recognising this and in light of the overall aim of the thesis, researching ACT in those with sputum retention in chronic respiratory health, the homogeneity of a pure COPD cohort was sacrificed in place of those with COPD and sputum retention as a problem, which better aligns with real world application of ACT.

Weaknesses of our study:

We did not achieve the sample size. TIPTOP had access to many potential participants, screening 221 people across healthcare settings, and only 42 of 92 people who met the inclusion criteria consented to be involved. Interestingly we only excluded 26 people for low CAT and non-sputum production. Researching acutely ill people is difficult because of the chaotic (often cramped) environment, busy staff with urgent duties to perform and particularly ill people who, even if they are not confused, are scared and are weak and struggling with breathlessness. Only a larger team recruiting over a much longer period would obtain anywhere near the numbers of 50-100 per group to power the study adequately and likely 100+ per group to allow for study drop-out. This highlights the size of the team needed and the challenge of researching ACT. Nevertheless, TIPTOP provides valuable information

on feasibility, practical learning (in approach and use of clinical collaborators), study design, and valuable pilot data. The design of TIPTOP was to demonstrate any statistical or clinically important difference between two ACT interventions recommended in standard care.

The severity of the population studied can be categorised as suffering from a severe AECOPD, mean CAT ACBT (33) and OPEP (31). COVID-19 played a role in forcing this decision as at the start of the recruitment window we felt it appropriate to recruit from those already needing healthcare input. All participant in the trial were expected to have a CAT >15 this was introduced in the substantial amendment to included recruitment from acute to community settings. The high CAT was set to encourage homogeneity of the sample. However, this may have led to a number of unintended consequences including: a number of dropouts as the burden of illness and research participation was too great, and a large swing in the OCM's as people recovered. All participants were able to complete the interventions and increased work of breathing was not reported as an issue.

Losses to follow-up:

An HCP conducted follow-ups with experience in prescribing and teaching ACT; therefore, participants were offered the additional opportunity to review the ACT technique as part of the process. We felt that this was the ethical thing to be done. However, this may have led to an increased dropout rate as the participants developed a therapeutic relationship with the researcher and may have increased the feelings of guilt at not maintaining adherence. To ensure that the participants did not feel overburdened by the research protocol, every effort was made to ensure that data was collected. This included working evenings and weekends to fit in with patients' work and social lives and even cycling 10 miles in the wind and rain to recruit participants who could not attend research visits.

This study was conducted as the restrictions from the COVID-19 pandemic were still affecting clinical care, with follow-up visits performed virtually or over the phone, limiting the collection of sputum volume as an OCM. Interestingly, the participants requested phone call follow-up rather than video conference, with a proportion of the cohort not having a mobile phone, two participants preferred to return the OCM data

to the hospital personally. This highlights the disparity in digital equity in this population, with Alghamdi et al. (2023) able to complete all follow-ups using video conferencing calls.

Not blinded and overlapping interventions:

Those analysing data were aware of group allocation. Unfortunately, adequate funding was not available to resource a dedicated statistical team or independent physiotherapist to ensure at least single blinding.

The nature of ACT means patients will not be blinded as the treatment involves active participation. However, several solutions could be considered to mitigate this. Firstly, using a randomised cross-over trial (three-months for each technique), but that is labour intensive and can be affected by interim AECOPDs and disease progression. Secondly, a double-dummy placebo RCT would be ideal with the use of 'OPEP and a sham ACBT' or 'ACBT and a sham OPEP', but this would be very expensive and intensive for both the research team and participants. Thirdly, offering OPEP versus sham OPEP, half not getting any ACT, would be difficult to get through ethics as you are withholding a guideline-recommended treatment in half the patients. All these options were considered and discussed by the research team during the inception of the study.

The application of ACBT and OPEP in ACT often presents an area of functional and mechanistic overlap, which warrants nuanced discussion in both research and clinical practice. However, this is an inherent issue in all ACT trials as a huff cough clear technique is often required to expectorate sputum. The pragmatic design of the trial uses the interventions as would be delivered in clinical practice. However, effect sizes may be small in overlapping interventions therefore this increasing the importance of a well powered, large sample size, trial. A larger samples size would also allow subgroup analysis to identify the effect in different disease severities or adherence levels.

Strengths of the study:

Real-world:

During the study design phase, it was important to the research collaborators that TIPTOP collected real-world data that closely tracked patients' experiences in NHS Wales. Data collected during RCTs have been shown only to represent a narrow patient group, with real-world RCT representing a wider spectrum of comorbidities and lifestyle factors (Price et al., 2015). COPD guidelines are often informed by RCT where the data is less applicable to a wider population, with often large subgroups excluded from the trials (Krishnan & Calverley, 2022; Wing et al., 2018). (Whittaker et al., 2024) highlights that 11.2% of real-world patients would be eligible for studies of triple therapy inhalers due to age, co-morbidities, and current treatments.

Inpatient and outpatients:

The first half of the recruitment window concentrated on screening patients who had been admitted to hospital for AECOPD; however, due to low recruitment numbers an amendment was submitted to include a pathway for outpatient and emergency visits to be included as potential participants. This increased the numbers of patients that we were able to screen particularly in the site that we had the resource available to visit and screen in the emergency departments. The aim was to perform a post-hoc analysis of the subgroups, according to pathway, to evaluate the differences between the two pathways. Unfortunately, due to the overall recruitment, the sub-analysis was not possible.

Two-centres:

The aim was to establish this study in a single centre and then work to introduce a second centre. The research team felt that this would improve the rigour and external validity of the study. A meta-epidemiological study by Bafeta et al. (2012) reported that single-centre studies reported larger treatment effect than multicentre trials. Postulating that multi-centre trials had higher methodological quality and were less prone to publication bias. Bellomo et al. (2009) warns of the folly of using single-centre trials to inform wider practice as the research often has methodological floors that are specific to context and are less generalisable.

Way Forward

Although ACT is valued by HCPs and seen as an important treatment for people with COPD and a chronic bronchitis phenotype, further research and larger trials are needed to build a more robust evidence base. More research is also needed on why dropout rates are so high in ACT trials.

The next iteration of TIPTOP should explore options that enable a true measure of adherence and quality of ACT sessions and how ACT can be affected by immediate prior use of bronchodilators. The development of smart devices to capture this data may make this possible. Study design should capture OCM data that is meaningful to patients, better usage of routinely available health care utilisation data, and clinical measures endorsed by the research community to answer the specific research questions. Also, a less severe population may alleviate the high dropout rate and a flexible approach to data collection of follow up data using digital technology.

Conducting this study has given an insight into the complexities of collecting data on ACT with the NHS Wales ecosystem. Although the data collected from TIPTOP was unable to show a difference between the interventions, the sub analysis of responder rates and demonstration of improvements post AECOPD in this patient group. This has prompted dissemination to national and international audiences, informing the ongoing conversation around ACT in chronic respiratory health. Locally, it has informed quality improvement projects evaluating the provision of services to address the burdensome symptom of muco-hypersecretion in this patient group. Added to this research, collaborations initiated by this research have allowed the authors involvement in other projects in this research area.

Summary

The inception, creation and completion of TIPTOP over the last four years have been full of learning from the unique challenges of conducting research during a global pandemic and researching ACT in COPD within NHS Wales. This was the first real-world RCT trial comparing Aerobika and ACBT in COPD chronic bronchitis and the first investigator-led multi-centre trial of ACT in NHS Wales in the 2000s

The results from this chapter (TIPTOP) highlighted the practical and methodological challenges of delivering and evaluating airway ACT during acute exacerbations of COPD. Although both ACBT and OPEP showed clinically meaningful improvements from baseline, no statistically significant differences were observed between groups. This may reflect the overlapping mechanisms of the techniques, variability in delivery and adherence, and issues related to recruitment and retention. These findings reinforced the importance of understanding how interventions are used and experienced in real-world settings. The next chapter (CONNECT) builds on this by exploring the perspectives of patients and healthcare professionals on OPEP use, with a particular focus on the Aerobika device. The study also considers the potential role of smart technology in supporting adherence and remote monitoring. This qualitative approach offers new insight into the practical application and perceived value of OPEP, complementing the clinical findings from TIPTOP. Together, the studies provide a broader understanding of both the outcomes and the lived experience of airway clearance, with implications for future research, service design, and device development.

4 STUDY: CONNECT: THEMATIC QUALITATIVE ANALYSIS OF AEROBIKA AND SMART CONNECTED AEROBIKA IN CHRONIC RESPIRATORY CONDITIONS.

In this study, people with chronic lung conditions and the healthcare professionals who care for them were invited to give their opinions and thoughts on the use of OPEP (Aerobika). We further explored feelings about using smart technology and the data it creates to aid healthcare within the context of the imminent development of a smart 'connected' Aerobika.

The next generation Smart Connected Aerobika (internal communication Trudell Medical International) aims to offer a visual feedback interface to enable greater awareness of changing symptoms and treatment quality and aid self-management. The interface's aim, akin to a performance dashboard, is to empower patients to take more control of their condition and allow them to provide HCPs with accurate, personalised data during clinic consultations. The smart-connected Aerobika devices are still in development and are not yet routinely available in clinical care. However, proposed smart components will see a sensor on the device that is able to measure several metrics; flow, frequency, amplitude and pressure that will allow feedback both in real time to the user and through an app on a smart phone. The app on the smart phone will allow users to monitor adherence and trends in the data and share it with healthcare providers including respiratory physiotherapists to modify treatment technique.

4.1 INTRODUCTION

Previously, in this thesis, it has been outlined the literature and landscape that ACT and particularly OPEP holds in chronic respiratory health. Chapter 2, Bronch-UK, describes the value of ACT in bronchiectasis, outlines the level of usage in the UK, and supports the premise that it is an important treatment for patients and HCPs. Chapter 3, 'TIPTOP', reported results from a quantitative study and highlighted the need for more research using outcomes that matter to patients. There is little literature evaluating the lived experience of those who have experienced it. This

study adopts a qualitative approach to understand barriers and facilitators to the use of Aerobika for patients and professionals.

Whilst CONNECT is grounded in academic qualitative research its aims, methods, and outputs directly align with the objectives and practices of applied health market research. This can be seen through the common themes of product development, user experience and adoption and adherence strategies. Thematic analysis is useful in both of these domains as it captures authentic and professional feedback (Braun & Clarke, 2019; Greenhalgh et al., 2017). The insights hope to inform development of the smart OPEP device and supporting strategies for its implementation across healthcare settings.

4.2 BACKGROUND

The literature reporting the experiences of those using OPEP therapy is limited, with data from HCP and expert panels making up the majority of studies, with far fewer studies reporting patient views and experiences. The physiological rationale and a description of the different techniques used for airways clearance including OPEP have been described previously. The place that ACT holds in the guidelines for conditions with muco-hypersecretion can be found in chapters 1, 2 and 3. In summary, ACT appears to be an important adjunctive treatment in those with a chronic lung condition who struggle with mucus hypersecretion. However, although safe with no apparent long-term side effects (see side effects of, e.g. oral and inhaled steroids), ACT can be an effortful, burdensome and time-consuming treatment that requires significant diligence from the patient and regular support and often ongoing training and assessment from specialist HCP.

Herrero-Cortina et al. (2023) in a position statement from the ERS on ACT, discussed the perceived barriers and enablers to the use of ACT in adults with bronchiectasis. A review of the *qualitative* literature concluded that barriers from the patient's perspective included the burden of treatment, lack of perceived benefit and motivation. Whilst enablers included the development of individualised management plans, the recognition of disease burden and working with the HCP were recognised. Herrero-Cortina et al. (2023) the authors went on to describe HCP views, including their frustrations with the availability of resources, including time, space and access

to OPEPs. Enablers for HCP were working collaboratively with patients and implementing codesigned management plans.

Several RCTs have collected acceptability and tolerability measures of ACTs but only as secondary outcomes. Nayak et al. (2018), in a cross-sectional study of 140 people (31% male, mean age 57 years) with bronchiectasis in India, looked at different types of ACT reporting that OPEP was rated efficient, convenient, comfortable and cost-effective by 100% of respondents and was given an overall satisfaction rating of 97.5%. Naraparaju et al. (2010), also in India, in a comparator study with an inspiratory muscle trainer in bronchiectasis, recruited 30 patients (10 male, mean age 50.67 years) reported a slight increase in sputum volume in the OPEP group and a preference for the use of OPEP for airways clearance. Semwal et al. (2015) reported preferences for the use of OPEP against AD in a direct comparison of the two techniques in the same session in bronchiectasis in India (30 patients, 20 males, age 46.2 years). The use of OPEP was acceptable in a survey with 92% of a cohort of 176 people with COPD or bronchiectasis and 87% of respiratory physiotherapists prescribing the device were happy or very happy with it (Bracey et al., 2019).

DeSoyza et al. (2022) searched electronic databases, including CINAHL, Embase, Medline, Google Scholar and the Cochrane Library to inform a review article examining the breadth of data to support the delivery and sustainability of using ACT for people with non-CF bronchiectasis. No studies were identified in the literature highlighting the importance of RCTs comparing different ACT techniques. They called for more work on HRQoL measures and other surveys, such as those used by McLeese et al. (2023), to create a picture of use, adherence and factors influencing long-term and continuous use of ACT. Pan et al. (2023) concluded there is a need for more quantitative and qualitative data that records the needs and lived experiences of those using ACT as well as quantitative clinical outcomes.

Knox et al. (2021) evaluated the usability and acceptability of a self-management app for COPD, conceptualising users' experience to inform the future development of a digital interface in healthcare. Although this did not directly link to ACT, it provides an insight into the use of smart connected devices. Knox et al. (2021) invited patients

with COPD from Breathe Easy groups in Wales to attend a focus group that owned or had access to a smartphone. 11 patients, three female, age 66.5 (+/-5.7) years, FEV₁ 52.1 (+/-19.8) % predicted attended the focus group answering questions relating to the app. The themes developed included the app being easy to use, the data needed to be useful, and the fact that this would be a barrier to engagement if the app became more complicated. This study demonstrates that participants are willing to engage in discussions about treatments and future developments of connected technologies.

Health Technology Wales (HTW) examined the clinical and economic impact of oscillating positive expiratory pressure (OPEP) devices, such as Aerobika, while noting the importance of contextual, real-world evidence to guide implementation decisions (Health Technology, 2020). The HTW appraisal used a combination of research and economic evaluation alongside expert opinion through interview. HTW reported potential benefits for certain subgroups but noted the need for user centred evidence on acceptability and real-world implementation. Greenhalgh et al. (2017) work on the non-adoption and abandonment of health technologies also highlights the significance of understanding patient and clinician attitudes of digital innovations. These studies highlight the overlap between applied qualitative health research and market research in the context of medical devices and self-management tools. CONNECT study builds on this approach by generating qualitative insights into the usability, acceptability, and perceived value of smart airway clearance technologies, contributing to both academic knowledge and practical innovation in respiratory care.

Research methods

The value of qualitative research is that it provides a deep understanding of a complex phenomenon within a context that the researcher can set. Data can be collected that explores participants' meanings, experiences, and perspectives in a way that quantitative methods cannot cover. Qualitative methods allow the development of theories grounded in real-world experiences (Creswell & Poth, 2017).

The use of focus groups in this context allowed the collection of data to gain a deeper understanding of the psychological and sociological aspects surrounding the subject (Merton, 1987). Synchronously collected data from focus groups have previously been used to gather group-specific information as participants can listen and respond to each other's comments to reveal rich insights that may not be elicited from individual interviews (Krueger, 2014).

Online focus groups are an effective way to access the desired population and overcome barriers such as distance, time, and other social barriers to face-to-face groups. This has become increasingly popular as internet access and digital literacy has become ubiquitous (Kite & Phongsavan, 2017). The COVID-19 pandemic may have further popularised this. However, although virtual data collection is popular, the effect that this will have on the sample should be considered during the analysis (Lathen & Laestadius, 2021).

The literature suggests the size of focus groups varies, with larger groups enabling a wider range of experiences to be gathered, whilst smaller groups can be more useful when discussing emotional or highly charged topics, including healthcare (Tran et al., 2021).

4.2.1 Objectives

This project aimed to assess the lived experience of Aerobika users through focus groups with HCP and patient groups. The project intended to fully explore the issues around the use of a next-generation device, Smart Connected Aerobika, using thematic analysis.

See Table 4.1 for key questions and links to why thematic analysis was chosen.

Table 4.1 Connect research questions and TA linkage

CONNECT Research Question	Thematic Analysis Linkage
1. How do patients and HCPs experience the use of the Aerobika device?	Enables exploration of subjective experiences across diverse contexts, allowing themes to emerge from participants.
2. What are the perceived barriers and facilitators to using the Aerobika and Smart Connected Aerobika?	Identifies patterns across user groups, capturing barriers (e.g., cost, technique, IPC) and facilitators (e.g., effectiveness, reminders).
3. How do patients and HCPs perceive the role of monitoring and feedback in supporting adherence?	Captures nuanced views on monitoring (e.g., manometer use, self-tracking), allowing for the development of practice-oriented themes.
4. What are the views on using a smart device to track ACT use and provide feedback?	Allows for the interpretation of complex, evolving views on digital health technologies, including ethical and practical considerations.

4.3 METHODS

Semi-structured focus groups were conducted with the patients and HCP participants to facilitate conversation regarding OPEP use and Smart Connected Aerobika.

The group was led by an experienced qualitative researcher in addition to an observer and was audio-recorded for transcription. The focus group began with introductions to help develop a positive relationship between the participants and the researcher. This method is supported by Spradley's (1979) model of interviewer-interviewee rapport and helps progress through the apprehension stage to the exploration stage (Berner-Rodoreda et al., 2020). Once introductions had been completed, questions were asked about the usability and acceptability of OPEP use and smart connected Aerobika. The focus group lasted 60 +/- 10 minutes. If at any time a participant became breathless, they were reminded that they could pause or stop participating entirely.

4.3.1 Approvals and Funding

Ethical approval was sought from Swansea University Medical School (SUMS) Research Ethics Sub-Committee, and approval was granted on the 7th of December 2022, see Appendix 11 The study was conducted outside of the NHS with participants self-selecting from advertisements; therefore, ethical approval from SUMS was all that was required.

The study was discussed at the Respiratory Innovation Wales (RIW) patient public involvement forum in October 2022 and received positive feedback from the group. Comments from the group included offering gift vouchers for participant involvement and a suggestion that an online forum would increase uptake. These suggestions were embedded in the study design.

Funding for CONNECT was provided by Trudell Medical International (TMI) to help inform market research for product development. This funding was managed in the

same way as the PhD studentship by RIW. Funding allocated to this study included time for the research team (£3K), administrative help, Creation of advertising materials (£1K) and funding of gift vouchers for participants (£300). TMI had no direct financial dealings with the study team or participants.

4.3.2 Focus group process

Participants were asked for a preference for online or face-to-face attendance during the first screening questionnaire, with 92% choosing online. The focus groups were organised and conducted using Microsoft Teams / Outlook/ Forms. Prior to the focus groups, a short questionnaire was sent to participants to gather demographic data. Participants were also provided with an outline of the behavioural and procedural expectations during the sessions and some instructional videos and marketing material on the device for them to consider prior to the focus group, see Appendix 10. Verbal consent was gained at the start of the sessions for recording and transcription. The author conducted the focus groups as lead facilitator with a second experienced qualitative facilitator present to sense check and aid the smooth running of the sessions. Research collaborators from TMI, who were present during the sessions, were introduced at the start and then asked to turn off their cameras to allow a spotlight on the other contributors.

4.3.3 Thematic Analysis

A thematic analysis was undertaken to explore the views of people with chronic respiratory conditions and the healthcare professionals who support them. This approach was selected to allow rich, detailed insights to emerge from the data without imposing a pre-determined theoretical framework. The method was guided by the principles set out by (Braun & and Clarke, 2006; Braun & Clarke, 2014; Braun & Clarke, 2019) and allowed for the identification, analysis and reporting of themes across the dataset.

This study adopts a realist experiential epistemological position within a critical realist ontological framework. It assumes that participants' accounts reflect real

experiences, while acknowledging that those experiences are affected by language and interpretation. The analysis was both inductive and reflexive, with themes developed from participants' accounts without reliance on predefined frameworks. This approach enabled the data to guide the process, while also recognising the researcher's active role which is consistent with the principles of reflexive thematic analysis (Braun & Clarke, 2019).

All recordings were transcribed verbatim using the play script method, where pauses, emphasis and notable expressions were annotated to help retain context. Transcripts were anonymised, stored securely. The researcher read each transcript multiple times to become familiar with the content before beginning initial coding.

The process followed Braun and Clarke's six stages of thematic analysis:

Familiarisation

Repeated reading of transcripts and early memo-writing.

Generating initial codes

Carried out inductively, coded to identify content directly relevant to the experience of OPEP and Aerobika use. Coding was performed line-by-line to ensure attention to detail.

Searching for themes

Involved organising codes into broader categories that reflected meaningful patterns. Initial groupings were developed into a provisional thematic map (see figure 4.1).

Included team discussions and refining themes based on internal coherence and relevance to the research questions.

Defining and naming themes

Five final themes captured key facets of the data: Device Choice, Learning and Teaching, Doing, Monitoring (Compliance and Adherence), and Smart Devices – Tracking and Monitoring.

Familiarisation and generating initial codes were conducted by each researcher separately.

Provisional Thematic map

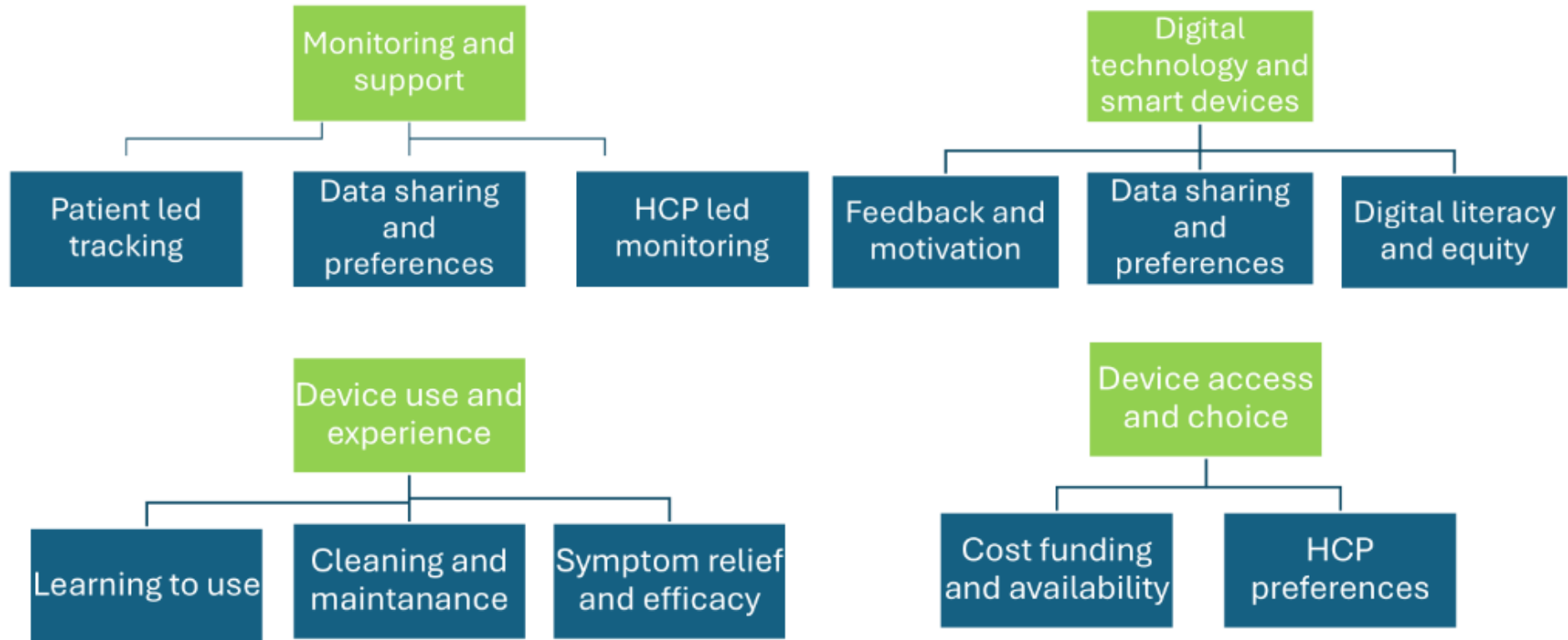


Figure 4.1 Provisional Thematic map

Producing the report

Included mapping the themes and subthemes against the original research questions, using direct quotations from participants to illustrate key points.

Themes were developed with input from a second qualitative researcher to provide a 'critical friend' perspective and to challenge assumptions. Final themes were chosen for their relevance to the research aims and consistency across the dataset. A final thematic map (see figure 4.4) was developed. Tables were produced to summarise key subthemes across the patient and HCP datasets.

The focus was on surface level meaning rather than latent content, in keeping with the study's intention to reflect participants expressed views and experiences. This analysis was suited to the exploration of usability and acceptability, areas which require patient- and clinician-led insight to inform future device development and implementation.

Reflexivity was integral throughout the process. The lead researcher (CB) acknowledged their professional background in respiratory physiotherapy, which may have influenced both data collection and interpretation. Reflexive notes and peer debrief were used to minimise undue influence and maintain analytical rigour.

The application of thematic analysis in this context enabled the project to capture patient and HCP views on current practice and future developments with smart OPEP technologies. This was especially important given the evolving nature of self-management in chronic respiratory care and the growing role of digital health interventions.

Additionally, Yardley's (2000) four characteristics of good quality qualitative research in a health domain (sensitivity to context, commitment and rigour, transparency and coherence, and impact and importance), have become accepted criteria to assess qualitative research validity (Robinson, 2014; Tindall, 2009), were adhered to.

Non-harm

Participants were monitored for stress or discomfort during the focus group sessions. They underwent no examination or medical procedures, so we believe this was a low-risk study. It was agreed that anyone who showed any distress during the

process could debrief with the research team. During the process of the study, no incidence of distress or harm was noted /or recorded.

Justice

All participants meeting the inclusion criteria were eligible, encouraging equity of access across geographical locations.

Autonomy

The participant information sheet and consent form (process) emphasised that participation was voluntary and that they could have withdrawn at any time.

Confidentiality

All audio and transcription data were anonymised and coded, so no individual was identified in the final report. The audio and transcribed Word documents were stored in a digital repository for 10 years, encrypted and password-protected after the completion of the study. Once ten years have passed, the data will be deleted, as per the requirements of the SUMS Research Ethics Sub-Committee. GCP principles were adhered to throughout the study.

4.3.4 Recruitment

Advertisement of the study was conducted via social media with RIW, TMI, PCD Support UK, Association of Chartered Physiotherapists in Respiratory Care (ACPRC) and Asthma and Lung UK all promoting the study by posting an e-poster (see Appendix 12) on their social media platforms X (formally Twitter), Facebook and via supporters' networks, see Figure 4.2. As can be seen in Figure 4.3 the response rate to the e-poster came in two waves, corresponding with the first 24-48 hours after its release on social media.

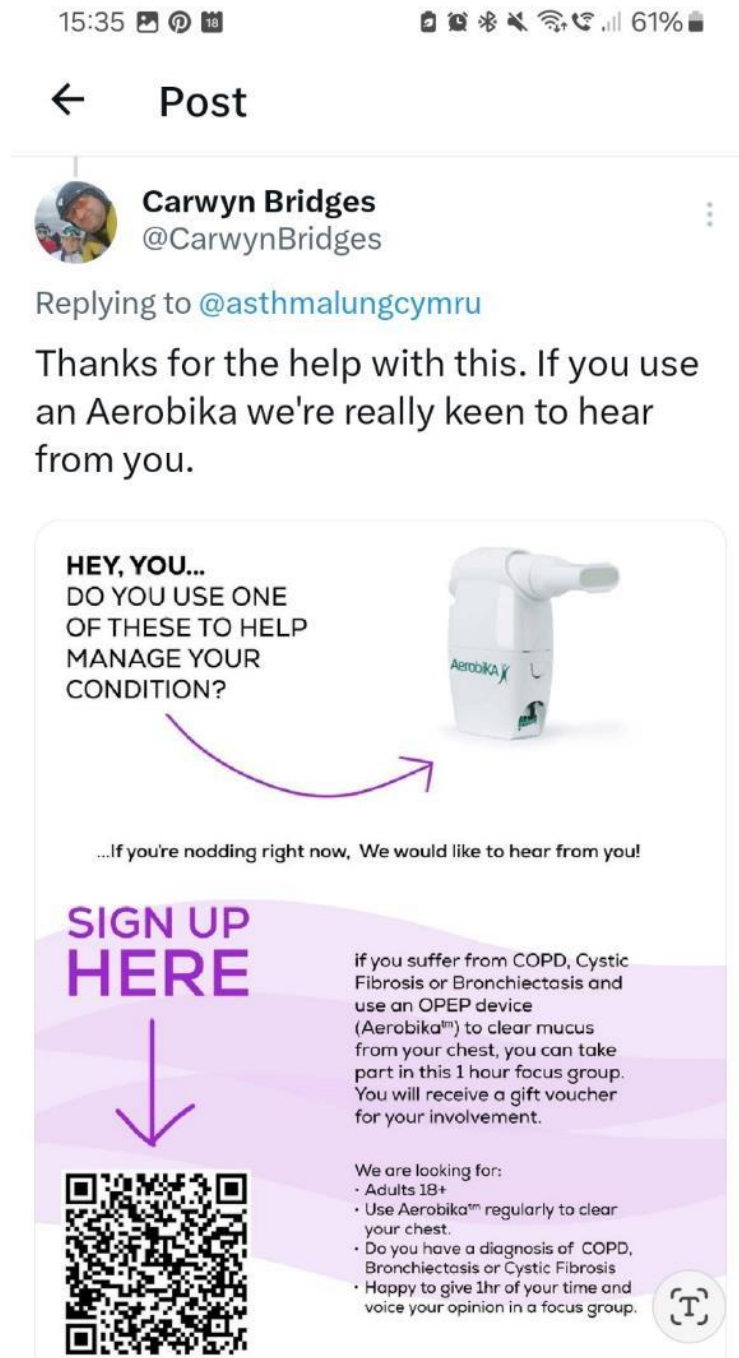


Figure 4.2 Social media post to recruit to CONNECT

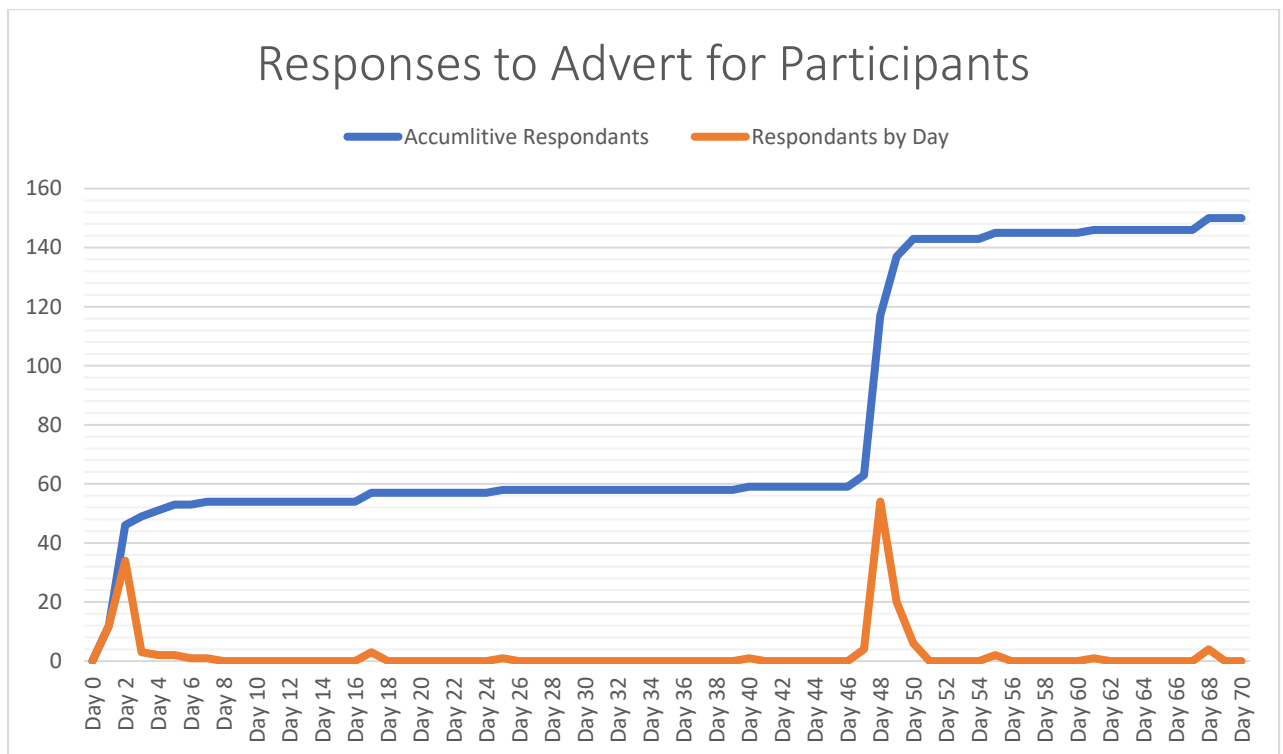


Figure 4.3 Response Rate to Advert Over Time

Interested Participants were directed to fill in the contact detail form online, and a PIS-ICF was posted/emailed along with an invitation letter see Appendix 13. Contact details were provided on the PIS-ICF in case a participant had any questions concerning the research study. The participant was asked to contact the research team via telephone/ email to indicate they wish to participate. Electronic consent was accepted on a first come, first served process until the target number was achieved.

We invited 10 participants to attend each focus group, of which we expected a minimum of eight to attend. An additional incentive of a retail gift voucher (£20) was offered for participation; this was provided electronically via email following the completion of the focus group. Due to the recruitment approach outside of the NHS participants were asked to confirm their time since diagnosis including length of time using device. As can be seen from Figure 4.3 many people responded (n=>140).

4.3.5 Participants/Sampling

The sample consisted of three focus groups. A fourth focus group was organised and abandoned during the introductions as the participants were not prepared to answer any questions or actively participate in the focus group.

HCP Focus Group

The first was made up of five HCPs. An additional two consented and were provided with the link to attend but, due to unforeseen circumstances, did not attend. All HCPs were specialist respiratory physiotherapists with three or more years' experience of prescribing Aerobika with clinical experience spanning COPD, Bronchiectasis, CF in adults, and paediatrics in the acute hospital, community and outpatient settings, see Table 4.2.

Inclusion criteria for HCP:

- Willing and able to sign informed consent
- Current relevant professional registration
- Currently involved in the clinical care of people with COPD, Bronchiectasis or Cystic Fibrosis

- Experience of implementing the use of Aerobika
- Consent to attend focus group online and for these to be recorded

Exclusions:

- Unwilling or unable to provide written informed consent.
- Cognitive, visual, or hearing impairment, which would affect communication in a group setting or online

Table 4.2 Table of demographics for Healthcare Professionals

Identifier (ID)	Conditions you work with?	Experience Using Device	Aerobika with manometer	Do you encourage patients to keep track of their symptoms? If so, how?
1	Cystic Fibrosis Paediatric;	>3 Years (15)	Yes	No set method, but if problematic and not clear, then symptom diary.
2	Bronchiectasis COPD	3 Years	No	Yes - self-tracking
3	Cystic Fibrosis Bronchiectasis COPD Paediatric	>3 Years	No	yes, just clinical history and patient report
4	Bronchiectasis COPD	>3 Years (17)	Yes	Bronchiectasis management plan
5	Bronchiectasis COPD	>3 Years (5)	Sometimes	Yes, sputum colour consistency and volume, general symptoms of sputum

Patient Focus Groups

Participants with COPD (n=2) and Bronchiectasis (n=7), see Table 4.3, were invited to attend online focus groups. Ages ranged from 27-76 years, with one female. The mean time since respiratory diagnosis was 14 years and time using the Aerobika device ranged from two weeks to six years. All patients reported that excess sputum was a problem. The inclusion and exclusion criteria are outlined below.

Inclusion criteria:

- Willing and able to sign informed consent.
- Clinical diagnosis of COPD or Bronchiectasis
- Has used or is using Aerobika
- Sputum as a persistent symptom
- Any gender and most co-morbidities (see below)
- Consent to attend focus group online and for these to be recorded

Exclusions:

- Unwilling or unable to provide written informed consent.
- Cognitive, visual, or hearing impairment, which affects communication in a group setting, online, or in the ability to see and use a smartphone.
- Active transmissible infection for the face-to-face sessions on the discretion of the clinical team (such as COVID-19, Tuberculosis, resistant PsA) for face-to-face sessions.

Tables of demographics

Table 4.3 Table of demographics Participants with Chronic lung condition

Group	Patient number	Age	Gender	Condition	Who taught	Time since diagnosis	Time using device	Any other methods	Sputum is a problem	Clearing chest takes a lot of time
1	6	30	Male	Bronchiectasis	HCP	5 Years	4 Years	Nil	Agree	agree
1	7	30	Female	Bronchiectasis	HCP	5 Years	3 Years	Exercise	Strongly Agree	Strongly Agree
1	8	28	Male	Bronchiectasis	Pharmacist	10 Years	3 Years		Agree	disagree
1	9	45	Male	Bronchiectasis/COPD	doctor	7 Years	4 Years	Breathing Exercise	Agree	Strongly agree
1	10	28	Male	COPD	parents	8 Years	6 Years	Breathing Exercise	Agree	Agree
1	11	27	Male	Bronchiectasis	Doctor	4 Years	3 Years		Strongly agree	Agree
2	12	76	Male	Bronchiectasis	Physiotherapist	70 years	5 Years	Postural Drainage	Agree	Agree
2	13	72	Male	Bronchiectasis	Video and leaflets	20+	2 weeks	Other OPEP	Agree	Neither agree nor disagree

4.4 RESULTS

Figure 4.1 and 4.4 show provisional and thematic maps developed during data analysis

Final Thematic map

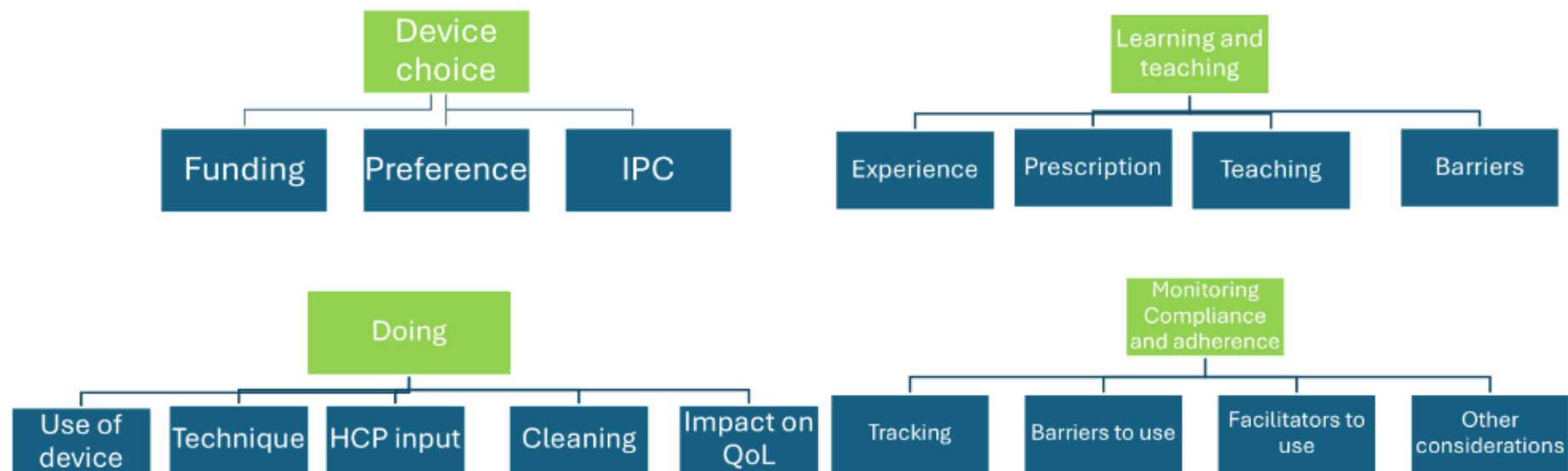


Figure 4.4 Final Thematic map

Following transcription and thematic analysis, themes emerged and were broken down into the main themes:

- Device choice
- Learning and teaching
- Doing
- Monitoring
- Smart device

Tables have been collated to display the key themes in each section, followed by a narrative description to provide context from the data. A copy of the guiding questions can be found in Appendix 10.

Device choice

The main impacts on device choice were discussed with both patients and professionals, and the following sub-themes emerged:

- Funding
- Preference
- IPC

Table 4.4 provides a summary of the key sub-themes surrounding device choice.

Table 4.4 Summary of Comments on Device Choice

Key themes	Patient	Professional
Funding	Costly	Cost, especially with Manometer
Preference	HCP led but would recommend	Good oscillation and easy cleaning
Infection Prevention Control (IPC)	Time to clean and how to do it	Cleaning (CF) is negative, small parts but easy to put together, no metal to rust

Device choice is primarily made by the HCP in the NHS environment with funding, preference, and infection prevention control (IPC) being the key themes of influencing choice. Patients seemed happy to use the device if recommended by their healthcare team but did report barriers and facilitators.

“I really like it because ever since my physician recommended it for me, I’m finding it very helpful”. (Participant 9, Line 60, Page 3)

HCP discussed the creative ways in which they were able to provide the devices with comments about not having a regular/dedicated funding stream for these devices, and other HCPs reported they were only able to provide OPEP devices to certain patient groups like CF where funding was ring-fenced.

Aerobika was recognised as “*a relatively new kid on the block*” in comparison to other devices on the market. HCP commented that the devices are easy to prescribe, they went on to explain that a small stock is held in the clinic, and then a request is sent for the GP to prescribe. It was said that although they are available on prescription, providing them from a secondary care setting was complicated by the procurement process.

“So, it’s probably not used as much as I would potentially like until funding is resolved”. (Participant 4, Line 21, Page 1)

The cost of the device was discussed, and although the HCP thought it cost a bit extra compared to other devices on the market, they were happy to recommend it, commenting that they thought it was the best OPEP device.

“It’s just been really, really helpful, a lovely piece of kit”. (Participant 1, Line 65, Page 3)

The use of a manometer, as an optional extra, on the device was discussed as a useful teaching aid. However, some reported the extra cost was prohibitive with the HCP needing to think laterally, either choosing who would benefit most or using the device with multiple patients, allowing them to use it in certain circumstances where the feedback was necessary.

All the HCPs agreed that the main reason for preference over other devices was the strength of the oscillation when patients use the device. The patients did not comment on this, presumably because they had not tried alternatives. One HCP commented that the device was easy to put together, and you can only put it together one way. The internal components, being all plastic, were raised as a positive as this avoided corrosion over time compared to the Acapella, the other commonly used device.

IPC was highlighted as a concern among the HCPs, especially those with a clinical interest in CF. One commented on the number of small parts inside the device, making drying the device after cleaning difficult and potentially increasing the likelihood of contamination.

Learning and teaching

The main issues of learning and teaching were discussed with both patients and HCPs, and the following sub-themes emerged:

- Experience
- Prescription
- Teaching
- Barriers

Table 4.5 provides a summary of the key themes surrounding learning and teaching.

Table 4.5 Summary of Comments on Learning and Teaching

Key themes	Patient	Professional
Experience	Used before or used another device or cleared chest before	Choose a device/prescription based on experience and knowledge
Prescription	Unsure correct dose	How know prescription linked to patient cohort, technique and individual differences – age/condition/acute vs chronic and length of use
Teaching	Mixed report if any teaching	Videos and learning materials
Barriers	Unsure of technique and how to know it is done correctly	Perceived patient barriers including cleaning and how to know done correctly

Starting an ACT regime in those with acute or chronic retained secretions requires a level of understanding and intuition by both the patient and the HCP. Learning how a new device or technique is best implemented can be confusing for patients, particularly if this is their first experience. Meanwhile, the HCP should bring a greater level and variety of experience and an understanding of the pathophysiology to guide the implementation of OPEP.

“Listening to them is almost just as important as seeing what is going on with the airways”. (Participant 5, Line 381, Page 12)

There was a broad breadth of length of patient experience with using OPEP ranging from two-weeks to six-years see Table 2.2. The majority of participants agreed that clearing their chest takes a lot of time. Those who shared their thoughts on how they cleared their chest commented on the best time of day, timing the use of bronchodilators and using other methods such as breathing techniques and exercise as useful things to do alongside the device. Also considering the importance of using sputum thickness and viscosity to guide the use of the device. Amongst the HCPs, they all had three or more years of using the device, with two reporting >15 years of experience. HCPs noted that they adapt the use of ACT to suit the clinical situation and their perceived ability of the patient they are treating. It was recognised that sometimes having a device was a benefit as it is a reminder that they need to clear their chest and was something more tangible than breathing techniques.

“We tend to use it in conjunction with our ACBT and keep it quite short and sharp because our patients are very severely short of breath. They kind of take to it a lot, a lot easier”. (Participant 2, Line 84, Page 3)

“I always start with ACBT, mainly because of breathing control, and then I incorporate it “. (Participant 3, Line 114, Page 4)

“It’s more tangible than just doing breathing exercises, it reminds me to clear my chest.” (Participant 13 Line 410, Page 14)

Patients and HCPs frequently referred to ACBT as a starting technique, with Aerobika being used in conjunction or as an adjunct rather than a complete replacement. These statements suggest that the skills of ACBT remains, but the Aerobika is perceived as more engaging, easier to structure, or perhaps more motivating for some patients. In some cases, it was described as easier to use when breathless. This insight is particularly valuable for TIPTOP, where one goal is to understand which ACTs are acceptable and manageable during high-symptom states, such as during exacerbations of bronchiectasis or COPD

Settling on the correct prescription and technique when using an Aerobika elicited a wide range of responses from both the patients and the HCPs. One patient commented on being uncertain about the technique, while others reported never having been formally shown how to use the device but feeling it was working effectively.

“It's working really effectively I don't feel you need to seek the advice from anyone else”. (Participant 13, Line 325, Page 6)

A patient who had received his teaching from a respiratory physiotherapist was able to give a clear prescription which he performed twice daily. Of the patients who had seen the resources provided, prior to the focus group, all agreed that they were useful and that they had taken some pointers or already used it to adapt their techniques. It was reported that it had raised a few questions that contradicted the advice of his physiotherapist and that he would need to seek some clarity at the next opportunity.

“It definitely helps me. No question about it and I would say well, as I doubt there a day goes by that don't use it”. (Participant 12, Line 341, Page 7)

“The instructions did help. Though I had a feeling it may not work at first, but I am super happy, and I can definitely recommend it”. (Participant 10, “chat”)

When asked about prescription and teaching, the HCPs talked about the need to adapt to the clinical markers and condition of the patient with consideration for variables such as resistance settings, length of breaths and how easy an Aerobika is to use compared to other devices on the market. There was variance in the exact prescriptions used from 2-3 cycles of 8-10 breaths with a breath hold, ensuring expiration lasted for six-seconds. While adapting the rate and depth of breaths to elicit the best effect prior to clearing the sputum. The use of a monometer was recognised as useful but as discussed previously it was not available to all.

“If I had a manometer would be ideal, but at the moment it's just about getting that oscillation and then getting the breathing control and clearing”. (Participant 3, Line 160, Page 11)

“I guess in terms of the resistance, I would probably want to understand a little bit more about kind of the pathophysiology of their lungs that I'm dealing with”. (Participant 5, Line 184, Page 11)

When discussing the materials shared prior to the focus group none of the HCP had seen them before and reported that they would use them in the future and one reported forwarding them on to respiratory colleagues already.

Barriers to the patients' use of Aerobika included a lack of clarity on the correct technique, cleaning, and prescription and how this is addressed. However, despite some of the above uncertainties in the comments, the device was recognised as effective and useful. HCPs also recognised the variance in technique leading to ineffective treatment. The HCPs were also worried about treatment adherence and noted that patients receiving follow-up were confused about technique or had stopped treatment due to uncertainty.

Doing

The key themes identified have been broken down into sections of performing the task, and the following sub-themes emerged:

- Use of device
- Technique
- HCP input
- Cleaning
- Impact on daily life

Table 4.6 outlines the key themes of doing.

Table 4.6 Summary of comments on the theme of Doing.

Key themes	Patient	Professional
Use of device	Posture Breathing Time Strenuous	Posture Breathing Comfort
Technique	Uncertainty about technique and dose. Individual differences and learning from experience.	Concern not done correctly to have benefit. Performance is good when done regularly.
HCP Input	Variable but desired	Providing learning and monitoring
Cleaning	Infection control. Frequency and how thorough.	Mixed Small parts, easy to clean for some, IPC, not rust, easy to put together
Impact on daily life	Time	N/A
Compliance	Feedback was compliance – part of regime but with flexibility	Reminders for use – getting in regime

Dexterity when using a device for ACT is a consideration that HCPs consider when prescribing Aerobika, with comments on how easy it is to assemble and how good it is for people with rheumatoid arthritis.

Regular use of the device was deemed important by both HCPs and patients. Factors affecting use were posture, breathing and time to undertake. HCP noted that they wanted patients to be comfortable using the device to ensure technique and regular use were promoted, with poor posture leading to poor technique. It was noted that the device was strenuous to use, requiring a lot of effort. However, this did not distract from his use, reporting the lasting benefits of clearing the chest using this device, regarding chest feeling and sounding clearer.

“I have found since being on these regimes in the past, say two years, that the volume of sputum that I pass has reduced”. (Participant 13, Line 420, Page 14)

Remarks were made that the commitment to using the device was extensive, requiring 30-40 minutes twice daily, meaning it needed to be built into their morning and evening regimes. However, this could be disrupted if they needed to attend an early morning appointment. Cleaning the device was deemed unrealistic, and cleaning after every use was “*not on.*”

HCPs prescribe the device in conjunction with other therapies, such as positioning autogenic drainage and including the addition of nebulised medication through the device. Cleaning of the device was a concern to the HCP, particularly in the CF community. One of the risks of not regularly cleaning the device is that it can lead to some of the components not working correctly. However, it was felt that patients found it easy to clean. Compliance with OPEP and ACT, in general, was raised as an issue with written plans and nursing prompts for those in acute settings, a recognition that the lack of follow-up in outpatients once OPEP was initiated due to service constraints was not ideal.

“I only see them in Bronchiectasis clinic will be a one off within an MDT clinic”. (Participant 4, Line 257, Page 3)

Prescription of specific sessions using Aerobika varied across the data with patients discussing their different regimes and how they have evolved to suit the needs of their chest using pieces of information that have been gained from HCP, medics, groups, information leaflets, instructional videos and trial and error to settle on their current regime. One patient talked about using bronchodilators followed by 10-20 breaths plus huffing, whilst another spends 10 minutes twice a day doing repeats of 20 breaths and clearing with a cough at the end of each set.

“I use it every day, sometimes once or twice a day”. (Participant 7, Line 401, Page 12)

They went on to talk about differences between techniques and those shown in the pre meeting information. One patient chose to inhale with the device out of his mouth for IPC reasons.

*“Could I possibly reintroduce bugs by keeping it in my mouth?”.
(Participant 12, Line 186, Page 8)*

When discussing prescriptions with the HCP, the variance was the same. Some prescribed 10 breaths, aiming for a longer expiration than inspiration, while others tailored the number of breaths to the patient, using characteristics including length of breath and patient comfort to tailor a session. Interestingly, the HCP discussed the adjustable resistance, but the patients did not mention it.

Both HCPs and patients valued the time they had together to review a treatment session with OPEP, although only one had attended any follow-up sessions with an HCP.

Monitoring – Compliance and Adherence

The key themes of Monitoring - Compliance, and adherence have been identified and broken down, and the following sub-themes emerged:

- Tracking
- Barriers to use
- Facilitators to use
- Other considerations

Table 4.7 outlines the key themes of monitoring.

Table 4.7 Summary of comments on monitoring compliance and adherence

Key themes	Patient	Professional
Tracking	Manometer, use a diary but also linked to how patient feels. Need HCP input to support	Manometer but some have follow-up clinic – link to setting
Barriers to use	Prescription – is it correct and time to take	Remembering to use it, especially during exacerbation.
Facilitators to use	Feel it is working during stable state and exacerbation	Length of use, Manometer, encouraging feedback
Considerations	Experts in their own condition, cleaning	Technique, cleaning

Compliance and adherence to OPEP therapy has many factors and this was highlighted by the range of techniques used by patients to keep on track and HCPs to monitor and encourage correct use. The manometer was seen as an important tool by the HCP, not only for teaching but for ongoing feedback. Patients and HCP recognised the importance of symptom diaries, immediate feedback and follow-up by a trained professional as key.

“It gives the patient visual feedback. It's nice to know they're doing the treatment in the right zone”. (Participant 4, Line 26, Page 1)

Patients commented on the importance of recognising an increase in symptoms, including laboured breath, feeling clogged and increased volume of secretions, to indicate the need for therapy but still felt unguided post-treatment, although they showed a good understanding of their condition.

“I don't know whether I'm using them properly. I've only just done it by, you know, just intuition”. (Participant 13, Line 201, Page 7)

Participants described using the Aerobika flexibly, often increasing frequency or adjusting technique during episodes of worsening symptoms, such as chest congestion, increased sputum, or breathlessness.

“I know when I need to use it more—when my chest feels tight or I'm bringing up more. I'll use it a few more times that day and I find it really helps.” (Patient 13, Line 236, Page 8)

Illustrating that patients were not rigidly adhering to a standardised prescription but were self-adjusting use based on symptom changes, particularly during exacerbations.

However, several patients also expressed uncertainty about whether they were using the device "correctly" exacerbation, suggesting a gap in guidance and feedback.

"When things get worse, I use it more, but I don't know if I'm doing it right or if it's even helping properly." (Participant 9, Line 421 page 13,)

It was felt that a manometer would improve treatments but currently is only able to use oscillations to guide therapy. HCPs discussed the importance of follow-up visits to adjust treatment regimens, with some having access to this resource. HCPs recognised that good technique and the opportunity to review patients can improve continued use and real-world compliance.

"I teach them once send them home and then they can return for a short follow up in a month". (Participant 3, Line 157, Page 6)

Comments around monitoring were consistent, patients were keen to be able to monitor their performance and provide data to the HCP to inform the therapeutic relationship, while the HCP valued the data and felt that it enabled ongoing therapy.

Smart Device / Tracking and Monitoring

The main impacts on smart devices -tracking and monitoring were discussed with both patients and professionals, and the following sub-themes emerged.

- Information on adherence and use
- Feedback
- Barriers
- Data
- Other considerations

Table 4.8 outlines the key themes of smart devices -tracking and monitoring

Table 4.8 Summary of comments on tracking and monitoring / smart device

	Patient	Professional
Information on adherence and use	Useful for monitoring use	Useful for monitoring use
Feedback	Feedback to aid compliance and performance and see if using properly	Feedback to aid compliance and performance
Barriers	How to interpret data and support available	Infrastructure – rurality, funding, age & ability - may lead to inequalities
Data	Monitoring, data tracking, privacy, happy to share to with clinician not 3 rd party	Consider data sharing, use of data, data management
Considerations	Able to use technology, cost, size, HCP input, value for money	Cleaning, personalisation, cost

Discussions around the use of smart devices were split between using information to enhance patients' health and acknowledging that the use of such data was complicated by negative views of the management of complex health data.

Patients and HCPs noted that there is a wide spectrum of digital literacy amongst the patient groups that use OPEP. The HCPs recognised that some patients would not be able to use a smartphone, and patients commented that younger people let technology run their lives.

*“My only concern is the population of patients, the majority are in their late sixties, seventies, eighties and they don’t have a mobile phone”.
(Participant 2, Line 396, Page 13)*

“Let alone understand what the data would mean and how it would implicate on their medical treatment”. (Participant 2, Line 398, Page 13)

However, both groups recognised the power of data to offer feedback in real time and to be used as a clinical tool during consultations, of the patients present in the focus groups, only one used a step counter occasionally, one tracked oxygen levels in a diary, and another monitored their weight using an app.

“I wouldn’t object to information being shared with my medical team. I wouldn’t have any objection to that. No, provided it wasn’t used by a third party in my name”. (Participant 13, Line 260, Page 10)

Data sharing was raised by both HCPs and patients, with the agreement that the data should not be used by third parties. HCPs noted from previous experience that data like this can be seen as intrusive into people's lives and needs to be handled carefully to ensure that it remains a positive tool.

*“I know a lot of my patients are in their sixties, seventies and eighties and are nervous about Big Brother watching them and sharing data”.
(Participant 4, Line 429, Page 14)*

HCPs were worried about the infrastructure, time, and funding necessary to support the procurement of devices and the use of the data collected, with a request that it be linked with other platforms to avoid replication. Patients were also concerned about the cost and felt that it would stop them from using the technology. HCPs and patients commented on the complexity of the data and how it would be interpreted with one solution offered as having a patient and HCP platform.

*“If you can pick up on the habits of the how people are using it and be able to like reminders of something like that, I think would be massive”.
(Participant 5, Line 500, Page 22)*

However, HCPs were excited about the prospect of having access to the data and quickly started to talk about how the data may be used to inform their practice. There was recognition that adherence data, including length of sessions, would be useful, with the possibility of big data being used to identify patient groups that were more likely to be adherent.

4.5 DISCUSSION

Summary of findings

The HCPs and patients had a resoundingly positive view of Aerobika across the Key themes:

“Device choice” led by the HCP, who were informed by the clinical characteristics of the device, comparing it favourably to other devices with the ease of cleaning, assembly, and absence of metal components in its favour. The cost of the device and the added cost of a manometer were a consideration that influenced the procurement processes. This shows that HCPs consider the features of the device when choosing it for the patients and consider its ongoing use. However, the comments about the cost and procurement of the device, including whether the added cost of the manometer was acceptable/achievable, suggest that using/purchasing these devices in complex organisations like the NHS is a challenge.

“Learning and teaching” prior experience of OPEP and ACT was seen as a positive by both patients and HCP groups. This highlights the benefit of having specialist input to provide tailored teaching. Prescriptions for use were tailored to the individual needs, with a wide variance across the data. Some uncertainty over the correct dose and technique was highlighted as a common barrier from both groups. The lack of clear evidence surrounding the best prescription allows tailoring during the patient / HCP sessions. However, as seen through the comments leads to some confusion. The materials shown were considered useful, but some contradicted previous advice acting as a barrier and increasing uncertainty. Again, due to the lack of clear evidence and variance in prescription any materials may come across as confusing or different to previous advice.

“Doing” is seen as a process including preparation, performance, and cleaning that draws from learning and teaching. Important factors for “*doing*” include posture, breathing, comfort, and time, with a desire from patients to be reassured through prompts or HCP input. This aligns with the current literature, which acknowledges

that ACT regimens are time-consuming, demanding, and require a high level of skill and comprehension.

“Monitoring – compliance and adherence” the manometer was seen as a key tool to provide feedback during use to patients and HCPs, valued to improve treatment quality. This suggests that visual feedback in treatment sessions may be an important consideration for future devices. Patients also use diaries to track symptoms and use intuitive feelings to monitor treatments, technologies to support this may be useful in future care. Both groups felt that remembering to do treatments was a barrier to consistent use. Similarly, “doing” anything that helps decrease the burden of treatment or acts as an aid to prompt engagement was seen as a positive for both patients and HCPs.

Patients were not rigidly adhering to a standardised prescription but were self-adjusting use based on symptom changes, particularly during exacerbations. This pattern of self-regulation links directly to TIPTOP’s interest in understanding patient-driven ACT decision-making in response to acute symptom burden. This supports the need for focus on structured support and education during exacerbation management as discussed in TIPTOP.

“Smart device - tracking and monitoring” was viewed as important for monitoring during treatments and the longer-term data of compliance and adherence, additionally the data was seen as potentially useful to track health and adapt performance. Patients would be able to use instant feedback to decrease uncertainty, and HCPs would be able to use the data to inform therapeutic relationships. Although sharing data was seen as a positive within trusted relationships there was concern about data safety and misuse. The impact that a smart device can have on “learning and teaching”, “doing”, and “monitoring – compliance and adherence” was clear from both patients and HCPs. However, this was conditional on the interface and that data would be used in a positive and supportive way protecting the privacy of the user.

Compare findings with others

Although there are limited studies to draw direct comparisons within this field, a few studies have identified similar themes around ACT. Patient satisfaction was based

on perceived difficulty and symptom relief in the ERS statement on ACT. Barriers to ACT such as lack of motivation and the time it takes to complete a routine (Herrero-Cortina et al., 2023), were also reflected in the current study, with patients reporting a lived experience of these challenges.

McCullough, Ryan, et al. (2015), developing a behaviour change intervention, interviewed people with bronchiectasis and HCP. Discussing barriers and enablers to treatment adherence, including airways clearance, but not specifically OPEP, they identified common themes, including knowledge, skills, and beliefs, and behaviour change domains for effective adherence, including monitoring, self-monitoring, feedback, and problem-solving. This aligns with the findings of the current study.

S. M. Alghamdi et al. (2023), in a survey of HCPs in Saudi Arabia, reported that 31.8% are given mucus clearance devices without prescription. This may support the level of uncertainty in the patients who reported not receiving any advice or teaching on the use of an Aerobika. However, we should be cautious as this data may not translate to our cohort but may offer insight into the findings.

The findings reported by (Knox et al., 2021) mirror the messages on smart devices with ease of use and usefulness being important. The current study appeared to convey a stronger emphasis on data privacy, possibly due to a difference in the cohorts, as Knox et al. (2021) only included participants with a smart device. The two years between studies may reflect a general shift towards greater awareness of data safety. Furthermore, participants were willing to share data with their clinicians but wary of non-clinical use echoing findings that trust is essential for digital health uptake (Honkoop et al., 2022; Ottewill et al., 2024). Highlighting the need for transparent data governance and co-designed consent models.

While participants recognised the potential value of monitoring and feedback through technology this also highlights implementation challenges seen in digital healthcare adoption. Digital exclusion was raised as an issue in older adults with low digital literacy and rural living highlighted as barriers. This is backed up by (Greenhalgh et al., 2017) who also identified concerns about patients operating digital tools, interpreting data or managing app-based platforms. Participants also indicated a preference for face-to-face input. While smart devices offer efficiencies they should

be viewed as supportive rather than in place of therapeutic relationships. This is a message that is backed up in the literature (Ottewill et al., 2024; Steele Gray et al., 2024).

It is reassuring to see similarities between ACT research using different methods and the current study. However, the current study has been able to explore the context of these themes in greater detail, thanks to the conversational nature that focus groups allow. Furthermore, there is currently no qualitative research available in COPD or bronchiectasis exploring the potential acceptability of a smart ACT device.

Strengths and weaknesses of your study

A strength of CONNECT was how it captures detailed, real-world perspectives on the use of the Aerobika from both patients and HCPs, including reflections on usability, teaching, adherence, and future development. The qualitative design enabled a better understanding of how the Aerobika is integrated into daily routines and supported patient self-management. However, a limitation was the absence of structured data regarding exacerbation frequency or timing. While some participants referred to changes in device use during periods of symptom worsening, this information was not collected in a structured way. Given the specific focus of TIPTOP on Aerobika use during acute exacerbations, this represents a missed opportunity to explore how patient behaviour aligns with clinical needs during these critical periods. Future studies should consider incorporating targeted questions or collecting longitudinal data to better understand the relationship between exacerbations and ACT practice. One possible opportunity would be to recruit participants from an associated RCT.

Staff from TMI were present during the focus groups acting as observers only. At the start of the conversation everyone was introduced, and the observers were asked to turn cameras off. This was agreed to as it was felt that the benefits outweighed the risks. TMI benefited by getting information in real time from the focus groups that meant that it could be quickly included in the product development process whilst a final report was created. However, the limitations should also be considered. There is an increased risk of bias as both the participants and researchers change behaviour due to their presents. Attempts to mitigate this risk included an awareness

in the generation of the key questions, always asking open follow up questions, and maintaining a friendly non-judgmental style.

TMI used the outputs from CONNECT to inform both the parameters of the data collected and the way in which in real time feedback was provided to the user. Added to these comments about consent of data sharing opened up a larger conversation about data ownership and collaborative healthcare relationships.

Exploring the lived experiences of patients using the Aerobika has not been captured in this way previously. Additionally, the barriers and enablers to the use of Aerobika in clinical practice and application in the field have not been collectively examined and contextualised through semi-structured focus groups. Another strength is the themes have been fed back to TMI and included in the product design process to influence product development. The keen engagement of patients in the process and the rich context that they were able to give on this specific area of treatment highlights the role that patients can play in innovation through real-world insights. This feeds into key drivers around healthcare in Wales, ensuring patients are collaborators in the development of future services to drive prudent and value-based healthcare (Buss et al., 2022).

Attendance in the groups varied across the focus groups, with different dynamics influencing the nature and flow of the conversation. A strength of the HCP group was the depth and breadth of experience across conditions. Although groups were planned to include CF, uptake was poor, and further research should look to include underserved communities suffering from conditions of mucus-hypersecretion.

Educational resources were shared with participants prior to the focus groups with the intention of getting feedback on the content, clarity, and perceived usefulness. However, this approach may also be viewed as a potential limitation. Assuming a minimum level of familiarity, there is a risk that participants responses to device use were shaped and influenced by the materials. Additionally, while several participants used the resources to reflect on or adjust their technique, others may have felt obliged to respond positively due to the researcher's involvement in sharing the materials. Despite these limitations, the feedback generated was of good quality and critical, some participants identifying discrepancies between the materials and their

own practice. This highlights the value of integrating resource evaluation within qualitative research while also acknowledging the influence such materials may have on participant responses.

Due to the nature of the sampling, diagnosis and use of the Aerobika were self-reported by participants in the patient groups, and the level of understanding of their underlying respiratory condition varied across the cohort. As recruitment was conducted via social media advertisements and data collection took place through video conferencing, the sample is likely to have been biased towards individuals who were digitally literate and comfortable engaging with technology. This may have skewed the dataset towards early adopters within the community, those already inclined to engage with new devices and self-management strategies. However, the findings indicate that even within this relatively prepared and engaged group, there remain important considerations around ensuring optimal use of Aerobika and supporting future developments.

While the data provide valuable insight into the real-world use of the Aerobika, it is important to question whether these experiences, gathered from a self-selecting, first-come, first-served cohort are representative of the wider clinical population. These participants may reflect those most proactive in their self-management. This raises an important question, would patients recruited into a randomised controlled trial, like TIPTOP, demonstrate the same levels of understanding, adherence, and confidence in ACT, particularly during exacerbations? Further research is required to explore these issues within more diverse and clinically representative populations.

Way forward

This study provides a unique insight into the lived experience of both HCPs prescribing Aerobika and device users. The findings have already influenced the development of the smart device. Additionally, there is potential to develop resources to help train HCPs and patients that provide a coherent, supportive message. Future research could repeat the process once the smart device is in use to explore similar themes to compare the enablers and barriers.

Interestingly the identification of uncertainty and variance in prescription of devices opens several different avenues for future research and development. Future studies

could identify the specific phenotypes that benefit from specific prescriptions to inform clinical practice. The development of a tool to document prescription that could be tailored to the needs of the patient but that has messaging that is consistent with other resources provides another opportunity.

There is wide recognition in the community that adherence to ACT is a key component to making it an effective treatment, and there is ongoing work to develop decision-making tools to inform HCP practice. The body of literature could be added to by further data exploring the lived experiences of people with conditions of mucus-hypersecretion and different forms of ACT.

A key learning point from the CONNECT research process related to the recruitment and enrolment strategy. One scheduled focus group was discontinued during the opening moments, as it became evident that the participants did not meet the inclusion criteria, specifically regarding a confirmed chronic respiratory condition or prior use of an OPEP device. Recruitment for the study had been open and widely promoted through social media, with strong engagement from charities and organisations involved in respiratory care. However, the risk of ‘research catfishing’, where individuals misrepresent themselves to gain access to incentives, was a recognised concern. Demographic screening questions were used during enrolment, and clear terms of reference were provided to participants in advance. This enabled the research team to take the decision to abandon the session with confidence and transparency. On reflection, the transcript confirmed minimal participant engagement (only 10 words recorded in the first five minutes). Future research may benefit from revised strategies, such as avoiding the advertisement of incentives in public calls and recruiting through closed or verified communities where participant eligibility can be more reliably confirmed.

Findings from CONNECT could also be used to inform the next TIPTOP protocol by refining eligibility through a run-in phase, improving adherence via smart monitoring, and supporting engagement through structured training and remote follow-up. Clinician-focused tools and patient-centred outcomes will improve delivery and acceptability. These adaptations respond directly to usability and implementation

challenges identified in CONNECT, making the future trial more, patient-aligned, and methodologically robust.

THESIS: OVERALL CONCLUSIONS / PERSONAL REFLECTIONS

OPEP is being used in chronic respiratory health to help people manage excess secretions in several mucoid-obstructive lung conditions, including COPD, bronchiectasis, CF, and PCD.

Although the study was unable to show the superiority of OPEP over ACBT in TIPTOP, a significant amount of learning took place to inform future research. Careful consideration should be given to the study design to ensure it is appropriate for answering the specific research questions. Participants experiencing exacerbations provide an opportunity to study the dynamic flux created by the rollercoaster ride of the acute episodes within a chronic condition but, consequently, are a difficult population to recruit and keep in a research protocol. However, the results bring new data to the weight of evidence that shows the feasibility, safety and probable benefit of ACT, including OPEP, as a treatment in the chronic bronchitis phenotype of AECOPD.

The qualitative work carried out in CONNECT introduced the potential opportunity of smart devices in ACT and demonstrated the complexity of implementing and managing the burden of OPEP as part of an ACT routine. OPEP is valued by both HCPs and patients with chronic conditions who work together to increase efficacy and overcome barriers to continued use. Both groups were excited at the potential benefits of a smart device to provide user feedback and add data to HCP patient interaction. However, a certain amount of caution was voiced about the use, storage and way that the data will be stored and used. HCPs were particularly conscious about the integration of data into healthcare systems and the way that would affect clinical practice.

Registry and biobank data like that from Bronch-UK provide an opportunity to track large cohorts of a specific population over time, which is invaluable when looking at patterns and trends. The snapshot data that we analysed has shown that the number of people performing regular ACT is higher than previously reported and that there is a complex dynamic between which ACT is performed with OPEP use overlapping much more than expected with ACBT. The use of ACT overall was linked to disease severity. As this was the first study to report the wider UK data set, it opens several

future research questions that could explore the differences in provision and prescription and impacts of ACTs across the UK.

This research has required the input of a huge team of researchers as the projects have moved from design to approval and implementation. This has meant that several professional networks have been established across the NHS, academic institutions, HRA, HCRW, and industry to make them become a reality. The power of these networks should not be underestimated in any research project.

This PhD research has laid the foundation for a sustained and applied contribution to the landscape of respiratory care in Wales and beyond. In parallel with completing TIPTOP, CONNECT, and Bronch-UK studies, I have taken on a strategic leadership role as the National Allied Health Professional (AHP) Lead for the Respiratory Network of the NHS Executive, where I am leading a national 2025–26 objective to define and implement a standardised bronchiectasis care pathway. This work is complemented by contributions to the development of a national breathlessness pathway, designed to support early and accurate diagnosis, and by involvement in a task and finish group working towards national consensus on a core set of PROMs and PREMs for respiratory conditions. These activities reflect my commitment to translating research evidence into policy and practice, informed by the core themes of person-centred care, chronic condition management, digital inclusion, and equity identified through this PhD.

Ongoing research collaborations further extend the reach of this work. I am actively contributing to the SPITFIRE 2 and 3 studies, which aim to validate the use of induced sputum testing in haematology and respiratory populations and am working closely with TMI to explore opportunities for evaluating the Smart Connected Aerobika in future clinical trials, with a focus on measuring adherence, technique, and treatment optimisation. This series of projects has fostered a deep interest in improving respiratory patient pathways by ensuring that people living with chronic conditions have access to high-quality educational resources and evidence-based treatments, tailored to their individual circumstances. My PhD has been instrumental in shaping this agenda, offering valuable insight into real-world evidence and patient

experience, and will continue to inform the development of collaborative, data-informed respiratory care models across Wales.

APPENDIX 1: BRONCH-UK STUDY OUTLINE

ISRCTN17489966 <https://doi.org/10.1186/ISRCTN17489966>

Bronchiectasis observational cohort and biobank UK study

Submission date 18/06/2015	Recruitment status No longer recruiting	 Retrospectively registered
Registration date 28/07/2017	Overall study status Ongoing	 Protocol not yet added
Last Edited 28/07/2021	Condition category Respiratory	 SAP not yet added
		 Results not yet expected
		 Raw data not yet expected
		 Study ongoing and record not updated in last year

Plain English Summary

Background and study aims

Bronchiectasis is a long-term rare condition where the airways are abnormally widened (called bronchial dilatation), resulting in the build-up of mucus that can cause infection in the lungs. Symptoms include a persistent cough and breathlessness. There is a need to know more about how to treat bronchiectasis and how many patients there are in the UK with this condition. This study involves recording information about patients that are diagnosed with bronchiectasis and storing it in a registry. Currently there are very few drugs or treatments that are proven to work for bronchiectasis because very few clinical trials have been performed. The data collected in the registry will help us to evaluate how well treatments work and help to design better clinical trials by understanding more about the disease.

Who can participate?

Adults aged at 18 and older with bronchiectasis.

What does the study involve?

This study stores simple information about each participant, such as their age, the results of blood tests and x-rays and the treatments that they have or are receiving. This will help us to understand the impact of bronchiectasis on each participant, and on healthcare in the UK. Those asking for a data analysis to be conducted on the database may include doctors, university researchers and companies including the pharmaceutical industry. Participants that are willing to take part in clinical trials in the future are also identified and their contact details stored on file. Participants are asked to consent to the study period where funding is already identified namely a study duration of 36 months. The overall principle of the study is to collate data from routinely collected investigations as recommended in care guidelines with participants then followed up at least once a year.

What are the possible benefits and risks of participating?

There are no direct benefits or risks with participating.

APPENDIX 2: APPLICATION FOR ACCESS TO BRONCH-UK DATA



Application for access to BronchUK cohort & biobank

The application should be submitted electronically by email to the BronchUK Project Manager

Philip.Mawson@newcastle.ac.uk

Project title (including short title)
Trends and reported use of Airways Clearance adjuncts in the UK

Applicant Name	Mr Carwyn Bridges
Employing Institution	Cardiff and Vale University Health Board
Address	Cystic Fibrosis Centre, University Hospital of Llandough Cardiff
Telephone Number	[REDACTED]
Email Address	[REDACTED]

Are you a PhD Student?

☒ Yes

☐ No

If yes, please provide name, address and contact details of your supervisors.
Prof Keir Lewis [REDACTED] Respiratory Lead, Hywel Dda University Health Board, Prince Philip Hospital, Wales
Dr Mel McNarry [REDACTED] Swansea University Swansea

Please describe the nature of the question being addressed (250 words max)

Reference _____ (internal use only)

Application for Access to the BronchUK Cohort, v1.1, 27.05.2015

APPENDIX 3: HRA AND HEALTH AND CARE RESEARCH WALES (HCRW) APPROVAL LETTER (TIPTOP)



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales



Health Research
Authority

Prof Keir Lewis
Respiratory Centre
Prince Philip Hospital
Llanelli
SA14 8QFN/A

Email: approvals@hra.nhs.uk
HCRW_approvals@wales.nhs.uk

21 May 2021

Dear Prof Lewis

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title: A Pilot Feasibility Randomised Control Trial (RCT) of Aerobika TM verses Active Cycle of Airways Clearance (ACBT) in people with Chronic Obstructive Pulmonary Disease (COPD).
IRAS project ID: 289817
REC reference: 21/WA/0144
Sponsor Hywel Dda Health Board

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

APPENDIX 4: PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM (TIPTOP)

PARTICIPANT INFORMATION SHEET – Version 5, 6th April 2022

Title of research study: “expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP)

Rec reference: 21/WA/0144

IRAS reference: 289817

You are being invited to take part in a research study. Before you make a decision, it is important to explain why the research is being done and what it will involve. Please take time to read the following carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is unclear or if you would like more information. Take your time to decide if you want to take part in our study.

1. What is the purpose of the study?

Clearing sputum for people with Chronic Obstructive Pulmonary Disease (COPD) can help breathlessness, lead to less medicines and hospital admissions. The National Institute of Clinical Excellence (NICE) recommends two ways of clearing sputum, but we do not know which one is more effective and is easier to do.

We hope to compare physiotherapy, breathing and cough exercises versus a handheld blowing device (flutter box). The results from this study will form part of a PhD.

2. Why have I been chosen to take part?

You are currently in hospital due to your COPD or you have had treatment at home for an exacerbation within the last 2 weeks.

3. Do I have to take part in this study?

It is up to you. If you decide to take part, you will be given this Participant Information Sheet and we will ask you to sign a Consent form. You are free to withdraw from the study at any time without providing us with a reason. Your information up to this point may be used.

4. What will happen to me if I agree to take part in this research study?

We will ask you some questions about your health. We will offer you one of two techniques, chosen by 50:50 chance (on a computer) so there is an equal chance that you will be given either treatment.

Treatment 1: You will have a 50% chance of receiving Active Cycle of Breathing Technique (**ACBT**) which involves breathing at different rates and depths followed by a forced breath out (Huff) and a cough. This cycle will need to be done 5 times per session as prescribed by your physiotherapist.

Treatment 2: You will have a 50% chance of using a small handheld device called an **OPEP** (Aerobika™). You place this device between your lips and breathe deeply through it 15 times followed by a forced breath out (Huff) and a cough. This cycle will need to be done 5 times per session as prescribed by your physiotherapist.

If you are in hospital, we will collect any data and provide teaching on the physiotherapy technique before you go home. If you are not in hospital, you will be invited to attend an appointment at the hospital to collect any data and provide teaching on the physiotherapy technique.

. When you are feeling well at home you would only need to do ACBT or Aerobika[™] session once per day. If your cough worsens you should do the treatment twice per day (morning, before breakfast and evening, before bed) for the duration of the study (12 months).

If you decide to participate in this study, we will need to get in touch with you after one, three, six, and 12 months from the start of the study to complete some questionnaires. This will mean a phone call or video call depending on your preference and you sending the responses to your questionnaire by email to the researcher. Your GP will be informed of your participation in this study.

5. What will I have to do?

There are no lifestyle restrictions. We will want you to continue your normal activities and all usual health treatments and medications. Completing your chest clearance technique should take you about 30 minutes a day. If you become unwell you should still contact your GP Practice, out-of-hours emergency service or hospital.

6. What are the side effects of being in this study?

Clearing your chest regularly has minimal side effects but can sometimes cause light headedness and temporary increased breathing rate. Using the correct technique can help avoid these side effects.

7. What are the benefits associated with me taking part in this research study?

Taking part will ensure an up-to-date clinical assessment by a physiotherapist and careful monitoring of you and your airways clearance techniques over the 12

months. You will be taught a way of managing your sputum yourself and we believe this can reduce breathlessness and the risk of you coming into hospital with more chest infections

Unfortunately, we cannot pay you for being in this study. No travel expenses would be reimbursed for attending hospital appointments.

8. What will happen if something goes wrong?

If you have concerns about this study, we encourage you to raise your concerns as soon as possible. Firstly, you should ask to speak to the researcher who will do their best to answer your questions. If you wish to speak to someone who is not part of the study team you can contact the Community Health Council (CHC):

<https://hywelddachc.nhs.wales/>

**Hywel Dda Community Health Council,
Suite 5,1st Floor,
Ty Myrddin,
Carmarthen, Wales, SA31 1LP.**

Phone: [REDACTED]

Email: [REDACTED]

More details can found at the hospital, if you want to take this further and complain. If you feel that you have any reason to complain about any aspect of the way you have been approached in the hospital or further treated during the course of the study, the normal National Health Service complaints mechanisms are available to you. www.wales.nhs.uk/ourservices/contactus/nhscomplaints

You can also raise a concern by contacting Patient Support Services at Hywel Dda University Health Board by:

Email: **hdhb.patientsupportservices@wales.nhs.uk**

Phone: **0300 0200 159**

Write a letter to FREEPOST FEEDBACK @ HYWEL DDA

9. How will we use information about you?

We will need to use information from you and from your medical records for this research project. This information will include

- NHS number
- Your initials, name and contact details
- Information about your health and wellbeing

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. The findings from our study may be published in scientific journals and presented at conferences / meetings. You are welcome to contact the researchers for a report after 2 years.

10. What are your choices about how your data is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep data about you that we already have.

- If you choose to stop taking part in the study, we would like to continue collecting information about your health from your hospital records. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study

11. Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet which you will receive with this information sheet.
- by asking one of the research team
- by sending an email to [REDACTED]

12. What will happen with the results generated by this research program?

The findings from our study may be published in scientific journals and presented at conferences, all of the results will be fully anonymised and it will not be possible to identify you as a participant. You are welcome to ask us for update reports of the research and we will also endeavour to send you an update from the final study report.

13. Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet which you will receive with this information sheet.
- by asking one of the research team
- by sending an email to [REDACTED]

14. Who is organizing and funding this research?

This research is the result of a collaboration between Hywel Dda University Health Board and Respiratory Innovation Wales. Some funding towards the study has come from Trudell Medical who make a device to help with airways clearance. No company will have any access to your personal information or how, when or where the study will be published.

15. Who has reviewed the study?

Our research study has undergone review by medical doctors and scientific researchers within Hywel Dda University Health Board and across Wales as well as an NHS Research Ethics Committee (WALES REC 4).

Contacts for further information:

If you have any further queries, please do not hesitate to contact:

Prof. Keir Lewis

Chief Investigator,

Hon. Consultant, Hywel Dda University Health Board &
Professor of Respiratory Medicine, Swansea University

Telephone: [REDACTED]

Email: [REDACTED]

Mr Carwyn Bridges

Principal Investigator

Respiratory Specialist Physiotherapist

Cardiff and Vale University Health Board

Llandough Hospital

Penarth

and Honorary Research Fellow

Hywel Dda University Health Board

Telephone: [REDACTED]

Email: [REDACTED]

For independent advice and support, you may also contact **Hywel Dda Community Health Council (CHC)**, Suite 5, 1st Floor, Ty Myrddin, Carmarthen, SA31 1LP.

Phone: 01646 697610

Email: hyweldda@waleschc.org.uk

INFORMED CONSENT FORM

Version 5 6th April 2022

**Study Title: expectOratlon of sPutum Techniques real wOrld data in coPd
(TIPTOP)**

Rec reference: 21/WA/0144

IRAS reference: 289817

Participant Identification Number: _____

N.B. Three copies will be made for: (1) Participant, (2) Researcher, (3) Hospital notes (if relevant).

Research Team Leads: Professor Keir Lewis **Carwyn Bridges,**

Contact Telephone Number: [REDACTED]

Read carefully the following statements and, if you agree, please write your INITIALS in the INITIAL BOX (do not tick).

INITIAL

BOX

1.	I confirm that I have read and understood the Participant Information Sheet – (Version 5, 6 th April 2022) for the above research study. I have had the chance to ask questions, and I am happy with the answers given.	
2.	I understand that my participation is voluntary and that I am free to change my mind at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I understand that sections of any of my medical notes may be looked at by: responsible individuals from the Research Team, regulatory authorities where it is relevant to my taking part in research and the sponsor in Hywel Dda University Health Board for monitoring the conduct of the study. I give permission for these individuals to have access to my records.	

4.	I understand that if I choose to withdraw from the study, any data about me already collected will be retained and data about me will continue to be collected from my hospital records. It will not be possible for me to see or change the data held about me.	
5.	I understand and agree that a letter will be sent to my GP telling them about my participation in the research study.	
6.	I confirm that I have understood all the above aspects and I agree to take part in the 'expectOratlon of sPutum Techniques real wOrld data in coPd (TIPTOP) research study.	
7.	I understand that in agreeing to take part in this study, I will have the option to take part in future research using the data saved from this study.	
Full Name of Participant (PRINT)		Date:
		Signature:

APPENDIX 5: LEICESTER COUGH QUESTIONNAIRE. © 2001 (BIRRING, 2003)

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never
3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None
12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

APPENDIX 6: COPD ASSESSMENT TEST (CAT)

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your health care professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your well-being and daily life. Your answers, and test score, can be used by you and your health care professional to help improve the management of your COPD and get the greatest benefits from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question

Example: I am very happy ☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very sad

	Score
I never cough ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I cough all the time	
I have no phlegm (mucus) in my chest at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very limited doing activities at home	
I am confident leaving my home despite my lung condition ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am not at all confident leaving my home because of my lung condition	
I sleep soundly ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I do not sleep soundly because of my lung condition	
I have lots of energy ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I have no energy at all	
Total score	

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APPENDIX 7: SF-36 SHORT FORM

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)

Excellent	☐
Very Good	☐
Good	☐
Fair	☐
Poor	☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)

Much better than one year ago	☐
Somewhat better now than one year ago	☐
About the same as one year ago	☐
Somewhat worse now than one year ago	☐
Much worse now than one year ago	☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Please circle **one** number on each line.)

Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c) Lifting or carrying groceries	1	2	3
3(d) Climbing several flights of stairs	1	2	3
3(e) Climbing one flight of stairs	1	2	3
3(f) Bending, kneeling, or stooping	1	2	3
3(g) Walking more than a mile	1	2	3
3(h) Walking several blocks	1	2	3
3(i) Walking one block	1	2	3
3(j) Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Please circle **one** number on each line.)

	Yes	No
4(a) Cut down on the amount of time you spent on work or other activities	1	2
4(b) Accomplished less than you would like	1	2
4(c) Were limited in the kind of work or other activities	1	2
4(d) Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)? (Please circle **one** number on each line.)

	Yes	No
5(a) Cut down on the amount of time you spent on work or other activities	1	2
5(b) Accomplished less than you would like	1	2
5(c) Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

Not at all ☐
 Slightly ☐
 Moderately ☐
 Quite a bit ☐
 Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

None ☐
 Very mild ☐
 Mild ☐
 Moderate ☐
 Severe ☐
 Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

Not at all ☐
 A little bit ☐
 Moderately ☐
 Quite a bit ☐
 Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

(Please circle one number on each line.)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a) Did you feel full of life?	1	2	3	4	5	6
9(b) Have you been a very nervous person?	1	2	3	4	5	6
9(c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d) Have you felt calm and peaceful?	1	2	3	4	5	6
9(e) Did you have a lot of energy?	1	2	3	4	5	6
9(f) Have you felt downhearted and blue?	1	2	3	4	5	6
9(g) Did you feel worn out?	1	2	3	4	5	6
9(h) Have you been a happy person?	1	2	3	4	5	6
9(i) Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

All of the time ☐
 Most of the time ☐
 Some of the time ☐
 A little of the time ☐
 None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

(Please circle one number on each line.)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a) I seem to get sick a little easier than other people	1	2	3	4	5
11(b) I am as healthy as anybody I know	1	2	3	4	5
11(c) I expect my health to get worse	1	2	3	4	5
11(d) My health is excellent	1	2	3	4	5

Thank You!

APPENDIX 8: ACCEPTABILITY AND TOLERABILITY (TIPTOP)

Measure of Tolerability and Acceptability of Intervention

Instructions

Please circle the number below to indicate how you feel you have done with your treatments over the last week. Treatments should be considered as OPEP.

I find doing
my
. . .

1 2 3 4 5 6 7 8 9 10

I find doing
my
. . .

I have done
none of my
. . .

1 2 3 4 5 6 7 8 9 10

I have done
all of my
. . .

I do not find
my
treatments

1 2 3 4 5 6 7 8 9 10

I find my
treatments
useful.

How have you found using OPEP for clearing your chest?

•

APPENDIX 9: SAMPLE TRANSCRIPT FROM HCP FOCUS GROUP (CONNECT)

Connect Focus Group 28.03.2023

Transcript one: HCP

BRIDGES C: First thing, I'd just like to ask is what your general views are of the Aerobika and what your experience is on a day-to-day basis of using the Aerobika. We're just going to go around in a circle, if that's alright. So I'll just call you up and see if you want to tell me a bit about your experience, I wonder actually if the first time you speak, whether you could introduce yourself a bit, you don't need to tell us where you work, but in what setting you work is fine.

0:0:50.240 -> 0:1:0.670

TL

I am TL, I work predominantly in pulmonary rehab, Bronchiectasis clinic and then a community COPD discharge team and oxygen service. I have been dealing with OPEP for 17 years or so, 18 years going through flutter acapella aerobika. Aerobika is a relatively new kid on the block, I suppose in my terms.

I just find it a lot more manageable and a lot easier to prescribe and the interface for the patients is a lot better than the old OPEP devices that we used. We don't have funding stream for these devices in most areas in our service. So, it's probably not used as much as I would potentially like until funding is resolved.

With the patient's compliance appears to be better, but I think for me that's more related to the use of the manometer I tend not to give out the Aerobika without a manometer and unless they are using a nebulised device. I always use the manometer versions if I can just because it gives the patient a visual feedback. It's the one benefit I see of the Aerobika has compared to any of the other devices. So not only do they get the oscillation, but it's nice to know they're doing the treatment in the right zone. And I think that's why I see compliance being better with this device

30 than anything else. I'm not sure it's because it's any more efficient than anything else
31 but that that addition of the manometer thing for me is a little bit of extra cost but it's
32 in my mind a no brainer.

33 0:2:49.890 -> 0:2:56.800

34 BRIDGES C. (2031176)

35 OK. Thanks. Thanks, TL. That's a really good to kick us off there. And Jen, I wonder
36 if you've got anything to add to that or?

37 0:2:59.660 --> 0:3:20.550

38 JK

39 I'm Jen. I work in a specialist tertiary centre in London. I've been working with
40 aerobika for probably four or five years now. I agree with TL I think they are the best
41 OPEP device, and I guess the main things that I would think of is I actually do think
42 that they give a stronger isolation than some of the other devices. I do think it's a little
43 bit from my own personal experience. I think it's a little higher on the aerobika than
44 things like the acapella. Other benefits, I think because it's plastic and it's plastic
45 inside doesn't tend to rust the way that the acapella do, which is another big bonus.
46 Patients find them quite easy to clean. I do see them as the best type of OPEP. I
47 would mainly be thinking of them for patients. But yeah, in terms of OPEP I, I do
48 think they're better than the competitors.

49 0:4:19.700 --> 0:4:49.40

50 KF

51 I work in cystic fibrosis, predominantly adults, but I also cover paediatrics as well. I've
52 been using Aerobika for probably 10-15 years. From the early stages onwards
53 though, I just absolutely adore it. I think it's brilliant and after they said you could do it
54 stood on your head if you wanted to. From that dexterity point of view, it's easy to put
55 together. One of my kind of issues maybe would be more from a CF point of view is
56 around cleaning. Just because there's lots of small parts within that middle centre
57 section. I'm just often really, really concerned with I've got issues with thinking that
58 people might not be that great about cleaning and drying them appropriately. I might
59 think twice about giving it to them, but that would be my only thing. Yeah. It's just so
60 easy to use. It's Kath proof. You can only put it together one way as well. And the

61 same with the others. The oscillations are fantastic. And you can really feel that. I
62 guess it's a little bit like Marmite. Some people have already use oscillatory pep and
63 if they have already used that for several years, then sometimes they don't
64 necessarily want to move away from it. But if they're started on it, they never want to
65 put it down. So that's certainly my experience. It's just been really, really helpful, a
66 lovely piece of kit.

67 0:5:49.440 --> 0:5:56.340

68 BRIDGES C. (2031176)

69 *Great. Thanks. Uh, can I just ask a quick question there? So if you so if you you're*
70 *worried about cleaning, what do you go for?*

71 0:5:58.10 --> 0:6:24.430

72 KF

73 we're still get them to clean it in the same way. It's just more along the lines of other
74 they shaking it out properly are they ensuring it's dry, are they showing it. So that
75 then when they go to use it again it is about trying and making sure that they're just
76 really thorough with it whereas some people don't necessarily wash it very regularly.

77 0:6:24.490 --> 0:6:29.320

78 BRIDGES C. (2031176)

79 *Thank you very much, Kath, thanks for that. That's really clear. And then Rachel.*

80 0:6:31.360 --> 0:7:2.650

81 RC

82 Yes, hello. I predominantly work in an acute setting, so I cover intensive care and
83 respiratory wards, and I've only been qualified maybe coming up to four years. So
84 have been using aerobika for that period of time and we tend to use a lot of it in
85 conjunction with other therapies such as positioning autogenic drainage and that
86 type of thing. We also tend to send our nebulized medication through it normally like
87 the saline, which can be really beneficial for some of our patients who are really
88 struggling even with aerobika or any oscillation device on top. However, having said
89 that, some of these patients don't actually clean it appropriately and the valve then
90 gets stuck. They still try to use it, but it isn't as effective. So, we tend to have to
91 changed that device more often, but it's more about compliance with the patients

92 than actually the device. I find it really useful. We did recently try it with a gentleman
93 who has a Laryngectomy with a paediatric mask. It didn't go very well because of the
94 Dead Space, but we were clutching at straws with that gentleman. I really enjoy
95 using that with our population of patients.

96 0:7:49.930 --> 0:7:55.680

97 *BRIDGES C. (2031176)*

98 *Great. Thanks. Great. That's great. And last but not least, LC, to finish our circle*
99 *here.*

100 0:7:56.90 --> 0:8:17.60

101 LC

102 Hi so yeah, I'm LC. I work in community respiratory, so a little bit like similar to TL's
103 service and but less than a year ago I had been working three years in Paediatrics,
104 chronic respiratory conditions. So, CF, bronchiectasis, PCD and all of that. I share all
105 the views really that everyone said. It is really good for my rheumatoid arthritis
106 patients; they have really liked it. With the children, the positioning is so easy to
107 trigger and that it doesn't matter where they upside down and they can still trigger it
108 and I think and that's basically it. There is a lot of trouble with getting funding for that
109 currently in the community because they get like specific budget for equipment. At the
110 moment what I'm doing, I buy a small lot and then I get the GP to prescribe one. I
111 give them one whilst teaching and then ask them to return once they are prescribed
112 one. It's a bit of a hassle at the moment it's working, we didn't have manometers
113 again because of the extra cost, but I think it helps compliance anyway. Just having
114 a device because I always start with ACBT, mainly because of the breathing control
115 and then incorporate it. But I feel like they like to have something physical. I've got a
116 lot of productive asthmatic patients that don't do well with the with the other PEP
117 devices or the oscillatory PEP devices.

118 0:10:0.210 --> 0:10:12.720

119 *BRIDGES C. (2031176)*

120 *That's really interesting and actually brings us on to my sort of next sort of question*
121 *is about when you're prescribing it, how you provide the teaching and you know*
122 *what?*

123 *What decides the resistance that you go for or the treatment duration or the*
124 *frequency of use? But I suppose around that as well as just thinking about things like*
125 *specific instructions that you might give to the patient whilst you're teaching? Do you*
126 *find yourself repeating quite regularly? Has anyone got any thoughts on that?*

127 0:11:0.220 --> 0:11:1.780

128 KF

129 I would be thinking about that peak respiratory flow rate flow rate, what they're able
130 to generate or what they're turnovers of air is like in the first place from a resistance
131 point. Also, looking at what other devices they've got too. Also, just with the
132 manometers, we do generally tend to use them kind of during assessment and then
133 at a review. But we didn't tend to keep them, it's just because they steam up quite a
134 lot. There's a lot of moisture within them. I just think about the infection control side
135 of things. It just makes me a little bit nervous. Generally tend to use them as an
136 assessment or if they kind of exacerbate and they've got secretions, I'm wanting to
137 then reassess and just see where we're at with it.

138 I'd be based off the manometer and just making sure that they're keeping that
139 sustained breath through the cycle all the way through it expiration, just ensuring that
140 their sustaining it rather than swinging through the breath there. Getting them to take
141 a medium to large sized breath and breath hold at the top the expiration for 6
142 seconds and then just holding out there and ensuring they're reaching that pressure.
143 Normally do 10 breaths and for at least two cycles. Obviously more if needed. If
144 they're able to do that and then with huffs and coughs as well, just to be able to
145 clear.

146 0:12:36.360 --> 0:12:41.770

147 *BRIDGES C. (2031176)*

148 *Kind of you to kick us off there as anyone got anything to add there, perhaps LG?*

149 0:12:43.910 --> 0:12:44.480

150 LG

151 So often would just do 3 cycles of 8 to 10 breaths but with more breathless patients,
152 then it might be even less to give them a break so that they can tolerate. Otherwise,
153 they might get dizzy. I find that the ones that have done airway clearance from a

154 younger age are more willing to trial other things at home and then let me know what
155 works for them. Also, in terms of combining with positioning, whereas if it's quite new
156 and they are over 70 also they don't they don't try it as much. And then normally I I'm
157 quite lucky really with my clinics. I teach them once, send them home and then they
158 can return for a short follow up in a month and then if I can do an annual review or
159 they've got an opportunity, I got through it again. And I think in terms of teaching,
160 that's it. If I had a manometer would be ideal, but at the moment it's just about getting
161 that oscillation and then getting the breathing control and clearing really.

162 0:14:45.190 --> 0:14:46.120

163 RC

164 Yeah, I think from an acute setting point of view, I'm seeing a lot of patients who are
165 already exacerbating anyway, so we can't even go anywhere near some of the
166 repetitions that that maybe community settings would do. We tend to use it in
167 conjunction with our ACBT and keep it quite short and sharp because our patients
168 are very severely short of breath, they're quite agitated and can be sometimes quite
169 aggressive with that. But I will chronic chest who kind of bounce in and out and we've
170 tried XY and Z with them previously. They kind of take to it a lot, a lot easier. I tend to
171 find myself telling patients to do it at least three times a day, and specifically first
172 thing in the morning and last thing at night just because of a lot of the patients tend
173 to stay up at night with their chronic chests and their chronic coughs because they
174 just haven't cleared their chest. Some will take to like a duck with water and run with
175 it, whereas others won't and they won't comply with it as well as others.

176 0:15:59.470 --> 0:16:26.170

177 *BRIDGES C. (2031176)*

178 *I recognized that the difference between acute settings and people who haven't*
179 *experienced it before is quite a lot, isn't it? That there is learning that's involved in*
180 *that. So just to move on to give Jen and TL an opportunity, just to consider that any*
181 *sort of teaching tips that you might give or perhaps a resistance that you start at?*

182 0:16:28.490 --> 0:16:56.830

183 JK

184 I guess in terms of the resistance, I would probably want to understand a little bit

185 more about kind of the pathophysiology of their lungs that I'm dealing with. Like
186 they're lung function, if it's particularly restricted, I'd be going down to lower
187 resistance, their kind of overall strength as well, maybe set them off on two of their
188 little bit more elderly or else maybe start them on three and then titrate according to
189 all the things that LG was talking about. For instance, if they're getting dizzy, if
190 they've had breakfast, that kind of thing. Looking at whether resistance is up or
191 down. There's some thought, I suppose, that you should have a ratio of 1 to 1.1 in
192 terms of your inspiratory and expiratory flow time, so I know some of my colleagues
193 do that kind of listen and see if the breath out is slightly longer and they would use
194 that as a way to titrate the resistance. It's not something that I usually do myself. I
195 find the main mistakes that patients make has something to do with the way that you
196 hold the Aerobika. Such as having some sort of poor posture of the neck. That way
197 the oscillations aren't getting right down to the chest and they're going into sort of like
198 the upper airway or the back of the mouth. So, a lot of the times when you're
199 teaching initially, they'll hold it like bad or they'll bend over a little bit too much. That's
200 one common mistake. Another thing I see people do is exhale way too much, like
201 right down into their reserve. And then I suppose you're impacting the breath on the
202 way back in. They're taking a huge breath and you're not getting that nice
203 recruitment of and accessibility of the secretions. So yeah, that would be the most
204 common tips that I would give, and I suppose starting off by explaining like what this
205 is, why I've chosen it. Sometimes I use an analogy like oh, you know, there's some
206 thought that this might shake the flame away from your lungs. Like, if you're trying to
207 get the last of the ketchup bottle or something like that and then the patient is like
208 'oh, yeah, yeah' and then they're on board with it a little bit more. I think definitely
209 when I'm teaching at, I explain how it works before it using it. Then it depends on the
210 patient practising this at home. It almost defeats the purpose, but you know a lot of
211 the time they think all I've done my Aerobika and that's it, whereas obviously the
212 huffs are just as important. So that would be another common pitfall.

213 0:19:5.580 --> 0:19:12.540

214 TL

215 I'm more based on patient comfort I suppose when using the manometer. Really
216 helps in terms of a visual guide. Just from observing the patients on the higher

217 resistance setting, four and five. They can generate that pressure for longer and you
218 seem to get a much a much finer amplitude of vibration. Whereas when you when
219 you turn it down to one, they've almost got to work really hard. I tend to find that
220 those that have much more
221 Peripheral secretion issues or sputum plugging tolerate setting four and five, and it's
222 much more efficient and effective for them. Whereas those that tend to struggle more
223 with central airway clearance then the lower resistance settings or almost mimic
224 more of a huff. I supposed at that point they do just have to generate much more
225 force to get anywhere near 15 and 20 centimetres of water pressure. It was the
226 same to a degree with the acapella, with the variation. But I don't think there is any
227 real treatment like tips and techniques that I give them specifically, I just take some
228 time to explain. What it's there for, why it's there. They love the device the same as
229 an inhaler. I think almost by offering them the device you've already got them
230 halfway on board. You know I think it's easy for them to get used to using this piece
231 of equipment rather than what they perceive is just some breathing techniques.

232 0:21:23.110 --> 0:21:44.900

233 *BRIDGES C. (2031176)*

234 *Thanks TL and thanks everyone. Actually it's you know really clear, you know how*
235 *you are using them. So we've given them [patients] an overview, we've taught them*
236 *how to use it, so the next time you see him in clinic how do you talk to them*
237 *Adherence to therapy, and what sort of language do they use to describe what*
238 *they've been doing? And do you think that people are able to follow the instructions*
239 *really well from one clinic to the next. Wonder if we can just put hands up if anyone*
240 *got anything to say on that.*

241 0:22:27.970 --> 0:22:40.640

242 KF

243 We've got people that have all sorts of names for the Aerobika because they can't
244 say aerobika, so there's all sorts like my Ribena or the white thing or the white
245 trumpet, or the all sorts of things that come out which is quite entertaining. When
246 people come back into clinic again, we try and get them to bring their Aerobika. We'll
247 put reminders in for them to bring all their equipment. When they come they can do
248 that and when they're staying as inpatients as well. We would just change resistance

249 if we need to based on how hard they're working, but also from a secretion
250 management point of view. We do find that when we go in and we're seeing them
251 day on day that actually just adjusting those techniques is really, really important
252 because they do forget and they don't necessarily always do it properly. And you do
253 have to remind them about technique and them not rushing through and ensuring
254 that they're doing more than a couple of cycles as well.

255 0:24:5.770 --> 0:24:20.420

256 TL

257 I only see them in in Bronchiectasis clinic will be a one off within an MDT clinic. It's a
258 bit of a one stop shop and then I won't see them for three to six months afterwards. I
259 try and encourage them to bring it in and on questioning. Are you using? They all
260 nod their head. And then when you delve into it and they're not. Show me how you
261 are using it and they get it out their bag and blowing it and the manometer pops off
262 the top. There is a big gap from what I see with what I do in that contact afterwards
263 that encouragement to continue with use that real idea of compliance. You know it's
264 based on self-report. There's no way of monitoring that, you know to a degree we
265 can fill in a diary as much as you like. It's not like a cohesive where you can
266 download all this stuff and so forth. So from a follow-up perspective, it's very much
267 almost the patient fessing up to not using it quite as much as they should do, but
268 we're talking six months in between, you know it's a heck of a long time. I think the
269 biggest issue is the patients that I see. Somebody said earlier on that its patients that
270 are slightly older, not used to sputum clearance regimes. You're trying to introduce
271 something that fundamentally 70% of the time for a lot of these patients is not
272 goanna make them productive. So trying to keep compliance up in someone who
273 isn't always going to be productive. It's compliance that is more of an issue at the
274 follow up I suppose.

275 0:26:17.780 --> 0:26:43.190

276 KF

277 Yes, sorry I remembered and all I was gonna say is that a lot of our clinics are now
278 virtual as well as we do have that blended approach. It's been brilliant because
279 actually when they do forget their devices and if they are actually using it, it will be to
280 hand or as otherwise it's like hidden in a drawer somewhere. We know that perhaps

281 that they're not necessarily sticking to it. If they're able to describe the technique and
282 they follow through and nearly how we've been teaching them then it's clear that
283 they're more likely to have been adhering to what they've been asked to do.

284 0:26:58.620 --> 0:27:17.190

285 JK

286 I think I would echo what you said. There's no real way to check what they're
287 adherence is, I guess there are sneaky ways that you could check it. About whether
288 they have to hand, you know, whether they remember how many reps and things like
289 that they're supposed to be doing. And then I've been looking out for other things
290 that mean either they haven't been doing it or hasn't been working properly, like for
291 example, if they tell me they're going to bed and as soon as they lie down, they're
292 coughing, or when I get to the gym and go on a treadmill, I'm coughing up flem and
293 things like that, that would maybe and make me suspicious that they have phlegm,
294 that they're not clearing. Whether that's due to non-adherence or because they're not
295 using it correctly. I guess if I would like to think that if they have been using it, I would
296 be able to have a sort of a discussion around it and it could be having it there as a
297 visual prompt. Some people find ACBT or ad works a bit better. If you're traveling a
298 lot or maybe you're stuck between two houses or something like that. I getting down
299 to the bottom of how the patient is getting on with it and then probably adjusting it if
300 needs be. I would often say that like their treatment burden should kind of match
301 their symptom burden as well. It could be that maybe you started them off on twice a
302 day or something like that, even if they terrible lung disease, it's just not doable for
303 them at the moment, maybe pairing it back and review. And then can we build it up. I
304 think, like the device itself and how they're doing with it is one part of the overall
305 picture of kind of the follow up and things like that.

306 0:28:59.160 --> 0:29:29.450

307 RC

308 It was really helpful when they're on the respiratory ward more than non- respiratory
309 wards. The nurses will prompt them to use these types of devices and we'll link it
310 with the medications and things. I have in the past written out an airway clearance
311 plan, put it above the bed, give it to the nurses, give it to the patient. So everyone's
312 kind of aware and they will help prompt it, which is really helpful. But they tend to

313 exacerbate, come straight in and you'll ask them. Oh, what about that piece of
314 equipment? And they nine times out ten don't remember the piece of equipment.
315 Can't remember it. We do ask our Community services to review them, but they're so
316 overstretched and we've got so many chronic, complex chests needing more
317 complex input that they tend to see them first and subsequently they exacerbate and
318 come straight back in. It's quite challenging from an acute point of view and then
319 which translates then to a Community point of view as well.

320 0:30:5.820 --> 0:30:36.970

321 BRIDGES C. (2031176)

322 *OK. Thank you very much, Rachel. If I can just show you a short video from Trudell,*
323 *just that introduces the next generation of row because and then after that, we'll just*
324 *have a bit of a chat about some of the issues or some of the advantages or some of*
325 *the things that we might want to consider.*

326 0:30:50.720 --> 0:30:54.130

327 *Rachel.E.Gemine (DHCW - Information Services)*

328 *Sorry, can I ask a really quick question? Does anyone use those [introductory*
329 *videos] when they're teaching their patients? If not is it because they're not useful or*
330 *you just don't have access to them?*

331 0:31:10.950 --> 0:31:18.680

332 KF

333 I didn't know they were there until you added them to the e-mail, to be honest, and
334 I've shared them already with some of my respiratory colleagues that these are
335 great.

336 0:31:22.630 --> 0:31:25.320

337 *Rachel.E.Gemine (DHCW - Information Services)*

338 *Is that the same for others? They didn't know they were there.*

339 0:31:23.540 --> 0:31:29.980

340 LC

341 Yeah. I didn't know about them.

342 0:31:30.610 --> 0:31:39.910

343 LC

344 Sometimes I do send that to the more tech able patients. I didn't know about both
345 actually.

346 0:31:41.570 --> 0:31:51.920

347 JK

348 I would usually send them their Bronchiectasis toolkit ones. I think it's like an
349 Australian website. It's the same technique but it's very acapella. I think it's slightly
350 clearer the video, but there's not much in it.

351 0:32:0.120 --> 0:32:16.50

352 JK

353 Yeah, those are the ones that we send. For whatever reason, they're really
354 American. I usually do send the Bronchiectasis one, which is actually, I think it's
355 targeted at physios, but I think demonstration is really good.

356 0:35:2.930 --> 0:35:32.520

357 *BRIDGES C. (2031176)*

358 *I think that this is a really interesting point in the product development, there's lots of*
359 *stuff that that is that is undecided and this is our opportunity to give as much*
360 *feedback as we can about what would be useful in that sort of device.*

361 0:35:32.980 --> 0:35:44.30

362 *BRIDGES C. (2031176)*

363 *I can ask then the first few questions, what do you think about the idea of a smarter*
364 *aerobika connected? Would there be anything that you'd be really excited about or*
365 *really cautious about? When this comes to fruition?*

366 0:36:1.230 --> 0:36:29.740

367 JK

368 Is it just me but at the moment we don't have any information about what the
369 consensus would be. It's just that it's going to be a big project in CF. I don't work in
370 CF, but there was a big project, and they did a collaboration with Microsoft where
371 they had sensors of some description. I don't have information on what exactly was
372 in those sensors, but it would be great to have like pressure and flow sensors.

373 People have spoken about Manometers already. And I guess if you could get some
374 sort of spirometry. That would be incredibly useful in terms of picking up what's going
375 on with the Airways on expiration, so you could pick up things like if they've got
376 phlegm, and if that's in the proximal airways, more central airways you know, that
377 this could even be fed back to the patient, you know, with enough development in
378 real time.

379 Trudell Medical could collect a lot of information about adherence and how long the
380 sessions are lasting and what types of patients are adhering to the device. So that
381 would be one thing. When I am looking at somebody doing the aerobika, listening to
382 them is almost just as important as seeing what's going on with the airways. I don't
383 know how you would do it, but I do think it'd be really interesting to have some sort of
384 an audio sensor of some description. Yeah, those are the things that I think would be
385 great to have in there. And then if you could some sort of feedback in real time with
386 your mobile phone, whether it's a moment or whatever it is, if it can be fed back by
387 Bluetooth, I think that will be very good and very user friendly as well.

388 0:38:0.810 --> 0:38:2.520

389 *BRIDGES C. (2031176)*

390 *OK. Thanks again so there will be a pressure sensor and it will be capable of almost*
391 *everything that that that we're talking about the possibilities are endless. But it just a*
392 *clean sheet. It'd be interesting to hear what you guys thinks off the bat, RC.*

393 0:38:26.790 --> 0:39:1.100

394 RC

395 And I think is a good thing as long as the patient has got that real time feedback. My
396 only concern is the population [of the patients], the majority are in their late sixties,
397 seventies, eighties and they don't have a mobile phone that they are able to work
398 and connect with, let alone understand what it would mean and how it would
399 implicate on their actual medical treatment. I know we've got data card so we can
400 pull the data cards and pull that information to see if they are actually using it, how
401 long they using it for and whether there was maybe a device that would come with it
402 so they could see it in real time for those patients who don't have access to those
403 devices. A lot of my patients don't even know how to use a phone.

404 0:39:18.10 --> 0:39:30.860

405 BRIDGES C. (2031176)

406 OK. Thanks. Thanks, Rachel. I definitely agree that you know data definitely a
407 massive thing in certain conditions. Thank you, LC.

408 0:39:36.370 --> 0:39:59.520

409 LC

410 Living in Cornwall, which is really rural, and some places that really far away, but
411 also at the same time I'm not as bothered. It reminds me of the nebulizer ineb,
412 sometimes he's used in CF and it's got a disk that records the length of their
413 treatment on. So in the past when I've used that with CF patients, sat down with
414 them and showed them, we looked at data a month back to set goals and be like
415 right so this month or the last three months you've done that much why don't we set
416 a more realistic goal. So potentially if a patient wasn't that tech literate. Then we
417 could just use it as an adherence tool with them. My worries are costs I feel from
418 generic service I'm already struggling to get funding for aerobika so let alone.

419 0:41:0.50 --> 0:41:2.790

420 BRIDGES C. (2031176)

421 Thank you, LC. TL.

422 0:41:24.260 --> 0:41:40.70

423 TL

424 I mean, obviously the points were making before about compliance to a degree and
425 so on. From the outside looking in, it looks like a brilliant idea, doesn't it how that
426 interface works, how it communicates with whatever you've got and so on. You know
427 that's gonna be quite complicated. I suppose it seems easy, but you know, with lack
428 of access to things with you, as the guys have been saying and I suppose it's about
429 patients coping as well because I know a lot of my patients are in their sixties,
430 seventies and eighties and are nervous about Big Brother watching them and
431 sharing this, that and the other. And is this little device in their aerobika gonna be
432 telling somebody and then the other side of the world, what they're watching on TV.
433 You know, they're just a different population to CF patients generally. So having said
434 that in terms of the IEP and things like that, it's like a consenting process, you know.

435 Is there something the patient would have to sign? To say that they're happy for this
436 type of data collection.

437 0:42:39.690 --> 0:42:49.760

438 BRIDGES C. (2031176)

439 *Yeah. So I think that that's really interesting, isn't it? So just thinking about the*
440 *people who scan their devices, that have that data themselves and then they choose*
441 *whether to share it with whoever, such as the GP. I wonder whether that's a model*
442 *that that might work that how you I don't know how you feel about that.*

443 0:43:30.660 --> 0:43:48.860

444 TL

445 It would be an interesting one, if they're happy to share that, then that I suppose it's
446 definitely a way around it.

447 0:43:54.660 --> 0:44:2.250

448 KF

449 Yeah. What TL was saying just about it being their data and is really, really
450 interesting. The CF population, they're nervous about sharing [data about
451 themselves] and it is a spotlight on them and it's so intrusive in their life already with
452 the amount of information that we know about them. So they've got to leave the
453 reviews, they've got the Nuvo air, they've got the CF healthhub which is the chip
454 nebulizers, you know the we're very much it's at such a spotlight on them all the
455 time. You can see the pressure. So, it's about how we approach it and you know how
456 we support it rather than actually pointing a finger. So as long as it's used in the right
457 way, I think people are willing to do it. They do need to be able to consent so it's
458 whether they give it over to you. And quite often we have a lot of people that just
459 forget to bring their own inebts through and that's them just not wanting to share their
460 information. That's the way around that one.

461 That was one of my points. The second one was about the cleaning. With that, we're
462 going to be able to actually clean it really effectively if it's got some kind of device on
463 it.. And also, just I suppose the level of information that's shared to patients, but also
464 then to the clinicians as well and what that would look like, how different that would
465 be. I guess you know, depending on what was shared with the patient, it'd be up for

466 a level of misinterpretation, or they might interpret it differently to what, clinically, we
467 can understand. I guess that would be just a thought in my mind as to how much
468 [information] would you give them until the clinician had a chance to review that
469 information themselves. But also then, it just gives us that objective information,
470 doesn't it? It's really helpful and actually they can look at that reproducibility and
471 actually ensure and have that confidence that they're doing the right thing for them.
472 We can see that from a home setting point of view as well. So that would be really
473 handy.

474

475 And I would say that if it was possible to link some of these platforms together so
476 that it's just not another place for connections. If that data is downloading, you know,
477 is it possible to link into other sources? Is it possible to then do something along
478 those lines as well so it's easier from the clinician side of things as it would be an
479 automatic upload as opposed to having to then separately download something?
480 Also this data being comparable and we can see over time that how things are
481 changing. We can see if resistance is changing and you know in line with other
482 objective outcomes like their FEV one, ect.

483 0:46:44.460 --> 0:47:14.650

484 BRIDGES C. (2031176)

485 *Great. That's, you know, and I think that one of the sort of the questions that Trudell*
486 *was trying to understand, does it need to be attached to an electric medical record, if*
487 *it can, would it be important that you just get it as a PDF? What would be important*
488 *for the patient is to just have a reminder about when they're doing their treatments or*
489 *another things like that. And then the spirometry thing that somebody brought up*
490 *earlier was a really interesting point. And I think that with acoustics they can do some*
491 *really clever things now. But that may only give us trends rather than pure values, so*
492 *it's not going to replace former tree. What people think about how we can make it*
493 *most useful to people living with longer term conditions? What are the symptom*
494 *trackers? What about that sort of stuff? JK?*

495 0:48:7.440 --> 0:48:33.730

496 JK

497 Yeah. I mean, I don't really know what the tech is going to be like, but some sort of
498 like deep learning where my iPhone could tell me that I usually listen to certain
499 podcasts at a certain time. Surely you know it's 4:00 PM, you usually do your aerobic
500 at this time. If you can pick up on the habits of the how people are using it and be
501 able to like reminders of something like that, I think would be massive. And then in
502 terms of how I'd like to see the data, I would not like a PDF. I would like a
503 spreadsheet or something where I can use the data a little bit more. It is an
504 interesting thing, isn't it? As to how much there will be available then and certain
505 patients would need to be aware and consent to that, but I think. What I've found in
506 my dealings with the patients that are actually a little bit older is that I often
507 underestimate how much they can do with their phones like scanning a QR code or
508 something like that. We have 78-year-olds that can actually do that, whereas I
509 thought they couldn't so. But if there could be some sort of deep learning, I think that
510 would be that would be the best thing.

511 0:50:00.520 --> 0:50:30.150

512 LC

513 I think for me is the education side of things. Like I can see how great it would be
514 that they can look at what's happening and spot trends. I think that can give you and
515 the patient and idea of what's happened during an exacerbation. That's why you
516 might need to do this. Just their education side of things based I guess it'll be a great
517 tool to justify all the things we say now that is harder to see because they might not
518 understand and yeah it gives them a more real time feedback, that's accurate.

519

520 0:51:19.860 --> 0:51:31.820

521 TL

522 How much is too much and how much is too little? But there's almost 2 levels of
523 data, isn't there? There's a data for the clinician and a data for the patient and that.
524 Really that needs to be kind of separated off, doesn't it? It's trying to gauge from the
525 patient what they would want. I suppose you know we can sit here and say we want
526 this, we want that we want the other, the patient just wants a little bit of feedback to

527 know they're doing it right and that that's probably going to be quite difficult to gain, I
528 think.

529 0:52:15.800 --> 0:52:46.40

530 KF

531 The people that want to engage in in technology, they're the ones that are generally
532 tending to be used already. And so you get real engagement from people that love
533 the kit and love, you know, the numbers and they've got their Apple watches. So
534 you'll probably find that those are the ones that do it, the ones that we really need to
535 see and want to pick up on and ones that move potentially a little bit more concerned
536 about are not engaging So yeah, it's being able to make it interesting enough for to
537 be able to capture those people.

538 0:53:2.750 --> 0:53:19.120

539 *BRIDGES C. (2031176)*

540 *Thanks, Kath. So just the last five minutes then, so just got one more question about*
541 *there being a patient interface and a clinician interface, would that be acceptable do*
542 *you think that?*

543 0:53:20.90 --> 0:53:40.580

544 *BRIDGES C. (2031176)*

545 *We, as clinicians might need to build the patient interface depending on the patient.*
546 *I've heard people say that some patients just didn't need a reminder or some*
547 *patients would value the manometer much more. if we could we could personalize*
548 *that for them as you gave it out to them, that would that be something that would be*
549 *interesting, do you think?*

550 0:53:57.550 --> 0:54:4.700

551 LC

552 Yeah. It sounds interesting. My only worry would be the more we can or the more we
553 need to personalize it, that's going to be a little more time consuming. But if it's easy
554 to just do some settings according to what the patient feels at the time and then it's
555 modifiable as their understanding improves then I think it's definitely useful because I
556 think just automatically reminding them etc. But it's not for everyone?

557 0:54:49.320 --> 0:55:8.860

558 BRIDGES C. (2031176)

559 OK. Thank you. Thank you very much for that, Laura. So just like to last couple of
560 minutes, any wrap up comments, anything we haven't covered that you really want to
561 see would be really good or anything?

562 0:55:9.620 --> 0:55:37.970

563 JK

564 I was just going to say on the interface bit I do think possibly, in the interest of
565 transparency and ease, it would be good to have 1 interfaces for patients and
566 clinicians similar to how we use to say the new value or something like that. The
567 patients just send us their report. And I do see definitely benefit in being able to log
568 in and see how they're doing. But definitely, I mean it would be crazy not to take
569 advantage of the opportunity to collect a lot more data about the particular sessions.
570 You know what you recorded during them, how long they last and things like that,
571 whether that needs to be accessible to the patients.

572 0:56:12.930 --> 0:56:22.660

573 KF

574 Have two different views the patients view and then we got the flow volume loops in
575 exactly the same so you know whilst they do have the same information we have
576 that more in depth data as well.

577

APPENDIX 10: QUESTIONS AND AREAS TO BE EXPLORED - CONNECT

Aerobika

- 1) How is using the Aerobika?
Who Taught you?
- 2) Was it easy to use?
What does your routine look like?
Cleaning?
How do you know it's working?
- 3) Did you have any problems? Describe/discuss
- 4) How does this compare to other ways you clear your chest?

Smart Aerobika Connected

- 1) What do you think about the Smart Aerobika Connected?
- 2) Do you think it could help you manage your condition?
 - a. If so, how?
- 3) How often would you like to interact with the app?
- 4) Would you be happy to share the data in the app with HCPs to help manage your condition?

Resources provided prior to the focus group

How it works - https://youtu.be/c_wrEZ5h780

How to use (animated) - <https://youtu.be/PzwNDnre6Ng>

How to use (live action) - <https://youtu.be/iy2oYadhF9Q>

APPENDIX 11: CONFIRMATION OF ETHICAL APPROVAL (CONNECT)

30/11/2023, 18:24

Email - BRIDGES C. (2031176) - Outlook

Re: SUMS RESC 2022-0113 Review notification

Ana Sergio Da Silva <[REDACTED]>
on behalf of
Medical School Research Ethics Sub-Committee <sumsresc@swansea.ac.uk>

Wed 07/12/2022 14:24

To: BRIDGES C. <[REDACTED]>
Cc: Keir Lewis <[REDACTED]>; Maddie Chesmore <[REDACTED]>

Dear Carwyn,

I am pleased to let you know that your application has been reviewed by chairs actions and has been given a favourable ethical opinion, you can now start your project. Ensure the reference above SUMS RESC reference is used within your project documents and in any correspondence with the committee, failing to do so may lead to delays.

[@Maddie Chesmore](#) can we send a letter of approval for this projects please.

Please note that all amendments including changes to the study team, study design or supporting documents (including minor amendments) must be notified to the Research Ethics Subcommittee. It is your responsibility to inform the RESC if the amendment affects the risk status of your project by submitting a notice of amendment form available from SUMS RESC webpages.

Wishing you all the success in conducting this study.
Ana

From: BRIDGES C. <[REDACTED]>
Date: Tuesday, 6 December 2022 at 15:55
To: Medical School Research Ethics Sub-Committee <sumsresc@swansea.ac.uk>
Cc: Keir Lewis <[REDACTED]>
Subject: Re: SUMS RESC 2022-0113 Review notification

Dear Ana,

Thank you for taking the time to review my application.
Please find attached Application with track changes addressing the comments.
Also, PIS-ICF with additional information. I have included a copy with track changes and a clean copy for clarity.
I hope that i have understood correctly and any changes are clear.

Please let me know if i need to add anything else? Will confirmation of a favorable opinion be sent via email?

Many Thanks

Carwyn

From: Ana Sergio Da Silva <[REDACTED]> on behalf of Medical School Research Ethics Sub-Committee <sumsresc@swansea.ac.uk>
Sent: 06 December 2022 10:31
To: BRIDGES C. <[REDACTED]>
Subject: SUMS RESC 2022-0113 Review notification

Dear Carwyn,

<https://outlook.office.com/mail/id/AAQKADQyZDBmZGYyLTlhOWEiNDhOS1hMzgwLT15MjMyZWU2ZTwNAQAAP59EBot26hCokkNM6D83lc...> 1/2

APPENDIX 12: CONNECT ADVERTISEMENT E-POSTER

HEY, YOU...
DO YOU USE ONE
OF THESE TO HELP
MANAGE YOUR
CONDITION?



...If you're nodding right now, We would like to hear from you!

**SIGN UP
HERE**



if you suffer from COPD, Cystic Fibrosis or Bronchiectasis and use an OPEP device (Aerobika[™]) to clear mucus from your chest, you can take part in this 1 hour focus group. You will receive a gift voucher for your involvement.

We are looking for:

- Adults 18+
- Use Aerobika[™] regularly to clear your chest.
- Do you have a diagnosis of COPD, Bronchiectasis or Cystic Fibrosis
- Happy to give 1hr of your time and voice your opinion in a focus group.

APPENDIX 13: PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM (CONNECT)

CONNECT: Thematic qualitative analysis of Aerobika™ and Smart Connected Aerobika™ in chronic respiratory conditions.

PARTICIPANT INFORMATION SHEET

Please ask us if you would like this Participant Information Sheet translated into Welsh.

Version number: 1.1

Date: 06-12-2022

Hosted By: Respiratory Innovation Wales (RIW)

Sponsor: Swansea University

Ethical Reviewed by Swansea University Medical School (SUMS) Reference:

SUMS RESC 2022-0113

Chief Investigator: Mr Carwyn Bridges

Co-investigators: Prof. Keir Lewis, Dr. Rachel Gemine, Jem Patel, Sarah Humphrey

1. Invitation and summary

You are being invited to take part in a research study. Before you decide, it is important to explain why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. Do not hesitate to ask us if there is anything that is not clear or if you would like additional information. Take time to decide whether or not you wish to take part in the research study.

This study aims to gather the experiences of people using an Aerobika, Oscillatory Positive Expiratory pressure (OPEP) device to clear the sputum from their chests. We are also interested in hearing your views on a new generation of devices and the digital display that may be used. The OPEP device has been produced Trudell international Ltd. Swansea University Health Board are helping them to see if people with chronic lung conditions like it. To do this, we wish to bring together groups of people with COPD, Bronchiectasis, Cystic Fibrosis and Health care professionals providing the devices, then ask the group questions relating to Aerobika and Smart Aerobika.

2. What is the purpose of the research study?

People with chronic lung conditions often have several treatments to do every day and clearing the mucus from your chest can be time consuming and difficult. This study aims to get a better understanding of the opinions of people who use an Aerobika regularly to help further the understanding of its use and inform the development of the next generation of devices that could offer feedback to help you make the most of your treatment time.

We aim to conduct 4 focus groups of 10-15 people with COPD, Bronchiectasis, Cystic Fibrosis and Health Care Professionals (HCP) who work with people with these conditions. The results of this research will be written up as part of a PhD thesis.

3. Why have I been asked to take part?

We are inviting you to take part in this research study because you have COPD, Bronchiectasis, Cystic fibrosis or you are a HCP who teaches people how to use OPEP devices and we would like to hear your views on the Aerobika and Smart Connected Aerobika.

4. Do I have to participate in this study?

No, it is up to you to decide whether you would like to participate, we will ask you to read this Participant Information Sheet and sign the attached Consent Form. If you have any questions, please feel free to discuss them with your friends, family, or GP. You can also contact the lead researcher (Carwyn Bridges) using the contact details at the bottom of this sheet. If at any point you change your mind, you can withdraw from the study, without giving a reason.

5. What will happen to me if I agree to take part in the research study?

If you agree to take part in this research study, we will phone you to arrange a time which is best suited for all 15 people to come to The Beacon Enterprise Centre, Llanelli, SA14 8LQ or meet virtually on Microsoft Teams. We will collect your signed Consent Forms and make copies for both your and our records. If the meeting is Virtual, then electronic consent forms will be collected.

We will then present a 5 min presentation on Aerobika and Smart Connected Aerobika and show you some material including screen shots of the devices and digital interfaces. We will then bring all 15 people together and hold a focus group, asking you questions about your experience and thoughts. This focus group will be audio recorded and will take approximately 60 minutes.

We will then create a word for word account of what was said but remove any identifiable information, such as your name. We will then analyse this to identify common themes throughout the account and give these back to you at a later date to see if you agree with what we found. Trudell international. will then be given a final report of our findings to help them develop the product further. They will not be given any information which could identify you.

6. What are the possible benefits of taking part in the research study?

The results of the research will have no direct benefits to you but may help further develop Aerobika use which could help others in the future. Unfortunately, we cannot pay you for participating in this study, but we can pay for reasonable travel expenses. If you take a taxi, we do ask that you get a receipt. All participants will be offered a retail gift voucher to the value of £20 to thank you for your involvement.

7. What are the possible disadvantages and risks of taking part in this research study?

There are no known side effects from taking part in this study. There is the possibility that you may feel breathless during the focus group. If this happens, you are free to take a break, or stop completely if you would like.

8. What will happen if something goes wrong?

If you have concerns about this study, we encourage you to raise your concerns as soon as possible. Firstly, you should ask to speak to the researcher who will do their best to answer your questions.

If you wish to speak to someone who is not part of the study team you can contact the [Research Governance and Conduct Complaints contact Swansea University](#).

researchintegrity@swansea.ac.uk

9. Will my taking part in this research study be kept confidential?

Swansea University is the sponsor for this study. We will be using information from you to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. We will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

10. What will happen with the results generated by this research program?

The findings from our study may be published in scientific journals and presented at conferences, all the results will be fully anonymised. An anonymised report will be given to Trudell International, the manufacturer of Aerobika™ and it will not be possible for them to identify you as a participant. You are welcome to ask us for reports of the research and we can also send you a copy of the report we provide Trudell international. Please note that the data we will collect for our study will be made anonymous, as soon as it is transcribed, within 1 month of recording thus it will not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. Therefore, if at the end of this research you decide to have your data withdrawn, please let us know before you leave. Data will be kept for a minimum of ten years.

11. Who is organising and funding this research?

This research is the result of a collaboration between Swansea University, Respiratory Innovation Wales and Trudell international. It is hosted by Respiratory Innovation Wales and funded by Trudell international. Trudell international are acting as collaborators in this research and will have access to the data. However, they will not have any influence over the questions asked or data collection during this research.

12. Who has reviewed the study?

The research has been approved by Swansea University Medical School Research Ethics Committee. and RIW PPI group.

13. Data Protection Privacy Notice

The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data and can be contacted at the Vice Chancellors Office.

Your personal data will be processed for the purposes outlined in this information sheet. Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you.

The legal basis that we will rely on to process your personal data will be processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by the Medical School Research Ethics Committee, Swansea University.

The legal basis that we will rely on to process special categories of data will be processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

14. How long will your information be held?

Data will be preserved and accessible for a minimum of 10 years after completion of the research. Records from studies with major health, clinical, social, environmental or heritage importance, novel intervention, or studies which are on-going or controversial should be retained for at least 20 years after completion of the study. It may be appropriate to keep such study data permanently within the university, a national collection, or as required by the funder's data policy.

15. What are your rights?

You have a right to access your personal information, to object to the processing of your personal information, to rectify, to erase, to restrict and to port your personal information. Please visit the University Data Protection webpages for further information in relation to your rights.

Any requests or objections should be made in writing to the University Data Protection Officer:-

University Compliance Officer (FOI/DP)

Vice-Chancellor's Office

Swansea University

Singleton Park

Swansea

SA2 8PP

Email: dataprotection@swansea.ac.uk

16. How to make a complaint

If you are unhappy with the way in which your personal data has been processed you may in the first instance contact the University Data Protection Officer using the contact details above.

If you remain dissatisfied, then you have the right to apply directly to the Information Commissioner for a decision. The Information Commissioner can be contacted at: -

Information Commissioner's Office,

Wycliffe House,

Water Lane,

Wilmslow,

Cheshire,

SK9 5AF

www.ico.org.uk

17. What if I have other questions?

If you have further questions about this study, please do not hesitate to contact us:

Chief Investigator:

Mr Carwyn Bridges

Email:

████████████████████

Telephone: ██████████

Co-investigators

Prof. Keir Lewis

Email:

████████████████████

Telephone: ██████████

Dr. Rachel Gemine

Email:

████████████████████

Telephone: ██████████

Focus Group identifier: _____

Participant Identification Number: _____

CONSENT FORM

Title of Project: CONNECT: Thematic qualitative analysis of Aerobika™ and Aerobika™ – ‘connected’ in chronic respiratory conditions

Name of Researcher: _____

Please initial box

1. I confirm that I have read the Information Sheet dated 06/12/2022 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researcher collaborators.

☐

4. I understand that the information held and maintained by Swansea University (SU) and Respiratory Innovation Wales (RIW) may be used to contact me regarding this research project.

☐

5. I agree to take part in the above study.

☐

Name of Participant

Date

Signature

Name of Person
seeking consent

Date

Signature

REFERENCES

- AbdelHalim, H. A., AboElNaga, H. H., & Fathy, K. A. (2016). Comparison between active cycles of breathing with postural drainage versus conventional chest physiotherapy in subjects with bronchiectasis. *Egyptian Journal of Chest Diseases and Tuberculosis*, 65(1), 157-165.
<https://doi.org/https://doi.org/10.1016/j.ejcdt.2015.08.006>
- Abelson, D., Di Michiel, J., Frater, C., Pearson, M., Russo, R., Wechselberger, M., Cottee, A., & Morgan, L. (2024). Mucus clears from the trachea in a helix: a new twist to understanding airway diseases. *Thorax*, 79(7), 607-614.
<https://doi.org/10.1136/thorax-2023-221052>
- Abrami, M., Biasin, A., Tescione, F., Tierno, D., Dapas, B., Carbone, A., Grassi, G., Conese, M., Di Gioia, S., Larobina, D., & Grassi, M. (2024). Mucus Structure, Viscoelastic Properties, and Composition in Chronic Respiratory Diseases. *International Journal of Molecular Sciences*, 25(3).
<https://doi.org/10.3390/ijms25031933>
- Adcock, I. M., Caramori, G., & Barnes, P. J. (2011). Chronic obstructive pulmonary disease and lung cancer: new molecular insights. *Respiration*, 81(4), 265-284. <https://karger.com/res/article-pdf/81/4/265/3904136/000324601.pdf>
- Agustí, A., Celli, B. R., Criner, G. J., Halpin, D., Anzueto, A., Barnes, P., Bourbeau, J., Han, M. K., Martinez, F. J., Montes de Oca, M., Mortimer, K., Papi, A., Pavord, I., Roche, N., Salvi, S., Sin, D. D., Singh, D., Stockley, R., López Varela, M. V.,...Vogelmeier, C. F. (2023). Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary.

Archivos de Bronconeumología, 59(4), 232-248.

<https://doi.org/https://doi.org/10.1016/j.arbres.2023.02.009>

Agustí, A., & Hogg, J. C. (2019). Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, 381(13), 1248-1256.

<https://doi.org/10.1056/NEJMra1900475>

Agustí, A., Melén, E., DeMeo, D. L., Breyer-Kohansal, R., & Faner, R. (2022).

Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene–environment interactions across the lifespan. *The Lancet Respiratory Medicine*, 10(5), 512-524.

[https://doi.org/https://doi.org/10.1016/S2213-2600\(21\)00555-5](https://doi.org/https://doi.org/10.1016/S2213-2600(21)00555-5)

Aksamit, T., Bandel, T. J., Criollo, M., De Soyza, A., Elborn, J. S., Operschall, E., Polverino, E., Roth, K., Winthrop, K. L., & Wilson, R. (2017). The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. *Contemporary Clinical Trials*, 58, 78-85.

<https://doi.org/10.1016/j.cct.2017.05.007>

Aksamit, T., O'Donnell, A. E., Barker, A., Olivier, K. N., Winthrop, K. L., Daniels, M. L. A., Johnson, M., Eden, E., Griffith, D., Knowles, M., Metersky, M., Salathe, M., Thomashow, B., Tino, G., Turino, G., Carretta, B., & Daley, C. L. (2017). Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. *CHEST*, 151(5), 982-992.

<https://doi.org/10.1016/j.chest.2016.10.055>

Albert, R. K., Connett, J., Bailey, W. C., Casaburi, R., Cooper, J. A., Jr., Criner, G. J., Curtis, J. L., Dransfield, M. T., Han, M. K., Lazarus, S. C., Make, B., Marchetti, N., Martinez, F. J., Madinger, N. E., McEvoy, C., Niewoehner, D. E., Porsasz, J., Price, C. S., Reilly, J.,...Network, C. C. R. (2011). Azithromycin for prevention of exacerbations of COPD. *New England Journal of Medicine*, 365(8), 689-698.
<https://doi.org/10.1056/NEJMoa1104623>

Alderwick, H., & Dixon, J. (2019). The NHS long term plan. *Bmj*, 364, l84.
<https://doi.org/10.1136/bmj.l84>

Alghamdi, S. M., Alsulayyim, A. S., Alasmari, A. M., Philip, K. E. J., Buttery, S. C., Banya, W. A. S., Polkey, M. I., Birring, S. S., & Hopkinson, N. S. (2023). Oscillatory positive expiratory pressure therapy in COPD (O-COPD): a randomised controlled trial. *Thorax*, 78(2), 136-143.
<https://doi.org/10.1136/thorax-2022-219077>

Alghamdi, S. M., Alzahrani, A., Alshahrani, Y. M., Al Ruwaithi, A. A., Aldhahir, A. M., Alsulayyim, A. S., Siraj, R. A., Almansour, A. H., Alasmari, A. M., Alqahtani, J. S., Alanazi, A. M., Jaishi, S. T., Allehyani, B. A., & Hopkinson, N. S. (2023). Perception and clinical practice regarding mucus clearance devices with chronic obstructive pulmonary disease: a cross-sectional study of healthcare providers in Saudi Arabia. *BMJ Open*, 13(9), e074849.
<https://doi.org/10.1136/bmjopen-2023-074849>

Alghamdi, S. M., Barker, R. E., Alsulayyim, A. S. S., Alasmari, A. M., Banya, W. A. S., Polkey, M. I., Birring, S. S., & Hopkinson, N. S. (2020). Use of oscillatory

positive expiratory pressure (OPEP) devices to augment sputum clearance in COPD: a systematic review and meta-analysis. *Thorax*, 75(10), 855-863. <https://doi.org/10.1136/thoraxjnl-2019-214360>

Aliberti, S., Goeminne, P. C., O'Donnell, A. E., Aksamit, T. R., Al-Jahdali, H., Barker, A. F., Blasi, F., Boersma, W. G., Crichton, M. L., & De Soyza, A. (2022). Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. *The Lancet Respiratory Medicine*, 10(3), 298-306.

Aliberti, S., Ringshausen, F. C., Dhar, R., Haworth, C. S., Loebinger, M. R., Dimakou, K., Crichton, M. L., De Soyza, A., Vendrell, M., Burgel, P. R., McDonnell, M., Skrgat, S., Maiz Carro, L., de Roux, A., Sibila, O., Bossios, A., van der Eerden, M., Kauppi, P., Wilson, R.,...Chalmers, J. D. (2024). Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). *European Respiratory Journal*, 63(4). <https://doi.org/10.1183/13993003.01554-2023>

Andreeva, E., Pokhaznikova, M., Lebedev, A., Moiseeva, I., Kuznetsova, O., & Degryse, J.-M. (2017). Spirometry is not enough to diagnose COPD in epidemiological studies: a follow-up study. *npj Primary Care Respiratory Medicine*, 27(1), 62. <https://doi.org/10.1038/s41533-017-0062-6>

Antunes, M. B., & Cohen, N. A. (2007). Mucociliary clearance—a critical upper airway host defense mechanism and methods of assessment. *Current opinion in allergy and clinical immunology*, 7(1), 5-10.

- ASH. (2018). *10-years-of-smoking-ban*. <https://ash.wales/wp-content/uploads/2018/05/10-years-of-smoking-ban-1.pdf>
- ASH. (2024). *Position statement on Vaping*Blog. <https://ash.wales/campaign/electronic-cigarettes/>
- ASH, C. (2022). *National Campaign Helps School to Safeguard Against Illegal Tobacco* <https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community>
- Asthma-Lung-UK. (2024). *saving-your-breath-how-better-lung-health-benefits-us-all-us-wales-english (1).pdf*>. <https://www.asthmaandlung.org.uk/saving-your-breath-how-better-lung-health-benefits-us-all-us-wales-english>
- Asthma Australia. (2022, June 6). *'Huff'* [Video]. YouTube. <https://www.youtube.com/watch?v=wBxxhAmfxTw>
- Avci, E., Sarvari, P., Savai, R., Seeger, W., & Pullamsetti, S. S. (2022). Epigenetic Mechanisms in Parenchymal Lung Diseases: Bystanders or Therapeutic Targets? *International Journal of Molecular Sciences*, 23(1). <https://doi.org/10.3390/ijms23010546>
- Bafeta, A., Dechartres, A., Trinquart, L., Yavchitz, A., Boutron, I., & Ravaud, P. (2012). Impact of single centre status on estimates of intervention effects in

- trials with continuous outcomes: meta-epidemiological study. *Bmj*, 344, e813. <https://doi.org/10.1136/bmj.e813>
- Bailey, K. L., LeVan, T. D., Yanov, D. A., Pavlik, J. A., DeVasure, J. M., Sisson, J. H., & Wyatt, T. A. (2012). Non-typeable *Haemophilus influenzae* decreases cilia beating via protein kinase C epsilon. *Respiratory Research*, 13, 1-8.
- Bansal, A., Patel, K., & Katakwar, M. (2023). *Assessment of the Clinical Value of an Oscillating Positive Expiratory Pressure (OPEP) Device for Chronic Obstructive Pulmonary Disease (COPD) Patients in India: A 6 Week Field Study Using the COPD Assessment Test (CAT)* C27. OPTIMIZING THE INTERVENTIONS AND PROGRAM MODELS OF PULMONARY REHABILITATION, https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A4681
- Barker, R., Lavery, A. A., & Hopkinson, N. S. (2017). Adjuncts for sputum clearance in COPD: clinical consensus versus actual use. *BMJ Open Respiratory Research*, 4(1), e000226. <https://doi.org/10.1136/bmjresp-2017-000226>
- Barnes, P. (1994). *Therapeutics in respiratory disease / Peter J. Barnes ... [et al.], with contribution by Robert F. Miller*. New York : Churchill Livingstone.
- Barnes, P. J. (2009). The cytokine network in chronic obstructive pulmonary disease. *American journal of respiratory cell and molecular biology*, 41(6), 631-638.
- Barnes, P. J. (2022). Oxidative Stress in Chronic Obstructive Pulmonary Disease. *Antioxidants (Basel)*, 11(5). <https://doi.org/10.3390/antiox11050965>

- Barnes, P. J., Shapiro, S. D., & Pauwels, R. A. (2003). Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *European Respiratory Journal*, 22(4), 672-688.
<https://doi.org/10.1183/09031936.03.00040703>
- Bartlett, J. A., Fischer, A. J., & Paul Jr, B. (2008). Innate immune functions of the airway epithelium. *Trends in Innate Immunity*, 15, 147-163.
- Barto, T. L., Maselli, D. J., Daignault, S., Stiglich, J., Porter, J., Kraemer, C., & Hansen, G. (2020). Real-life experience with high-frequency chest wall oscillation vest therapy in adults with non-cystic fibrosis bronchiectasis. *Therapeutic Advances in Respiratory Disease*, 14, 1753466620932508.
<https://doi.org/10.1177/1753466620932508>
- Basavaraj, A., Choate, R., Addrizzo-Harris, D., Aksamit, T. R., Barker, A., Daley, C. L., Anne Daniels, M. L., Eden, E., DiMango, A., Fennelly, K., Griffith, D. E., Johnson, M. M., Knowles, M. R., Metersky, M. L., Noone, P. G., O'Donnell, A. E., Olivier, K. N., Salathe, M. A., Schmid, A.,...Winthrop, K. L. (2020). Airway Clearance Techniques in Bronchiectasis: Analysis From the United States Bronchiectasis and Non-TB Mycobacteria Research Registry. *CHEST*, 158(4), 1376-1384.
<https://doi.org/https://doi.org/10.1016/j.chest.2020.06.050>
- Basavaraj, A., Choate, R., Becker, B. C., Aksamit, T. R., & Metersky, M. L. (2024). Severity of bronchiectasis predicts use of and adherence to high frequency chest wall oscillation therapy - Analysis from the United States

Bronchiectasis and NTM research registry. *Respiratory Medicine*, 223, 107555. <https://doi.org/10.1016/j.rmed.2024.107555>

Bedi, P., Carlidge, M. K., Zhang, Y., Turnbull, K., Donaldson, S., Clarke, A., Crowe, J., Campbell, K., Graham, C., Franguylan, R., Rossi, A. G., & Hill, A. T. (2021). Feasibility of shortening intravenous antibiotic therapy for bronchiectasis based on bacterial load: a proof-of-concept randomised controlled trial. *European Respiratory Journal*, 58(6), 2004388. <https://doi.org/10.1183/13993003.04388-2020>

Bell, B. T., Deighton-Smith, N., & Hurst, M. (2021). 'When you think of exercising, you don't really want to think of puking, tears, and pain': Young adolescents' understanding of fitness and #fitspiration. *Journal of health psychology*, 26(7), 1046-1060. <https://doi.org/10.1177/1359105319869798>

Belli, S., Prince, I., Savio, G., Paracchini, E., Cattaneo, D., Bianchi, M., Masocco, F., Bellanti, M. T., & Balbi, B. (2021). Airway Clearance Techniques: The Right Choice for the Right Patient. *Frontiers in medicine*, 8, 544826-544826. <https://doi.org/10.3389/fmed.2021.544826>

Bellomo, R., Warrillow, S. J., & Reade, M. C. (2009). Why we should be wary of single-center trials. *Critical care medicine*, 37(12), 3114-3119. <https://doi.org/10.1097/CCM.0b013e3181bc7bd5>

Bennett, W. D., Foster, W. M., & Chapman, W. F. (1990). Cough-enhanced mucus clearance in the normal lung. *Journal of Applied Physiology*, 69(5), 1670-1675.

- Bennett, W. D., Wu, J., Fuller, F., Balcazar, J. R., Zeman, K. L., Duckworth, H., Donn, K., O'Riordan, T. G., Boucher, R. C., & Donaldson, S. H. (2015). Duration of action of hypertonic saline on mucociliary clearance in the normal lung. *Journal of Applied Physiology*, 118(12), 1483-1490.
- Benzo, R. (2011). Lung volume reduction surgery: nonpharmacological approach. *Current Opinion in Anesthesiology*, 24(1), 44-48.
<https://doi.org/10.1097/ACO.0b013e3283420608>
- Berkhof, F. F., Boom, L. N., Ten Hertog, N. E., Uil, S. M., Kerstjens, H. A., & Van Den Berg, J. W. (2012). The validity and precision of the leicester cough questionnaire in COPD patients with chronic cough. *Health and quality of life outcomes*, 10(1), 4. <https://doi.org/10.1186/1477-7525-10-4>
- Berner-Rodoreda, A., Bärnighausen, T., Kennedy, C., Brinkmann, S., Sarker, M., Wikler, D., Eyal, N., & McMahon, S. A. (2020). From doxastic to epistemic: A typology and critique of qualitative interview styles. *Qualitative inquiry*, 26(3-4), 291-305.
- Bilton, D., Tino, G., Barker, A. F., Chambers, D. C., Soyza, A. D., Dupont, L. J. A., O'Dochartaigh, C., Haren, E. H. J. v., Vidal, L. O., Welte, T., Fox, H. G., Wu, J., & Charlton, B. (2014). Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. *Thorax*, 69(12), 1073-1079.
<https://doi.org/10.1136/thoraxjnl-2014-205587>

Birring, S. S. (2003). Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*, 58(4), 339-343. <https://doi.org/10.1136/thorax.58.4.339>

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research*, 52(2), 69-77. [https://doi.org/10.1016/s0022-3999\(01\)00296-3](https://doi.org/10.1016/s0022-3999(01)00296-3)

Blanco-Aparicio, M., Saleta Canosa, J. L., Valiño López, P., Martín Egaña, M. T., Vidal García, I., & Montero Martínez, C. (2019). Eradication of *Pseudomonas aeruginosa* with inhaled colistin in adults with non-cystic fibrosis bronchiectasis. *Chronic Respiratory Disease*, 16, 1479973119872513. <https://doi.org/10.1177/1479973119872513>

Blanco, I., Bueno, P., Diego, I., Pérez-Holanda, S., Casas-Maldonado, F., Esquinas, C., & Miravittles, M. (2017). Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 561-569. <https://doi.org/10.2147/copd.S125389>

Blanco, I., Diego, I., Bueno, P., Casas-Maldonado, F., & Miravittles, M. (2019). Geographic distribution of COPD prevalence in the world displayed by Geographic Information System maps. *European Respiratory Journal*, 54(1), 1900610. <https://doi.org/10.1183/13993003.00610-2019>

- BLF. (2023). *Chronic obstructive pulmonary disease (COPD) statistics*. British Lung Foundation. Retrieved 29/6/2023 from <https://statistics.blf.org.uk/copd>
- Bolton, C. E., Singh, S. J., Walker, P. P., & Group, B. T. S. P. R. G. (2013). Commentary: the British Thoracic Society guideline on pulmonary rehabilitation in adults. *Thorax*, 68(9), 887-888.
<https://thorax.bmj.com/content/thoraxjnl/68/9/887.full.pdf>
- Borgerding, M., & Klus, H. (2005). Analysis of complex mixtures--cigarette smoke. *Experimental and Toxicologic Pathology*, 57 Suppl 1, 43-73.
<https://doi.org/10.1016/j.etp.2005.05.010>
- Bose, S., Pascoe, C., & McEvoy, C. (2023). Lifetime lung function trajectories and COPD: when the train derails. *The Lancet Respiratory Medicine*, 11(3), 221-222. [https://doi.org/10.1016/s2213-2600\(22\)00391-5](https://doi.org/10.1016/s2213-2600(22)00391-5)
- Bourbeau, J., Bafadhel, M., Barnes, N. C., Compton, C., Di Boscio, V., Lipson, D. A., Jones, P. W., Martin, N., Weiss, G., & Halpin, D. M. G. (2021). Benefit/Risk Profile of Single-Inhaler Triple Therapy in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 16, 499-517.
<https://doi.org/10.2147/copd.S291967>
- Bracey, A., Suggett, J., & Conway, J. (2019). A national audit of the Aerobika* Oscillatory Positive Pressure (OPEP) device when used to assist airway clearance for those with cystic fibrosis, bronchiectasis and COPD. *European Respiratory Journal*, 54(suppl 63), PA5267.
<https://doi.org/10.1183/13993003.congress-2019.PA5267>

- Brasch, F., Johnen, G., Winn-Brasch, A., Guttentag, S. H., Schmiedl, A., Kapp, N., Suzuki, Y., Muller, K. M., Richter, J., & Hawgood, S. (2004). Surfactant protein B in type II pneumocytes and intra-alveolar surfactant forms of human lungs. *American journal of respiratory cell and molecular biology*, 30(4), 449-458.
- Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research In Psychology*, 3(2), 77-101.
- Braun, V., & Clarke, V. (2014). What can "thematic analysis" offer health and wellbeing researchers? *International journal of qualitative studies on health and well-being*, 9, 26152. <https://doi.org/10.3402/qhw.v9.26152>
- Braun, V., & Clarke, V. (2019). Reflecting on reflexive thematic analysis. *Qualitative research in sport, exercise and health*, 11(4), 589-597.
- Bridges, C., Carter, H., Ketchell, R., Lau, D., & Duckers, J. (2018). EPS6. 01 Shaking it up: a look at our centre experience with high frequency chest wall oscillation (HFCWO). *Journal of Cystic Fibrosis*, 17, S48.
- Bridges, C., Graham-Wollard, L., Morris, H., Annandale, J., & Lewis, K. (2023). S56 A feasibility randomised control trial (RCT) of OPEP verses active cycle of breathing technique (ACBT) in people with chronic obstructive pulmonary disease (COPD). *Thorax*, 78(Suppl 4), A43-A44. <https://doi.org/10.1136/thorax-2023-BTSabstracts.62>
- Bridges, C., Suggett, J., & Lewis, K. (2024). Assessment of the Clinical Value of an Oscillating Positive Expiratory Pressure (OPEP) Device and Active Cycle of

Breathing Technique (COPD) for Chronic Obstructive Pulmonary Disease (COPD) Post Exacerbation: A 12 Week Prospective, Randomized Study Using the Leicester Cough Questionnaire (LCQ) and COPD Assessment Test (CAT). In *D29. INSIGHTS INTO MECHANISMS AND EFFECTIVENESS OF DIFFERENT COMPONENTS OF PULMONARY REHABILITATION* (pp. A7169-A7169). American Thoracic Society.
https://doi.org/doi:10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A7169

Brill, S. E., Patel, A. R., Singh, R., Mackay, A. J., Brown, J. S., & Hurst, J. R. (2015). Lung function, symptoms and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respiratory Research*, 16(1), 1-9.

Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D. S., Weinrauch, Y., & Zychlinsky, A. (2004). Neutrophil extracellular traps kill bacteria. *science*, 303(5663), 1532-1535.
<https://www.nature.com/articles/nri1340.pdf>

Bronchiectasis Toolbox. (n.d). *Autogenic Drainage*.

<https://bronchiectasis.com.au/resources/videos/autogenic-drainage>

Buhl, R., Criée, C. P., Kardos, P., Vogelmeier, C. F., Kostikas, K., Lossi, N. S., & Worth, H. (2018). Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. *International Journal of Chronic Obstructive Pulmonary Disease*, 13, 2557-2568. <https://doi.org/10.2147/copd.S169958>

- Burgel, P.-R., Nesme-Meyer, P., Chanez, P., Caillaud, D., Carré, P., Perez, T., & Roche, N. (2009). Cough and Sputum Production Are Associated With Frequent Exacerbations and Hospitalizations in COPD Subjects. *CHEST*, 135(4), 975-982. <https://doi.org/10.1378/chest.08-2062>
- Burholt, V., & Nash, P. (2011). Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. *Journal of Public Health*, 33(4), 587-603. <https://doi.org/10.1093/pubmed/fdr006>
- Burnham, P., Stanford, G., & Stewart, R. (2021). Autogenic drainage for airway clearance in cystic fibrosis. *The Cochrane Database of Systematic Reviews*, 12(12), Cd009595. <https://doi.org/10.1002/14651858.CD009595.pub3>
- Burudpakdee, C., Seetasith, A., Dunne, P., Kauffman, G., Carlin, B., Coppolo, D., & Suggett, J. (2017). A Real-World Study of 30-Day Exacerbation Outcomes in Chronic Obstructive Pulmonary Disease (COPD) Patients Managed with Aerobika OPEP. *Pulmonary Therapy*, 3(1), 163-171. <https://doi.org/10.1007/s41030-017-0027-5>
- Bush, A., Payne, D., Pike, S., Jenkins, G., Henke, M. O., & Rubin, B. K. (2006). Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. *CHEST*, 129(1), 118-123.
- Buss, P., Howson, H., O'Neill, C., & Berwick, D. (2022). 'Values to value' for recovery and renewal: prudent healthcare the key to transforming the health and care system. *Journal of the Royal Society of Medicine*, 115(12), 482-483. <https://doi.org/10.1177/01410768221142026>

Button, B., Cai, L.-H., Ehre, C., Kesimer, M., Hill, D. B., Sheehan, J. K., Boucher, R. C., & Rubinstein, M. (2012). A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia. *science*, 337(6097), 937-941.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633213/pdf/nihms407560.pdf>

Button, B., Heine, R., Catto - Smith, A., & Phelan, P. (1998). Postural drainage in cystic fibrosis: is there a link with gastro - oesophageal reflux? *Journal of paediatrics and child health*, 34(4), 330-334.

Cazzola, M., & Molimard, M. (2010). The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulmonary pharmacology & therapeutics*, 23(4), 257-267.
<https://doi.org/10.1016/j.pupt.2010.03.003>

Cazzola, M., Santangelo, G., Piccolo, A., Salzillo, A., Matera, M. G., D'Amato, G., & Rossi, F. (1994). Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease. *Pulmonary Pharmacology*, 7(2), 103-107.
<https://doi.org/10.1006/pulp.1994.1012>

Celli, B., Fabbri, L., Criner, G., Martinez, F. J., Mannino, D., Vogelmeier, C., Montes de Oca, M., Papi, A., Sin, D. D., & Han, M. K. (2022). Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *American Journal of Respiratory and Critical Care Medicine*, 206(11), 1317-1325.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9746870/pdf/rccm.202204-0671PP.pdf>

Celli, B., Fabbri, L., Criner, G., Martinez, F. J., Mannino, D., Vogelmeier, C., Montes de Oca, M., Papi, A., Sin, D. D., Han, M. K., & Agusti, A. (2022). Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. *American Journal of Respiratory and Critical Care Medicine*, 206(11), 1317-1325. <https://doi.org/10.1164/rccm.202204-0671PP>

Celli, B. R., Fabbri, L. M., Aaron, S. D., Agusti, A., Brook, R., Criner, G. J., Franssen, F. M. E., Humbert, M., Hurst, J. R., O'Donnell, D., Pantoni, L., Papi, A., Rodriguez-Roisin, R., Sethi, S., Torres, A., Vogelmeier, C. F., & Wedzicha, J. A. (2021). An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *American Journal of Respiratory and Critical Care Medicine*, 204(11), 1251-1258. <https://doi.org/10.1164/rccm.202108-1819PP>

Celli, B. R., Fabbri, L. M., Aaron, S. D., Agusti, A., Brook, R. D., Criner, G. J., Franssen, F. M. E., Humbert, M., Hurst, J. R., Montes de Oca, M., Pantoni, L., Papi, A., Rodriguez-Roisin, R., Sethi, S., Stolz, D., Torres, A., Vogelmeier, C. F., & Wedzicha, J. A. (2023). Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting: Best Practice. *American Journal of Respiratory and Critical Care Medicine*, 207(9), 1134-1144. <https://doi.org/10.1164/rccm.202209-1795CI>

- Chalmers, J. D. (2017). Macrolide resistance in *Pseudomonas aeruginosa*: implications for practice. *European Respiratory Journal*, 49(5).
<https://doi.org/10.1183/13993003.00689-2017>
- Chalmers, J. D., Aliberti, S., & Blasi, F. (2015). Management of bronchiectasis in adults. In *European Respiratory Journal* (Vol. 45, pp. 1446-1462): European Respiratory Society (ERS).
- Chalmers, J. D., Aliberti, S., Filonenko, A., Shteinberg, M., Goeminne, P. C., Hill, A. T., Fardon, T. C., Obradovic, D., Gerlinger, C., Sotgiu, G., Operschall, E., Rutherford, R. M., Dimakou, K., Polverino, E., De Soyza, A., & McDonnell, M. J. (2018). Characterization of the “Frequent Exacerbator Phenotype” in Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 197(11), 1410-1420. <https://doi.org/10.1164/rccm.201711-2202oc>
- Chalmers, J. D., Boersma, W., Lonergan, M., Jayaram, L., Crichton, M. L., Karalus, N., Taylor, S. L., Martin, M. L., Burr, L. D., & Wong, C. (2019). Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. *The Lancet Respiratory Medicine*, 7(10), 845-854.
- Chalmers, J. D., Goeminne, P., Aliberti, S., McDonnell, M. J., Lonni, S., Davidson, J., Poppelwell, L., Salih, W., Pesci, A., Dupont, L. J., Fardon, T. C., De Soyza, A., & Hill, A. T. (2014). The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*, 189(5), 576-585.
<https://doi.org/10.1164/rccm.201309-1575OC>

Chalmers, J. D., Haworth, C. S., Metersky, M. L., Loebinger, M. R., Blasi, F., Sibila, O., O'Donnell, A. E., Sullivan, E. J., Mange, K. C., & Fernandez, C. (2020). Phase 2 trial of the DPP-1 inhibitor brensocatic in bronchiectasis. *New England Journal of Medicine*, 383(22), 2127-2137.

Chalmers, J. D., Moffitt, K. L., Suarez-Cuartin, G., Sibila, O., Finch, S., Furrie, E., Dicker, A., Wrobel, K., Elborn, J. S., & Walker, B. (2017). Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 195(10), 1384-1393.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443898/pdf/rccm.201605-1027OC.pdf>

Chalmers, J. D., Polverino, E., Crichton, M. L., Ringshausen, F. C., De Soyza, A., Vendrell, M., Burgel, P. R., Haworth, C. S., Loebinger, M. R., & Dimakou, K. (2023). Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). *The Lancet Respiratory Medicine*.

Chalmers, J. D., Smith, M. P., McHugh, B. J., Doherty, C., Govan, J. R., & Hill, A. T. (2012). Short-and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 186(7), 657-665.

Chalmers, J. D., Elborn, S., & Greene, C. M. (2023). Basic, translational and clinical aspects of bronchiectasis in adults. *European Respiratory Review*, 32(168), 230015. <https://doi.org/10.1183/16000617.0015-2023>

- Chang, A. B., Bell, S. C., Torzillo, P. J., King, P. T., Maguire, G. P., Byrnes, C. A., Holland, A. E., O'Mara, P., & Grimwood, K. (2015). Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Medical Journal of Australia*, 202(1), 21-23.
https://core.ac.uk/reader/47206145?utm_source=linkout
- Chatterjee, M., van Putten, J. P., & Strijbis, K. (2020). Defensive properties of mucin glycoproteins during respiratory infections—relevance for SARS-CoV-2. *MBio*, 11(6), 10.1128/mbio.02374-02320.
- Chatwin. (2008). How to use a mechanical insufflator–exsufflator “cough assist machine”. *Breathe*, 4(4), 320-329.
<https://breathe.ersjournals.com/content/breathe/4/4/320.full.pdf>
- Chatwin, M., Ross, E., Hart, N., Nickol, A., Polkey, M., & Simonds, A. (2003). Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. *European Respiratory Journal*, 21(3), 502-508.
- Chatwin, M., & Wakeman, R. H. (2023). Mechanical Insufflation-Exsufflation: Considerations for Improving Clinical Practice. *Journal of Clinical Medicine*, 12(7), 2626. <https://www.mdpi.com/2077-0383/12/7/2626>
- Chen, P., Abacherli, L. E., Nadler, S. T., Wang, Y., Li, Q., & Parks, W. C. (2009). MMP7 shedding of syndecan-1 facilitates re-epithelialization by affecting $\alpha 2\beta 1$ integrin activation. *PLoS One*, 4(8), e6565.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719060/pdf/pone.0006565.pdf>

- Cheyne, L., Irvin - Sellers, M. J., & White, J. (2015). Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(9). <https://doi.org/10.1002/14651858.CD009552.pub3>
- Chisholm, J. F., Shenoy, S. K., Shade, J. K., Kim, V., Putcha, N., Carson, K. A., Wise, R., Hansel, N. N., Hanes, J. S., & Suk, J. S. (2019). Nanoparticle diffusion in spontaneously expectorated sputum as a biophysical tool to probe disease severity in COPD. *European Respiratory Journal*, 54(2).
- Choi, H., Yang, B., Kim, Y. J., Sin, S., Jo, Y. S., Kim, Y., Park, H. Y., Ra, S. W., Oh, Y. M., Chung, S. J., Yeo, Y., Park, D. W., Park, T. S., Moon, J. Y., Kim, S. H., Kim, T. H., Yoon, H. J., Sohn, J. W., & Lee, H. (2021). Increased mortality in patients with non cystic fibrosis bronchiectasis with respiratory comorbidities. *Scientific reports*, 11(1), 7126. <https://doi.org/10.1038/s41598-021-86407-8>
- Chung, K. F., & Adcock, I. M. (2008). Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *European Respiratory Journal*, 31(6), 1334-1356. <https://doi.org/10.1183/09031936.00018908>
- Clarke, V., & Braun, V. (2018). Using thematic analysis in counselling and psychotherapy research: A critical reflection. *Counselling and psychotherapy research*, 18(2), 107-110.

Cloonan, S. M., Kim, K., Esteves, P., Trian, T., & Barnes, P. J. (2020). Mitochondrial dysfunction in lung ageing and disease. *European Respiratory Review*, 29(157).

Cole, P. J. (1986). Inflammation: a two-edged sword--the model of bronchiectasis. *European Journal Respiratory Diseases*, 147, 6-15.

Comer, D. M., Kidney, J. C., Ennis, M., & Elborn, J. S. (2013). Airway epithelial cell apoptosis and inflammation in COPD, smokers and nonsmokers. *European Respiratory Journal*, 41(5), 1058-1067.
<https://doi.org/10.1183/09031936.00063112>

Coppolo, D. P., Schloss, J., Suggett, J. A., & Mitchell, J. P. (2022). Non-Pharmaceutical Techniques for Obstructive Airway Clearance Focusing on the Role of Oscillating Positive Expiratory Pressure (OPEP): A Narrative Review. *Pulmonary Therapy*, 8(1), 1-41. <https://doi.org/10.1007/s41030-021-00178-1>

Cosio, B. G., Soriano, J. B., Lopez-Campos, J. L., Calle, M., Soler, J. J., de-Torres, J. P., Marin, J. M., Martinez, C., de Lucas, P., Mir, I., Peces-Barba, G., Feu-Collado, N., Solanes, I., Alfageme, I., & study, C. (2016). Distribution and Outcomes of a Phenotype-Based Approach to Guide COPD Management: Results from the CHAIN Cohort. *PLoS One*, 11(9), e0160770.
<https://doi.org/10.1371/journal.pone.0160770>

Costa, J. C., Machado, J. N., Ferreira, C., Gama, J., & Rodrigues, C. (2018). The Bronchiectasis Severity Index and FACED score for assessment of the

severity of bronchiectasis. *Pulmonology*, 24(3), 149-154.

<https://doi.org/https://doi.org/10.1016/j.rppnen.2017.08.009>

Cox, M. J., Turek, E. M., Hennessy, C., Mirza, G. K., James, P. L., Coleman, M., Jones, A., Wilson, R., Bilton, D., & Cookson, W. O. (2017). Longitudinal assessment of sputum microbiome by sequencing of the 16S rRNA gene in non-cystic fibrosis bronchiectasis patients. *PLoS One*, 12(2), e0170622.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5295668/pdf/pone.0170622.pdf>

Cranston, J. M., Crockett, A. J., Moss, J. R., & Alpers, J. H. (2005). Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(4), CD001744.
<https://doi.org/10.1002/14651858.CD001744.pub2>

Creswell, J. W., & Poth, C. N. (2017). *Qualitative Inquiry and Research Design: Choosing Among Five Approaches*. SAGE Publications.
<https://books.google.co.uk/books?id=Pz5RvgAACAAJ>

Daviskas, E., Anderson, S. D., Gomes, K., Briffa, P., Cochrane, B., CHAN, H. K., Young, I. H., & Rubin, B. K. (2005). Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. *Respirology*, 10(1), 46-56.

Davison, J., Robinson-Barella, A., Davies, G., Campos-Hinojosa, M., Collins, C., Husband, A., Okeowo, D., Hester, K. L., Lee, R., Rapley, T., & Soyza, A. D. (2023). Patient attitudes to nebulised antibiotics in the treatment of

bronchiectasis: a mixed-methods study. *ERJ Open Research*, 00735-02022.
<https://doi.org/10.1183/23120541.00735-2022>

Dawson, M., Wirtz, D., & Hanes, J. (2003). Enhanced viscoelasticity of human cystic fibrotic sputum correlates with increasing microheterogeneity in particle transport. *Journal of Biological Chemistry*, 278(50), 50393-50401.

de la Rosa-Carrillo, D., Suárez-Cuartín, G., Golpe, R., Máiz Carro, L., & Martinez-Garcia, M. A. (2022). Inhaled Colistimethate Sodium in the Management of Patients with Bronchiectasis Infected by *Pseudomonas aeruginosa*: A Narrative Review of Current Evidence. *Infection and Drug Resistance*, 15(null), 7271-7292. <https://doi.org/10.2147/IDR.S318173>

De Rose, V., Molloy, K., Gohy, S., Pilette, C., & Greene, C. M. (2018). Airway epithelium dysfunction in cystic fibrosis and COPD. *Mediators of inflammation*, 2018.

De Soyza, A., Aksamit, T., Bandel, T. J., Criollo, M., Elborn, J. S., Operschall, E., Polverino, E., Roth, K., Winthrop, K. L., & Wilson, R. (2018). RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*, 51(1). <https://doi.org/10.1183/13993003.02052-2017>

Demchuk, A. M., & Chatburn, R. L. (2021). Performance Characteristics of Positive Expiratory Pressure Devices. *Respiratory Care*, 66(3), 482-493.
<https://doi.org/10.4187/respcare.08150>

DeSoyza, A., Bradley, J., Moloney, S., Butler, J., & McCallion, P. (2022). A systematic review to determine the presence and effectiveness of shared

decision making interventions for airway clearance techniques in adults with bronchiectasis. *Journal of the Association of Chartered Physiotherapists in Respiratory Care. Volume 54. Issue 2. 2022., 54(2), 60-91.*

<https://www.acprc.org.uk/publications/acprc-journal/2022-journal-vol-54-issue-2/a-systematic-review-to-determine-the-presence-and-effectiveness-of-shared-decision-making-interventions-for-airway-clearance-techniques-in-adults-with-bronchiectasis/>

DeSoyza, A., Mawson, P., Hill, A. T., Elborn, S., Bradley, J. M., Haworth, C. S., Floto, R. A., Wilson, R., Loebinger, M. R., Carroll, M., Crichton, M., Chalmers, J. D., Sullivan, A., Brown, J., Hurst, J. R., Duckers, J., Kelly, M., Steer, J., Gatheral, T.,...McNally, R. (2021). BronchUK: protocol for an observational cohort study and biobank in bronchiectasis. *ERJ Open Research, 7(2), 00775-02020.* <https://doi.org/10.1183/23120541.00775-2020>

Dey, S., Eapen, M. S., Chia, C., Gaikwad, A. V., Wark, P. A. B., & Sohal, S. S. (2022). Pathogenesis, clinical features of asthma COPD overlap, and therapeutic modalities. *American Journal of Physiology-Lung Cellular and Molecular Physiology, 322(1), L64-L83.* <https://doi.org/10.1152/ajplung.00121.2021>

DHSC, M. T. (2024, 15/04/2024). <https://healthmedia.blog.gov.uk/2024/04/15/creating-a-smokefree-generation-and-tackling-youth-vaping-what-you-need-to-know/>

Diaz, A. A., Orejas, J. L., Grumley, S., Nath, H. P., Wang, W., Dolliver, W. R., Yen, A., Kligerman, S. J., Jacobs, K., Manapragada, P. P., Abozeed, M., Aziz, M.

U., Zahid, M., Ahmed, A. N., Terry, N. L., San José Estépar, R., Kim, V.,
Make, B. J., Han, M. K.,...San José Estépar, R. (2023). Airway-Occluding
Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary
Disease. *JAMA*, 329(21), 1832-1839.
<https://doi.org/10.1001/jama.2023.2065>

Dicker, A. J., Lonergan, M., Keir, H. R., Smith, A. H., Pollock, J., Finch, S., Cassidy,
A. J., Huang, J. T., & Chalmers, J. D. (2021). The sputum microbiome and
clinical outcomes in patients with bronchiectasis: a prospective observational
study. *The Lancet Respiratory Medicine*, 9(8), 885-896.

Diver, W. R., Jacobs, E. J., & Gapstur, S. M. (2018). Secondhand Smoke Exposure
in Childhood and Adulthood in Relation to Adult Mortality Among Never
Smokers. *American journal of preventive medicine*, 55(3), 345-352.
<https://doi.org/10.1016/j.amepre.2018.05.005>

Doe, G., Taylor, S. J., Topalovic, M., Russell, R., Evans, R. A., Maes, J., Orshovon,
K. V., Sunjaya, A., Scott, D., Prevost, A. T., El-Emir, E., Harvey, J.,
Hopkinson, N. S., Kon, S. S., Patel, S., Jarrold, I., Spain, N., Man, W. D.-C.,
& Hutchinson, A. (2023). Spirometry services in England post-pandemic and
the potential role of AI support software: a qualitative study of challenges
and opportunities. *British Journal of General Practice*, 73(737), e915-e923.
<https://doi.org/10.3399/bjgp.2022.0608>

Dubin, R., Robinson, S., & Widdicombe, J. (2004). Secretion of lactoferrin and
lysozyme by cultures of human airway epithelium. *American Journal of
Physiology-Lung Cellular and Molecular Physiology*, 286(4), L750-L755.

Dunican, E. M., Elicker, B. M., Gierada, D. S., Nagle, S. K., Schiebler, M. L., Newell, J. D., Raymond, W. W., Lachowicz-Scroggins, M. E., Di Maio, S., Hoffman, E. A., Castro, M., Fain, S. B., Jarjour, N. N., Israel, E., Levy, B. D., Erzurum, S. C., Wenzel, S. E., Meyers, D. A., Bleecker, E. R.,...Fahy, J. V. (2018). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *The Journal of Clinical Investigation*, 128(3), 997-1009.

<https://doi.org/10.1172/jci95693>

Eaton, T., Young, P., Zeng, I., & Kolbe, J. (2007). A randomized evaluation of the acute efficacy, acceptability and tolerability of flutter and active cycle of breathing with and without postural drainage in non-cystic fibrosis bronchiectasis. *Chronic Respiratory Disease*, 4(1), 23-30.

<https://doi.org/10.1177/1479972306074481>

Elkins, M., & Dentice, R. (2020). Timing of hypertonic saline inhalation for cystic fibrosis. *Cochrane Database of Systematic Reviews*, 2(2), Cd008816.

<https://doi.org/10.1002/14651858.CD008816.pub4>

Everaerts, S., Vandervelde, C. M., Shah, P., Slebos, D. J., & Ceulemans, L. J. (2023). Surgical and bronchoscopic pulmonary function-improving procedures in lung emphysema. *European Respiratory Review*, 32(170).

<https://doi.org/10.1183/16000617.0004-2023>

Fabbri, L. M., Romagnoli, M., Corbetta, L., Casoni, G., Busljetic, K., Turato, G., Ligabue, G., Ciaccia, A., Saetta, M., & Papi, A. (2003). Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *American Journal of Respiratory and*

Critical Care Medicine, 167(3), 418-424.

<https://doi.org/10.1164/rccm.200203-183OC>

Faner, R., Sibila, O., Agustí, A., Bernasconi, E., Chalmers, J. D., Huffnagle, G. B., Manichanh, C., Molyneaux, P. L., Paredes, R., & Brocal, V. P. (2017). The microbiome in respiratory medicine: current challenges and future perspectives. *European Respiratory Journal*, 49(4).

Feng, T., Sun, Y., Shi, Y., Ma, J., Feng, C., & Chen, Z. (2024). Air pollution control policies and impacts: A review. *Renewable and Sustainable Energy Reviews*, 191, 114071.

<https://doi.org/https://doi.org/10.1016/j.rser.2023.114071>

Fernandez, E., De Santi, C., De Rose, V., & Greene, C. M. (2018). CFTR dysfunction in cystic fibrosis and chronic obstructive pulmonary disease. *Expert Review of Respiratory Medicine*, 12(6), 483-492.

Ferreira de Camillis, M. L., Savi, A., Goulart Rosa, R., Figueiredo, M., Wickert, R., Borges, L. G. A., Galant, L., & Teixeira, C. (2018). Effects of Mechanical Insufflation-Exsufflation on Airway Mucus Clearance Among Mechanically Ventilated ICU Subjects. *Respiratory Care*, 63(12), 1471-1477.

<https://doi.org/10.4187/respcare.06253>

Fishman, A., Fessler, H., Martinez, F., McKenna, R. J., Jr., Naunheim, K., Piantadosi, S., Weinmann, G., & Wise, R. (2001). Patients at high risk of death after lung-volume-reduction surgery. *New England Journal of Medicine*, 345(15), 1075-1083. <https://doi.org/10.1056/NEJMoa11798>

- Flume, P. A., Chalmers, J. D., & Olivier, K. N. (2018). Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *The Lancet*, 392(10150), 880-890.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6173801/pdf/nihms-1506383.pdf>
- Fortis, S., Shannon, Z. K., Garcia, C. J., Guillamet, R. V., Aloe, A. M., Schweizer, M. L., Kim, V., & Nair, R. (2022). Association of nonobstructive chronic bronchitis with all-cause mortality: a systematic literature review and meta-analysis. *CHEST*, 162(1), 92-100.
- Franks, L. J., Walsh, J. R., Hall, K., Jacuinde, G., Yerkovich, S., & Morris, N. R. (2019). Comparing the Performance Characteristics of Different Positive Expiratory Pressure Devices. *Respiratory Care*, 64(4), 434-444.
<https://doi.org/10.4187/respcare.06410>
- Franks, L. J., Walsh, J. R., Hall, K., & Morris, N. R. (2020). Measuring airway clearance outcomes in bronchiectasis: a review. *European Respiratory Review*, 29(156), 190161. <https://doi.org/10.1183/16000617.0161-2019>
- Gao, Y. H., Guan, W. J., Xu, G., Tang, Y., Gao, Y., Lin, Z. Y., Lin, Z. M., Zhong, N. S., & Chen, R. C. (2014). Macrolide therapy in adults and children with non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *PLoS One*, 9(3), e90047. <https://doi.org/10.1371/journal.pone.0090047>
- GBD Collaborators, Forouzanfar, M., Alexander, L., Bachman, V., Biryukov, S., Brauer, M., Casey, D., Coates, M., Delwiche, K., & Estep, K. (2015). Global, regional, and national comparative risk assessment of 79 behavioural,

environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, 386(10010), 2287-2323.

Gertsberg, I., Hellman, V., Fainshtein, M., Weil, S., Silberberg, S. D., Danilenko, M., & Priel, Z. (2004). Intracellular Ca²⁺ regulates the phosphorylation and the dephosphorylation of ciliary proteins via the NO pathway. *The Journal of General Physiology*, 124(5), 527-540. <https://doi.org/10.1085/jgp.200409153>

Glasgow, A. M., & Greene, C. M. (2022). Epithelial damage in the cystic fibrosis lung: the role of host and microbial factors. *Expert Review of Respiratory Medicine*, 16(7), 737-748.

Goeminne, P. C., Hernandez, F., Diel, R., Filonenko, A., Hughes, R., Juelich, F., Solomon, G. M., Upton, A., Wichmann, K., & Xu, W. (2019). The economic burden of bronchiectasis—known and unknown: a systematic review. *BMC Pulmonary Medicine*, 19(1), 1-11.

Goeminne, P. C., Nawrot, T. S., Ruttens, D., Seys, S., & Dupont, L. J. (2014). Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respiratory Medicine*, 108(2), 287-296. <https://doi.org/10.1016/j.rmed.2013.12.015>

GOLD. (2023). *Glogal Strategy for the diagnosis, management and prevention of COPD* (2023). https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf

- GOLD. (2024a). 2024 Report: GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: . <https://goldcopd.org/2024-gold-report/>
- GOLD. (2024b). *GOLD TEACHING SLIDE SET*. <https://goldcopd.org/2024-gold-report/>
- Gordon, C. S., Waller, J. W., Cook, R. M., Cavallera, S. L., Lim, W. T., & Osadnik, C. R. (2019). Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *CHEST*, 156(1), 80-91. <https://doi.org/10.1016/j.chest.2019.04.009>
- Gordon, M., Duffy, S., & Criner, G. J. (2018). Lung volume reduction surgery or bronchoscopic lung volume reduction: is there an algorithm for allocation? *Journal of Thoracic Disease*, S2816-S2823. <https://jtd.amegroups.org/article/view/21533>
- Government, W. (2022). *A-smoke-free-wales-our-long-term-tobacco-control-strategy-for-wales-and-towards-a-smoke-free-wales-delivery-plan-2022-to-2024*. Retrieved from <https://www.gov.wales/sites/default/files/consultations/2022-07/a-smoke-free-wales-our-long-term-tobacco-control-strategy-for-wales-and-towards-a-smoke-free-wales-delivery-plan-2022-to-2024.pdf>
- Griffiths, T. L., Burr, M. L., Campbell, I. A., Lewis-Jenkins, V., Mullins, J., Shiels, K., Turner-Lawlor, P. J., Payne, N., Newcombe, R. G., Ionescu, A. A., Thomas, J., & Tunbridge, J. (2000). Results at 1 year of outpatient multidisciplinary

pulmonary rehabilitation: a randomised controlled trial. *Lancet*, 355(9201), 362-368. [https://doi.org/10.1016/s0140-6736\(99\)07042-7](https://doi.org/10.1016/s0140-6736(99)07042-7)

Guan, W.-J., Gao, Y.-H., Xu, G., Li, H.-M., Yuan, J.-J., Zheng, J.-P., Chen, R.-C., & Zhong, N.-S. (2016). Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. *Journal of Thoracic Disease*, 8(1), 14.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740118/pdf/jtd-08-01-014.pdf>

Guo, M., Pegoraro, A. F., Mao, A., Zhou, E. H., Arany, P. R., Han, Y., Burnette, D. T., Jensen, M. H., Kasza, K. E., & Moore, J. R. (2017). Cell volume change through water efflux impacts cell stiffness and stem cell fate. *Proceedings of the National Academy of Sciences*, 114(41), E8618-E8627.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642688/pdf/pnas.201705179.pdf>

Gupta, N., Pinto, L. M., Morogan, A., & Bourbeau, J. (2014). The COPD assessment test: a systematic review. *European Respiratory Journal*, 44(4), 873-884.

<https://doi.org/10.1183/09031936.00025214>

Halpin, D. M. G., Kerkhof, M., Soriano, J. B., Mikkelsen, H., & Price, D. B. (2016).

Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. *Respiratory Research*, 17(1), 120.

<https://doi.org/10.1186/s12931-016-0433-5>

Hardinge, M., Annandale, J., Bourne, S., Cooper, B., Evans, A., Freeman, D., Green, A., Hippolyte, S., Knowles, V., MacNee, W., McDonnell, L., Pye, K.,

- Suntharalingam, J., Vora, V., Wilkinson, T., British Thoracic Society Home Oxygen Guideline Development, G., & British Thoracic Society Standards of Care, C. (2015). British Thoracic Society guidelines for home oxygen use in adults. *Thorax*, 70 Suppl 1, i1-43. <https://doi.org/10.1136/thoraxjnl-2015-206865>
- Hasani, A., Pavia, D., Agnew, J., & Clarke, S. (1994). Regional lung clearance during cough and forced expiration technique (FET): effects of flow and viscoelasticity. *Thorax*, 49(6), 557-561. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC474944/pdf/thorax00298-0037.pdf>
- Haworth, C. S., Bilton, D., Chalmers, J. D., Davis, A. M., Froehlich, J., Gonda, I., Thompson, B., Wanner, A., & O'Donnell, A. E. (2019). Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. *The Lancet Respiratory Medicine*, 7(3), 213-226. [https://doi.org/10.1016/s2213-2600\(18\)30427-2](https://doi.org/10.1016/s2213-2600(18)30427-2)
- Haworth, C. S., Bilton, D., & Elborn, J. S. (2014). Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. *Respiratory Medicine*, 108(10), 1397-1408. <https://doi.org/10.1016/j.rmed.2014.09.005>
- Henkle, E., Aksamit, T. R., Barker, A. F., Curtis, J. R., Daley, C. L., Anne Daniels, M. L., DiMango, A., Eden, E., Fennelly, K., Griffith, D. E., Johnson, M., Knowles, M. R., Leitman, A., Leitman, P., Malanga, E., Metersky, M. L., Noone, P. G., O'Donnell, A. E., Olivier, K. N.,...Winthrop, K. L. (2017).

Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *CHEST*, 152(6), 1120-1127.

<https://doi.org/10.1016/j.chest.2017.04.167>

Henkle, E., Aksamit, T. R., Daley, C. L., Griffith, D. E., O'Donnell, A. E., Quittner, A. L., Malanga, E., Prieto, D., Leitman, A., & Winthrop, K. L. (2018). US Patient-Centered Research Priorities and Roadmap for Bronchiectasis. *CHEST*, 154(5), 1016-1023. <https://doi.org/10.1016/j.chest.2018.06.032>

Henkle, E., Chan, B., Curtis, J. R., Aksamit, T. R., Daley, C. L., & Winthrop, K. L. (2018). Characteristics and health-care utilization history of patients with bronchiectasis in US Medicare enrollees with prescription drug plans, 2006 to 2014. *CHEST*, 154(6), 1311-1320.

Hennink, M., & Kaiser, B. N. (2022). Sample sizes for saturation in qualitative research: A systematic review of empirical tests. *Social Science & Medicine*, 292, 114523.

<https://doi.org/https://doi.org/10.1016/j.socscimed.2021.114523>

Herrero-Cortina, B., Lee, A. L., Oliveira, A., O'Neill, B., Jácome, C., Dal Corso, S., Poncin, W., Muñoz, G., Inal-Ince, D., Alcaraz-Serrano, V., Reyhler, G., Bellofiore, A., Tonia, T., Chalmers, J. D., & Spinou, A. (2023). European Respiratory Society statement on airway clearance techniques in adults with bronchiectasis. *European Respiratory Journal*, 2202053.

<https://doi.org/10.1183/13993003.02053-2022>

- Herrero-Cortina, B., Vilaró, J., Martí, D., Torres, A., San Miguel-Pagola, M., Alcaraz, V., & Polverino, E. (2016). Short-term effects of three slow expiratory airway clearance techniques in patients with bronchiectasis: a randomised crossover trial. *Physiotherapy*, 102(4), 357-364.
<https://doi.org/10.1016/j.physio.2015.07.005>
- Herrero Cortina, B., Aliberti, S., & Blasi, F. (2017). Chest physiotherapy in European patients with bronchiectasis: Data from the EMBARC registry. *European Respiratory Journal*, 50, PA4071.
- Hill, Button, B., Rubinstein, M., & Boucher, R. C. (2022). Physiology and pathophysiology of human airway mucus. *Physiological Reviews*, 102(4), 1757-1836. <https://doi.org/10.1152/physrev.00004.2021>
- Hill, A. T., Grillo, L., Gruffydd-Jones, K., Payne, K., Souto, M., Sullivan, A., Wildgoose, J., & Loebinger, M. R. (2022). British Thoracic Society Quality Standard for Clinically Significant Bronchiectasis in Adults 2022. *BMJ Open Respiratory Research*, 9(1), e001369. <https://doi.org/10.1136/bmjresp-2022-001369>
- Hill, A. T., Haworth, C. S., Aliberti, S., Barker, A., Blasi, F., Boersma, W., Chalmers, J. D., Soyza, A. D., Dimakou, K., Elborn, J. S., Feldman, C., Flume, P., Goeminne, P. C., Loebinger, M. R., Menendez, R., Morgan, L., Murriss, M., Polverino, E., Quittner, A.,...Aksamit, T. (2017). Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *European Respiratory Journal*, 49(6), 1700051.
<https://doi.org/10.1183/13993003.00051-2017>

- Hill, A. T., Routh, C., & Welham, S. (2014). National BTS bronchiectasis audit 2012: is the quality standard being adhered to in adult secondary care? *Thorax*, 69(3), 292-294. <https://doi.org/10.1136/thoraxjnl-2013-203739>
- Hill, A. T., Sullivan, A. L., Chalmers, J. D., De Soyza, A., Elborn, J. S., Floto, R. A., Grillo, L., Gruffydd-Jones, K., Harvey, A., & Haworth, C. S. (2019). British Thoracic Society Guideline for bronchiectasis in adults. *Thorax*, 74(Suppl 1), 1-69. https://thorax.bmj.com/content/thoraxjnl/74/Suppl_1/1.full.pdf
- Hill, A. T., Sullivan, A. L., Chalmers, J. D., De Soyza, A., Elborn, J. S., Floto, R. A., Grillo, L., Gruffydd-Jones, K., Harvey, A., Haworth, C. S., Hiscocks, E., Hurst, J. R., Johnson, C., Kelleher, W. P., Bedi, P., Payne, K., Saleh, H., Screaton, N. J., Smith, M.,...Loebinger, M. R. (2018). British Thoracic Society guideline for bronchiectasis in adults. *BMJ Open Respiratory Research*, 5(1), e000348. <https://doi.org/10.1136/bmjresp-2018-000348>
- Hill, D. B., Vasquez, P. A., Mellnik, J., McKinley, S. A., Vose, A., Mu, F., Henderson, A. G., Donaldson, S. H., Alexis, N. E., & Boucher, R. C. (2014). A biophysical basis for mucus solids concentration as a candidate biomarker for airways disease. *PLoS One*, 9(2), e87681. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928107/pdf/pone.0087681.pdf>
- Hoesterey, D., Das, N., Janssens, W., Buhr, R. G., Martinez, F. J., Cooper, C. B., Tashkin, D. P., & Barjaktarevic, I. (2019). Spirometric indices of early airflow impairment in individuals at risk of developing COPD: Spirometry beyond

FEV1/FVC. *Respiratory Medicine*, 156, 58-68.

<https://doi.org/https://doi.org/10.1016/j.rmed.2019.08.004>

Hopkinson, N. S., Molyneux, A., Pink, J., & Harrisingh, M. C. (2019). Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. *Bmj*, 366, l4486. <https://doi.org/10.1136/bmj.l4486>

Hosseini, M., Almasi-Hashiani, A., Sepidarkish, M., & Maroufizadeh, S. (2019). Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respiratory Research*, 20(1), 1-10.

Houtmeyers, E., Gosselink, R., Gayan-Ramirez, G., & Decramer, M. (1999). Regulation of mucociliary clearance in health and disease. *European Respiratory Journal*, 13(5), 1177-1188. <https://doi.org/10.1034/j.1399-3003.1999.13e39.x>

Hov, B., Andersen, T., Toussaint, M., Mikalsen, I. B., Vollsæter, M., Markussen, H., Indrekvam, S., & Hovland, V. (2023). User - perceived impact of long - term mechanical assisted cough in paediatric neurodisability. *Developmental Medicine & Child Neurology*, 65(5), 655-663.

Hoy, R. F., & Chambers, D. C. (2020). Silica-related diseases in the modern world. *Allergy*, 75(11), 2805-2817. <https://doi.org/10.1111/all.14202>

HRA. (2023). *UK Policy Framework for Health and Social Care*. N. H. R. Authority. <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/uk-policy-framework-health-and-social-care-research/>

<http://img.medscapestatic.com/>. (2023). *Proposed synergy of LABA and inhaled CS*.

Retrieved 31.01.2023 from

<http://img.medscapestatic.com/fullsize/migrated/editorial/cmelive/2007/6294/images/slide20.gif>

i.pinimg.com. (2023). *The distribution of beta receptors in the body*. Retrieved

31.01.2023 from

<https://i.pinimg.com/originals/a6/e2/e4/a6e2e403fd20cec1f4aaaa23a2508c08.png>

Jabbar, A. (2016). *Introduction to Human Physiology*.

Jaffé, A., & Bush, A. (2001). Anti - inflammatory effects of macrolides in lung

disease. *Pediatr Pulmonol*, 31(6), 464-473.

<https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.1076?sid=nlm%3Apubmed>

<https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/ppul.1076?download=true>

Jain, B., Rubinstein, I., Robbins, R. A., Leise, K. L., & Sisson, J. H. (1993).

Modulation of airway epithelial cell ciliary beat frequency by nitric oxide.

Biochem Biophys Res Commun, 191(1), 83-88.

<https://doi.org/10.1006/bbrc.1993.1187>

Janjua, S., Fortescue, R., & Poole, P. (2020). Phosphodiesterase - 4 inhibitors for

chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(5).

- Johns, D. P., Walters, J. A., & Walters, E. H. (2014). Diagnosis and early detection of COPD using spirometry. *Journal of Thoracic Disease*, 6(11), 1557-1569.
<https://doi.org/10.3978/j.issn.2072-1439.2014.08.18>
- Johnson, A., Paul, C., Duckers, J., & Bridges, C. (2020). P329 To evaluate adherence to NIV for airways clearance at the All Wales Adult Cystic Fibrosis Centre (AWACFC). *Journal of Cystic Fibrosis*, 19, S148.
[https://doi.org/10.1016/S1569-1993\(20\)30658-5](https://doi.org/10.1016/S1569-1993(20)30658-5)
- Jones, P. W., Harding, G., Berry, P., Wiklund, I., Chen, W. H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal*, 34(3), 648-654.
<https://doi.org/10.1183/09031936.00102509>
- Jones, P. W., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., & Leidy, N. K. (2012). Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. *CHEST*, 142(1), 134-140.
<https://doi.org/10.1378/chest.11-0309>
- Jones, P. W., Tabberer, M., & Chen, W.-H. (2011). Creating scenarios of the impact of copd and their relationship to copd assessment test (CAT™) scores. *BMC Pulmonary Medicine*, 11(1), 42. <https://doi.org/10.1186/1471-2466-11-42>
- Kanazawa, H., Tochino, Y., Asai, K., Ichimaru, Y., Watanabe, T., & Hirata, K. (2012). Validity of HMGB1 measurement in epithelial lining fluid in patients with COPD. *European journal of clinical investigation*, 42(4), 419-426.
- Karabis, A., Lindner, L., Mocarski, M., Huisman, E., & Greening, A. (2013). Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as

maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease*, 8, 405-423.

<https://doi.org/10.2147/copd.S48967>

Kavanaugh, J. S., Flack, C. E., Lister, J., Ricker, E. B., Ibberson, C. B., Jenul, C., Moormeier, D. E., Delmain, E. A., Bayles, K. W., & Horswill, A. R. (2019). Identification of extracellular DNA-binding proteins in the biofilm matrix. *MBio*, 10(3), 10.1128/mbio.01137-01119.

KC, R., Shukla, S. D., Gautam, S. S., Hansbro, P. M., & O'Toole, R. F. (2018). The role of environmental exposure to non-cigarette smoke in lung disease. *Clinical and Translational Medicine*, 7(1), 39. <https://doi.org/10.1186/s40169-018-0217-2>

Keir, H. R., & Chalmers, J. D. (2021). Pathophysiology of Bronchiectasis. *Seminars in Respiratory and Critical Care Medicine*, 42(4), 499-512. <https://doi.org/10.1055/s-0041-1730891>

Kendrick, A. H. (2007). Airway clearance techniques in cystic fibrosis: physiology, devices and the future. *Journal of the Royal Society of Medicine (Supplement)*, 100(47).

Khan, Q., Ismail, M., Haider, I., & Ali, Z. (2019). Prevalence of the risk factors for QT prolongation and associated drug-drug interactions in a cohort of medical inpatients. *Journal of the Formosan Medical Association*, 118(1 Pt 1), 109-115. <https://doi.org/10.1016/j.jfma.2018.01.016>

- Khoudigian-Sinani, S., Kowal, S., Suggett, J. A., & Coppolo, D. P. (2017). Cost-effectiveness of the Aerobika* oscillating positive expiratory pressure device in the management of COPD exacerbations. *International Journal of Chronic Obstructive Pulmonary Disease*, 12(null), 3065-3073.
<https://doi.org/10.2147/COPD.S143334>
- Kim, S. R., Kim, S. H., Kim, G. H., Cho, J. Y., Choi, H., Lee, H., Ra, S. W., Lee, K. M., Choe, K. H., Oh, Y. M., Shin, Y. M., & Yang, B. (2023). Effectiveness of the use of an oscillating positive expiratory pressure device in bronchiectasis with frequent exacerbations: a single-arm pilot study. *Frontiers in medicine (Lausanne)*, 10, 1159227. <https://doi.org/10.3389/fmed.2023.1159227>
- Kirkham, S., Sheehan, J. K., Knight, D., Richardson, P. S., & Thornton, D. J. (2002). Heterogeneity of airways mucus: variations in the amounts and glycoforms of the major oligomeric mucins MUC5AC and MUC5B. *Biochem J*, 361(Pt 3), 537-546. <https://doi.org/10.1042/0264-6021:3610537>
- Kite, J., & Phongsavan, P. (2017). Insights for conducting real-time focus groups online using a web conferencing service. *F1000Research*, 6.
- Knowles, M. R., & Boucher, R. C. (2002). Mucus clearance as a primary innate defense mechanism for mammalian airways. *The Journal of Clinical Investigation*, 109(5), 571-577. <https://doi.org/10.1172/JCI15217>
- Knowles, M. R., Zariwala, M., & Leigh, M. (2016). Primary ciliary dyskinesia. *Clinics in Chest Medicine*, 37(3), 449-461.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988337/pdf/nihms-800827.pdf>

- Knox, L., Gemine, R., Rees, S., Bowen, S., Groom, P., Taylor, D., Bond, I., Rosser, W., & Lewis, K. (2021). Using the Technology Acceptance Model to conceptualise experiences of the usability and acceptability of a self-management app (COPD.Pal®) for Chronic Obstructive Pulmonary Disease. *Health and Technology*, 11(1), 111-117. <https://doi.org/10.1007/s12553-020-00494-7>
- Kon, S. S., Canavan, J. L., Jones, S. E., Nolan, C. M., Clark, A. L., Dickson, M. J., Haselden, B. M., Polkey, M. I., & Man, W. D. (2014). Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *The Lancet Respiratory Medicine*, 2(3), 195-203.
- Kopsaftis, Z., Wood-Baker, R., & Poole, P. (2018). Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*, 6(6), Cd002733. <https://doi.org/10.1002/14651858.CD002733.pub3>
- Kourliouros, A., Hogg, R., Mehew, J., Al-Aloul, M., Carby, M., Lordan, J. L., Thompson, R. D., Tsui, S., & Parmar, J. (2018). Patient outcomes from time of listing for lung transplantation in the UK: are there disease-specific differences? *Thorax*, thoraxjnl-2018-211731.
- Krishnan, J. K., & Calverley, P. M. A. (2022). Understanding the People Excluded from Chronic Obstructive Pulmonary Disease Clinical Trials. *American Journal of Respiratory and Critical Care Medicine*, 206(3), 235-236. <https://doi.org/10.1164/rccm.202204-0688ED>

Krueger, R. A. (2014). *Focus groups: A practical guide for applied research*. Sage publications.

Landrigan, P. J., Fuller, R., Acosta, N. J. R., Adeyi, O., Arnold, R., Basu, N., Baldé, A. B., Bertollini, R., Bose-O'Reilly, S., Boufford, J. I., Breysse, P. N., Chiles, T., Mahidol, C., Coll-Seck, A. M., Cropper, M. L., Fobil, J., Fuster, V., Greenstone, M., Haines, A.,...Zhong, M. (2018). The Lancet Commission on pollution and health. *The Lancet*, 391(10119), 462-512.
[https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)32345-0](https://doi.org/https://doi.org/10.1016/S0140-6736(17)32345-0)

Laney, A. S., & Weissman, D. N. (2014). Respiratory diseases caused by coal mine dust. *Journal of Occupational and Environmental Medicine*, 56 Suppl 10(0 10), S18-22. <https://doi.org/10.1097/jom.0000000000000260>

Lapin, C. D. (2002). Airway physiology, autogenic drainage, and active cycle of breathing. *Respiratory Care*, 47(7), 778-785.

Laska, I. F., & Chalmers, J. D. (2019). Treatment to prevent exacerbations in bronchiectasis: macrolides as first line? *European Respiratory Journal*, 54(1), 1901213. <https://doi.org/10.1183/13993003.01213-2019>

Lathen, L., & Laestadius, L. (2021). Reflections on online focus group research with low socio-economic status African American adults during COVID-19. *International Journal of Qualitative Methods*, 20, 16094069211021713.

Le Rouzic, O., Roche, N., Cortot, A. B., Tillie-Leblond, I., Masure, F., Perez, T., Boucot, I., Hamouti, L., Ostinelli, J., Pribil, C., Poutchnine, C., Schück, S., Pourié, M., & Housset, B. (2018). Defining the "Frequent Exacerbator"

- Phenotype in COPD: A Hypothesis-Free Approach. *CHEST*, 153(5), 1106-1115. <https://doi.org/10.1016/j.chest.2017.10.009>
- Lee, A. L. (2023). Physiotherapy management of bronchiectasis in adults. *Journal of Physiotherapy*, 69(1), 7-14.
<https://doi.org/https://doi.org/10.1016/j.jphys.2022.11.013>
- Lee, A. L., Baenziger, S., Louey, A., Jennings, S., Solin, P., & Hoy, R. (2021). A review of physiotherapy practice for people with bronchiectasis. *ERJ Open Research*, 7(2), 00569-02020. <https://doi.org/10.1183/23120541.00569-2020>
- Lee, A. L., Burge, A. T., & Holland, A. E. (2017). Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis. *Cochrane Database of Systematic Reviews*(9).
<https://doi.org/10.1002/14651858.CD011699.pub2>
- Lee, J.-W., Chun, W., Lee, H. J., Min, J.-H., Kim, S.-M., Seo, J.-Y., Ahn, K.-S., & Oh, S.-R. (2021). The role of macrophages in the development of acute and chronic inflammatory lung diseases. *Cells*, 10(4), 897.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8070705/pdf/cells-10-00897.pdf>
- Leonard-Nimoy. (2015). X. Retrieved 25/08/2024 from
- Lewis, A., Cave, P., Stern, M., Welch, L., Taylor, K., Russell, J., Doyle, A. M., Russell, A. M., McKee, H., Clift, S., Bott, J., & Hopkinson, N. S. (2016). Singing for Lung Health-a systematic review of the literature and consensus statement. *npj Primary Care Respiratory Medicine*, 26, 16080.
<https://doi.org/10.1038/npjpcrm.2016.80>

Lewis, A., & Osadnik, C. R. (2023). Changing practice by changing pressures: a role for oscillating positive expiratory pressure in chronic obstructive pulmonary disease. *Thorax*, 78(2), 113-115. <https://doi.org/10.1136/thorax-2022-219451>

Lewis, A., Philip, K. E. J., Lound, A., Cave, P., Russell, J., & Hopkinson, N. S. (2021). The physiology of singing and implications for 'Singing for Lung Health' as a therapy for individuals with chronic obstructive pulmonary disease. *BMJ Open Respiratory Research*, 8(1). <https://doi.org/10.1136/bmjresp-2021-000996>

Lewis, L. K., Williams, M. T., & Olds, T. S. (2012). The active cycle of breathing technique: A systematic review and meta-analysis. *Respiratory Medicine*, 106(2), 155-172. <https://doi.org/10.1016/j.rmed.2011.10.014>

Li, L. S., Paquet, C., Johnston, K., & Williams, M. T. (2017). "What are my chances of developing COPD if one of my parents has the disease?" A systematic review and meta-analysis of prevalence of co-occurrence of COPD diagnosis in parents and offspring. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 403-415. <https://doi.org/10.2147/copd.S123933>

Lillehoj, E. P., Kato, K., Lu, W., & Kim, K. C. (2013). Cellular and molecular biology of airway mucins. *International review of cell and molecular biology*, 303, 139-202. <https://doi.org/10.1016/b978-0-12-407697-6.00004-0>

Lipson, D. A., Barnhart, F., Brealey, N., Brooks, J., Criner, G. J., Day, N. C., Dransfield, M. T., Halpin David, M. G., Han, M. K., Elaine, J. C., Kilbride, S.,

- Lange, P., Lomas, D. A., Martinez, F. J., Singh, D., Tabberer, M., Wise, R. A., & Pascoe, S. J. (2018). Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*, 378(18), 1671-1680. <https://doi.org/https://doi.org/10.1056/NEJMoa1713901>
- Livnat, G., Yaari, N., Stein, N., Bentur, L., Hanna, M., Harel, M., Adir, Y., & Shteinberg, M. (2021). 4-week daily airway clearance using oscillating positive-end expiratory pressure versus autogenic drainage in bronchiectasis patients: a randomised controlled trial. *ERJ Open Research*, 7(4), 00426-02021. <https://doi.org/10.1183/23120541.00426-2021>
- Loebinger, M. R., Wells, A. U., Hansell, D. M., Chinyanganya, N., Devaraj, A., Meister, M., & Wilson, R. (2009). Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *European Respiratory Journal*, 34(4), 843-849. <https://doi.org/10.1183/09031936.00003709>
- Long, M. B., Chotirmall, S. H., Shteinberg, M., & Chalmers, J. D. (2024). Rethinking bronchiectasis as an inflammatory disease. *The Lancet Respiratory Medicine*. [https://doi.org/10.1016/S2213-2600\(24\)00176-0](https://doi.org/10.1016/S2213-2600(24)00176-0)
- Mac Aogáin, M., Chandrasekaran, R., Lim, A. Y. H., Low, T. B., Tan, G. L., Hassan, T., Ong, T. H., Ng, A. H. Q., Bertrand, D., & Koh, J. Y. (2018). Immunological corollary of the pulmonary mycobiome in bronchiectasis: the CAMEB study. *European Respiratory Journal*, 52(1).
- Machin, M., Amaral, A. F., Wielscher, M., Rezwan, F. I., Imboden, M., Jarvelin, M.-R., Adcock, I. M., Probst-Hensch, N., Holloway, J. W., & Jarvis, D. L. (2017). Systematic review of lung function and COPD with peripheral blood DNA

- methylation in population based studies. *BMC Pulmonary Medicine*, 17, 1-10.
- Mackay, A. J., Donaldson, G. C., Patel, A. R., Jones, P. W., Hurst, J. R., & Wedzicha, J. A. (2012). Usefulness of the chronic obstructive pulmonary disease assessment test to evaluate severity of COPD exacerbations. *American Journal of Respiratory and Critical Care Medicine*, 185(11), 1218-1224.
- Magge, A., Ashraf, S., Quittner, A. L., & Metersky, M. L. (2019). Quality of life in patients with bronchiectasis: a 2-year longitudinal study. *Annals of Internal Medicine*, 7(14), 334. <https://doi.org/10.21037/atm.2019.06.62>
- Mahler, D. A., & Mackowiak, J. I. (1995). Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. *CHEST*, 107(6), 1585-1589. <https://doi.org/10.1378/chest.107.6.1585>
- Man, W., Chaplin, E., Daynes, E., Drummond, A., Evans, R. A., Greening, N. J., Nolan, C., Pavitt, M. J., Roberts, N. J., Vogiatzis, I., & Singh, S. J. (2023). British Thoracic Society Clinical Statement on pulmonary rehabilitation. *Thorax*, 78(Suppl 5), s2-s15. <https://doi.org/10.1136/thorax-2023-220439>
- Mandour, M. A., Helmi, A. M., El-Sheikh, M. M., El-Garem, F., & El-Ghazzawi, E. (1977). Effect of tympanic neurectomy on human parotid salivary gland: histopathologic, histochemical, and clinical study. *Archives of Otolaryngology*, 103(6), 338-341.

- Mark, S. C. v. d., Hoek, R. A. S., & Hellemons, M. E. (2020). Developments in lung transplantation over the past decade. *European Respiratory Review*, 29(157), 190132. <https://doi.org/10.1183/16000617.0132-2019>
- Marmor, M., & McShane, P. J. (2024). Mind the gap: challenges to overcome in airway clearance. *European Respiratory Journal*, 63(6). <https://doi.org/10.1183/13993003.00687-2024>
- Martínez-García, M., Oscullo, G., García-Ortega, A., Matera, M. G., Rogliani, P., & Cazzola, M. (2022). Rationale and Clinical Use of Bronchodilators in Adults with Bronchiectasis. *Drugs*, 82(1), 1-13. <https://doi.org/10.1007/s40265-021-01646-3>
- Matera, M. G., Page, C. P., Calzetta, L., Rogliani, P., & Cazzola, M. (2020). Pharmacology and Therapeutics of Bronchodilators Revisited. *Pharmacological reviews*, 72(1), 218-252. <https://doi.org/10.1124/pr.119.018150>
- Matthews, L. W., Doershuk, C. F., Wise, M., Eddy, G., Nudelman, H., & Spector, S. (1964). A therapeutic regimen for patients with cystic fibrosis. *The Journal of pediatrics*, 65(4), 558-575.
- McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(2). <https://doi.org/10.1002/14651858.CD003793.pub3>
- McCullough, A. R., Ryan, C., O'Neill, B., Bradley, J. M., Elborn, J. S., & Hughes, C. M. (2015). Defining the content and delivery of an intervention to Change

AdhereNce to treatment in BonchiEctasis (CAN-BE): a qualitative approach incorporating the Theoretical Domains Framework, behavioural change techniques and stakeholder expert panels. *BMC Health Services Research*, 15, 342. <https://doi.org/10.1186/s12913-015-1004-z>

McCullough, A. R., Tunney, M. M., Elborn, J. S., Bradley, J. M., & Hughes, C. M. (2015). Predictors of adherence to treatment in bronchiectasis. *Respiratory Medicine*, 109(7), 838-845.

McCullough, A. R., Tunney, M. M., Quittner, A. L., Elborn, J. S., Bradley, J. M., & Hughes, C. M. (2014). Treatment adherence and health outcomes in patients with bronchiectasis [Article]. *BMC Pulmonary Medicine*, 14(1), Article 107. <https://doi.org/10.1186/1471-2466-14-107>

McDonnell, M., Aliberti, S., Goeminne, P. a., Dimakou, K., Zucchetti, S., Davidson, J., Ward, C., Laffey, J., Finch, S., & Pesci, A. (2016). Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax*, thoraxjnl-2016-208481.

McGarvey, L. P., Birring, S. S., Morice, A. H., Dicpinigaitis, P. V., Pavord, I. D., Schelfhout, J., Nguyen, A. M., Li, Q., Tzontcheva, A., Iskold, B., Green, S. A., Rosa, C., Muccino, D. R., & Smith, J. A. (2022). Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet*, 399(10328), 909-923. [https://doi.org/10.1016/s0140-6736\(21\)02348-](https://doi.org/10.1016/s0140-6736(21)02348-5)

- McIlwaine, M., Bradley, J., Elborn, J. S., & Moran, F. (2017). Personalising airway clearance in chronic lung disease. *European Respiratory Review*, 26(143).
<https://doi.org/10.1183/16000617.0086-2016>
- McIlwaine, M., Button, B., & Nevitt, S. J. (2019). Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews*(11).
<https://doi.org/10.1002/14651858.CD003147.pub5>
- McIlwaine, M. P., Alarie, N., Davidson, G. F., Lands, L. C., Ratjen, F., Milner, R., Owen, B., & Agnew, J. L. (2013). Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. *Thorax*, 68(8), 746-751.
<https://doi.org/10.1136/thoraxjnl-2012-202915>
- McLeese, R. H., O'Neill, K., O'Neill, B., Chalmers, J. D., Boyd, J., De Soyza, A., McChrystal, R., Crichton, M. L., & Bradley, J. M. (2023). Airway clearance treatments in bronchiectasis: feasibility of linking survey results to registry data and a survey of patients' and physiotherapists' practices. *ERJ Open Research*, 9(2), 00540-02022. <https://doi.org/10.1183/23120541.00540-2022>
- McNamara, R. J., Epsley, C., Coren, E., & McKeough, Z. J. (2017). Singing for adults with chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*, 12(12), Cd012296.
<https://doi.org/10.1002/14651858.CD012296.pub2>
- McShane, A., Bath, J., Jaramillo, A. M., Ridley, C., Walsh, A. A., Evans, C. M., Thornton, D. J., & Ribbeck, K. (2021). Mucus. *Current Biology*, 31(15),

R938-R945.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8759706/pdf/nihms-1769811.pdf>

McShane, A., Philley, J. V., Prieto, D. A., & Aksamit, T. R. (2021). Global Attitudes of Health Care Providers About Aerosolized Airway Clearance Therapy in Bronchiectasis Patients During the Coronavirus Disease 2019 Pandemic. *Chronic Obstructive Pulmonary Diseases*, 8(3), 319-325.
<https://doi.org/10.15326/jcopdf.2021.0214>

Mead, J., Turner, J. M., Macklem, P. T., & Little, J. B. (1967). Significance of the relationship between lung recoil and maximum expiratory flow. *Journal of Applied Physiology*, 22(1), 95-108.

Merton, R. K. (1987). The focussed interview and focus groups: Continuities and discontinuities. *The Public opinion quarterly*, 51(4), 550-566.

Metersky, M. L., Choate, R., Addrizzo-Harris, D., Aksamit, T. R., Barker, A., Basavaraj, A., Daley, C. L., Daniels, M. L. A., Eden, E., & DiMango, A. (2021). The association of long-term macrolide therapy and nontuberculous mycobacterial culture positivity in patients with bronchiectasis. *CHEST*, 160(2), 466-469.

Mettler., S. K., Sonavane., S., Grumley., S., Nath., H. P., Yen., A. C., Pistenmaa., C., Nardelli., P., Estepar., R. S. J., Cho., M. H., & Diaz., A. A. (2024). Airway-occluding Mucus Plugs and Cause-specific Mortality in COPD. *American Journal of Respiratory and Critical Care Medicine*, 0(ja), null.
<https://doi.org/10.1164/rccm.202401-0121LE>

- Mikami, M., Llewellyn-Jones, C. G., Bayley, D., Hill, S. L., & Stockley, R. A. (1998). The chemotactic activity of sputum from patients with bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 157(3), 723-728.
- Milan, S., Bondalapati, P., Megally, M., Patel, E., Vaghasia, P., Gross, L., Bachman, E. M., Chadha, P., & Weingarten, J. A. (2019). Positive Expiratory Pressure Therapy With And Without Oscillation And Hospital Length Of Stay For Acute Exacerbation Of Chronic Obstructive Pulmonary Disease. *International Journal of Chronic Obstructive Pulmonary Disease*, 14, 2553-2561. <https://doi.org/10.2147/copd.S213546>
- Miravittles, M., & Ribera, A. (2017). Understanding the impact of symptoms on the burden of COPD. *Respiratory Research*, 18(1), 67. <https://doi.org/10.1186/s12931-017-0548-3>
- Mirra, V., Werner, C., & Santamaria, F. (2017). Primary ciliary dyskinesia: an update on clinical aspects, genetics, diagnosis, and future treatment strategies. *Frontiers in pediatrics*, 5, 135. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465251/pdf/fped-05-00135.pdf>
- Monteagudo, M., Rodríguez-Blanco, T., Barrecheguren, M., Simonet, P., & Miravittles, M. (2016). Prevalence and incidence of bronchiectasis in Catalonia, Spain: A population-based study. *Respiratory Medicine*, 121, 26-31. <https://doi.org/10.1016/j.rmed.2016.10.014>

- Morgan, K. T., Jiang, X.-Z., Patterson, D. L., & Gross, E. A. (1984). The nasal mucociliary apparatus: correlation of structure and function in the rat. *American Review of Respiratory Disease*, 130(2), 275-281.
- Morgan, S. E., Mosakowski, S., Giles, B. L., Naureckas, E., & Tung, A. (2019). Variability in expiratory flow requirements among oscillatory positive expiratory pressure. *Canadian Journal of Respiratory Therapy*, 56, 7-10.
<https://doi.org/10.29390/cjrt-2019-025>
- Morrison, C. B., Markovetz, M. R., & Ehre, C. (2019). Mucus, mucins, and cystic fibrosis. *Pediatr Pulmonol*, 54(S3), S84-S96.
<https://doi.org/https://doi.org/10.1002/ppul.24530>
- Muñoz, G., De Gracia, J., Buxó, M., Alvarez, A., & Vendrell, M. (2018). Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. *European Respiratory Journal*, 51(1), 1701926.
<https://doi.org/10.1183/13993003.01926-2017>
- Murgia, N., & Gambelunghe, A. (2022). Occupational COPD-The most under-recognized occupational lung disease? *Respirology*, 27(6), 399-410.
<https://doi.org/10.1111/resp.14272>
- Murray, M. P., Pentland, J. L., & Hill, A. T. (2009). A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*, 34(5), 1086-1092.
<https://doi.org/10.1183/09031936.00055509>

- Mwimbi, X. K., Muimo, R., Green, M. W., & Mehta, A. (2003). Making human nasal cilia beat in the cold: a real time assay for cell signalling. *Cell Signal*, 15(4), 395-402. [https://doi.org/10.1016/s0898-6568\(02\)00143-2](https://doi.org/10.1016/s0898-6568(02)00143-2)
- Nair, C., Shoemark, A., Chan, M., Ollosson, S., Dixon, M., Hogg, C., Alton, E. W., Davies, J. C., & Williams, H. D. (2014). Cyanide levels found in infected cystic fibrosis sputum inhibit airway ciliary function. *European Respiratory Journal*, 44(5), 1253-1261.
<https://erj.ersjournals.com/content/erj/44/5/1253.full.pdf>
- Naraparaju, S., Vaishali, K., Venkatesan, P., & Acharya, V. (2010). A comparison of the Acapella and a threshold inspiratory muscle trainer for sputum clearance in bronchiectasis-A pilot study. *Physiotherapy Theory and Practice*, 26(6), 353-357. <https://doi.org/10.3109/09593981003596616>
- Nayak, M. K., Alaparthi, G. K., Krishnan, K. S., Anand, R., & Acharya, V. (2018). Level of Patient Satisfaction with Chest Physiotherapy Airway Clearance Techniques in Bronchiectasis-A Survey. *Indian Journal of Public Health Research and Development*, 9, 90-95.
- Nettle, C. J., Jenkins, L., Curtis, D., Badiei, N., Lewis, K., Williams, P. R., & Daniels, D. R. (2018). Linear rheology as a potential monitoring tool for sputum in patients with Chronic Obstructive Pulmonary Disease (COPD). *Biorheology*, 54, 67-80. <https://doi.org/10.3233/BIR-17141>
- Nguyen, A. M., Schelfhout, J., Muccino, D., Bacci, E. D., La Rosa, C., Vernon, M., & Birring, S. S. (2022). Leicester Cough Questionnaire validation and clinically important thresholds for change in refractory or unexplained chronic cough.

- Therapeutic Advances in Respiratory Disease*, 16, 17534666221099737.
<https://doi.org/10.1177/17534666221099737>
- NICE. (2016). Motor neurone disease: assessment and management. In: National institute for clinical health and care excellence.
- NICE. (2018). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 69.
<https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245>
- NICE. (2023). <*Diagnosis - COPD _ Diagnosis _ Chronic obstructive pulmonary disease _ CKS _ NICE.pdf*>. Retrieved 04/05/2024 from
<https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/diagnosis/diagnosis-copd/>
- Nichol, K. L., Margolis, K. L., Wuorenma, J., & Von Sternberg, T. (1994). The Efficacy and Cost Effectiveness of Vaccination against Influenza among Elderly Persons Living in the Community. *New England Journal of Medicine*, 331(12), 778-784. <https://doi.org/10.1056/nejm199409223311206>
- NIH. (2020). *Marvels of Mucus and Phlegm. The Slime That Keeps You Healthy*. National Institutes of Health. Retrieved 26/08/2024 from
<https://newsinhealth.nih.gov/2020/08/marvels-mucus-phlegm>
- Nikolaou, V., Massaro, S., Fakhimi, M., Stergioulas, L., & Price, D. (2020). COPD phenotypes and machine learning cluster analysis: A systematic review and

future research agenda. *Respiratory Medicine*, 171, 106093.

<https://doi.org/https://doi.org/10.1016/j.rmed.2020.106093>

O'Donnell, A. E. (2022). Airway Clearance and Mucoactive Therapies in

Bronchiectasis. *Clinics in Chest Medicine*, 43(1), 157-163.

<https://doi.org/10.1016/j.ccm.2021.12.004>

O'Neill, K., O'donnell, A. E., & Bradley, J. (2019). Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. *Respirology*, 24, 227 - 237.

Oba, Y., Keeney, E., Ghatehorde, N., & Dias, S. (2018). Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD) : A systematic review and network meta-analysis.

<https://doi.org/10.1002/14651858.CD012620.pub2>

Okuda, K., Chen, G., Subramani, D. B., Wolf, M., Gilmore, R. C., Kato, T., Radicioni, G., Kesimer, M., Chua, M., & Dang, H. (2019). Localization of secretory mucins MUC5AC and MUC5B in normal/healthy human airways. *American Journal of Respiratory and Critical Care Medicine*, 199(6), 715-727.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6423099/pdf/rccm.201804-0734OC.pdf>

Olsén, M. F., Olofsson, P., Frejd, P., Lannefors, L., & Westerdahl, E. (2021).

Technical aspects of devices and equipment for positive expiratory pressure with and without oscillation. *Respiratory Care*, 66(5), 862-877.

Osadnik, C. R., McDonald, C. F., Miller, B. R., Hill, C. J., Tarrant, B., Steward, R.,

Chao, C., Stodden, N., Oliveira, C. C., Gagliardi, N., & Holland, A. E. (2014).

The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. *Thorax*, 69(2), 137-143.
<https://doi.org/10.1136/thoraxjnl-2013-203425>

Osei, A. D., Mirbolouk, M., Orimoloye, O. A., Dzaye, O., Uddin, S. M. I., Benjamin, E. J., Hall, M. E., DeFilippis, A. P., Bhatnagar, A., Biswal, S. S., & Blaha, M. J. (2020). Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. *American journal of preventive medicine*, 58(3), 336-342. <https://doi.org/10.1016/j.amepre.2019.10.014>

Osman, L. P., Roughton, M., Hodson, M. E., & Pryor, J. A. (2010). Short-term comparative study of high frequency chest wall oscillation and European airway clearance techniques in patients with cystic fibrosis. *Thorax*, 65(3), 196-200. <https://doi.org/10.1136/thx.2008.111492>

Otis, A. B., McKerrow, C. B., Bartlett, R. A., Mead, J., McIlroy, M., Selverstone, N., & Radford Jr, E. (1956). Mechanical factors in distribution of pulmonary ventilation. *Journal of Applied Physiology*, 8(4), 427-443.

Ouaalaya, E. H., Falque, L., Dupis, J. M., Sabatini, M., Bernady, A., Nguyen, L., Ozier, A., Nocent-Ejnaini, C., Le Guillou, F., Molimard, M., Zysman, M., & Raherison-Semjen, C. (2020). Susceptibility to frequent exacerbation in COPD patients: Impact of the exacerbations history, vaccinations and

comorbidities? *Respiratory Medicine*, 169, 106018.

<https://doi.org/https://doi.org/10.1016/j.rmed.2020.106018>

Paff, T., Omran, H., Nielsen, K. G., & Haarman, E. G. (2021). Current and Future Treatments in Primary Ciliary Dyskinesia. *International Journal of Molecular Sciences*, 22(18). <https://doi.org/10.3390/ijms22189834>

Pan, C.-X., Shi, M.-X., & Guan, W.-J. (2023). Airway clearance technique in the modern era of bronchiectasis management. In (Vol. 9): Eur Respiratory Soc.

Papi, A., Vestbo, J., Fabbri, L., Corradi, M., Prunier, H., Cohuet, G., Guasconi, A., Montagna, I., Vezzoli, S., Petruzzelli, S., Scuri, M., Roche, N., & Singh, D. (2018). Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet*, 391(10125), 1076-1084. [https://doi.org/10.1016/s0140-6736\(18\)30206-x](https://doi.org/10.1016/s0140-6736(18)30206-x)

Park, J. A., Crotty Alexander, L. E., & Christiani, D. C. (2022). Vaping and Lung Inflammation and Injury. *Annual review of physiology*, 84, 611-629. <https://doi.org/10.1146/annurev-physiol-061121-040014>

Pathak, U., Gupta, N. C., & Suri, J. C. (2020). Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. *International Journal of Environmental Health Research*, 30(1), 75-88. <https://doi.org/10.1080/09603123.2019.1575951>

Patterson, J. E., Bradley, J. M., & Elborn, J. S. (2004). Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques (incorporating postural drainage and vibration) versus test of

incremental respiratory endurance. *Chronic Respiratory Disease*, 1(3), 127-130. <https://doi.org/10.1191/1479972304cd034oa>

Patterson, J. E., Bradley, J. M., Hewitt, O., Bradbury, I., & Elborn, J. S. (2005).

Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques versus Acapella. *Respiration*, 72(3), 239-242. <https://doi.org/10.1159/000085363>

Peng, C., Yan, Y., Li, Z., Jiang, Y., & Cai, Y. (2020). Chronic obstructive pulmonary disease caused by inhalation of dust: A meta-analysis. *Medicine (Baltimore)*, 99(34), e21908. <https://doi.org/10.1097/md.00000000000021908>

Philip, K. E. J., Buttery, S. C., Bowen, S., Lewis, A., Jeffery, E., Alghamdi, S. M., Williams, P., Alasmari, A. M., Alsulayyim, A. S., Orton, C. M., Conway, F., Chan, L., Vijayakumar, B., Tana, A., Tonkin, J., Perkins, A., Garner, J. L., Srikanthan, K., Sadaka, A.,...Hopkinson, N. S. (2024). Singing for lung health in COPD: a multicentre randomised controlled trial of online delivery. *BMJ Open Respiratory Research*, 11(1), e002365. <https://doi.org/10.1136/bmjresp-2024-002365>

Phillips, J., Hing, W., Pope, R., Canov, A., Harley, N., & Lee, A. L. (2023). Active cycle of breathing technique versus oscillating PEP therapy versus walking with huffing during an acute exacerbation of bronchiectasis: a randomised, controlled trial protocol. *BMC Pulmonary Medicine*, 23(1). <https://doi.org/10.1186/s12890-023-02324-8>

- Phillips, J., Lee, A., Pope, R., & Hing, W. (2021). Physiotherapists' use of airway clearance techniques during an acute exacerbation of bronchiectasis: a survey study. *Archives of physiotherapy*, 11, 1-11.
- PHW. (2018). *UK smoking prevalence, age-standardised percentage, persons aged 18+, UK constituent countries, 2018*. Retrieved from <https://publichealthwales.shinyapps.io/smokinginwales/>
- PHW. (2020). *Smoking-attributable admissions, EASR per 100,000, males and females aged 35+, Wales by deprivation fifth, 2008/09-2010/11 to 2016/17-2018/19*. Retrieved from <https://publichealthwales.shinyapps.io/smokinginwales/>
- Pleasants, R. A., Riley, I. L., & Mannino, D. M. (2016). Defining and targeting health disparities in chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*, 11, 2475-2496. <https://doi.org/10.2147/copd.S79077>
- Polverino, E., Dimakou, K., Traversi, L., Bossios, A., Haworth, C. S., Loebinger, M. R., De Soyza, A., Vendrell, M., Burgel, P.-R., Mertsch, P., McDonnell, M., Škrgat, S., Carro, L. M., Sibila, O., van der Eerden, M., Kauppi, P., Hill, A. T., Wilson, R., Milenkovic, B.,...Goeminne, P. C. (2024). Bronchiectasis and asthma: Data from The European Bronchiectasis Registry (EMBARC). *Journal of Allergy and Clinical Immunology*. <https://doi.org/https://doi.org/10.1016/j.jaci.2024.01.027>
- Polverino, E., Goeminne, P. C., McDonnell, M. J., Aliberti, S., Marshall, S. E., Loebinger, M. R., Murris, M., Cantón, R., Torres, A., Dimakou, K., De Soyza,

- A., Hill, A. T., Haworth, C. S., Vendrell, M., Ringshausen, F. C., Subotic, D., Wilson, R., Vilaró, J., Stallberg, B.,...Chalmers, D., James. (2017). European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal*, 50(3), 1700629.
<https://doi.org/10.1183/13993003.00629-2017>
- Poncin, W., Reyckler, G., Leeuwerck, N., Bauwens, N., Aubriot, A.-S., Nader, C., Liistro, G., & Gohy, S. (2017). Short-term effect of autogenic drainage on ventilation inhomogeneity in adult subjects with stable non-cystic fibrosis bronchiectasis. *Respiratory Care*, 62(5), 524-531.
- Poncin, W., Reyckler, G., Liistro, M., & Liistro, G. (2020). Comparison of 6 Oscillatory Positive Expiratory Pressure Devices During Active Expiratory Flow. *Respiratory Care*, 65(4), 492-499.
<https://doi.org/10.4187/respcare.07271>
- Price, D., Brusselle, G., Roche, N., Freeman, D., & Chisholm, A. (2015). Real-world research and its importance in respiratory medicine. *Breathe (Sheff)*, 11(1), 26-38. <https://doi.org/10.1183/20734735.015414>
- Pryor, J. A. (2016). Active cycle of breathing techniques. *International Physiotherapy Group for Cystic Fibrosis Blue Booklet on Physiotherapy Techniques*. www.ecfs.eu/ipg_cf/booklet Date last accessed: October, 20.
- Public-Health-England. (2018). The 2nd Atlas of variation in risk factors and healthcare for respiratory in England, 2019. In. NHS England.
- Pumar, M. I., Gray, C. R., Walsh, J. R., Yang, I. A., Rolls, T. A., & Ward, D. L. (2014). Anxiety and depression-Important psychological comorbidities of

COPD. *Journal of Thoracic Disease*, 6(11), 1615-1631.

<https://doi.org/10.3978/j.issn.2072-1439.2014.09.28>

Quint, J. K., Millett, E. R. C., Joshi, M., Navaratnam, V., Thomas, S. L., Hurst, J. R., Smeeth, L., & Brown, J. S. (2016). Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal*, 47(1), 186-193.

<https://doi.org/10.1183/13993003.01033-2015>

Quittner, A. L., O'Donnell, A. E., Salathe, M. A., Lewis, S. A., Li, X., Montgomery, A. B., O'Riordan, T. G., & Barker, A. F. (2015). Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax*, 70(1), 12-20.

<https://doi.org/10.1136/thoraxjnl-2014-205918>

Rabe, K. F. (2011). Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *British journal of pharmacology*, 163(1), 53-67.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085868/pdf/bph0163-0053.pdf>

Rabe, K. F., Martinez, F. J., Ferguson, G. T., Wang, C., Singh, D., Wedzicha, J. A., Trivedi, R., St Rose, E., Ballal, S., McLaren, J., Darken, P., Aurivillius, M., Reisner, C., & Dorinsky, P. (2020). Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *New England Journal of Medicine*, 383(1), 35-48. <https://doi.org/10.1056/NEJMoa1916046>

- Raju, S. V., Solomon, G. M., Dransfield, M. T., & Rowe, S. M. (2016). Acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis and other diseases of mucus clearance. *Clinics in Chest Medicine*, 37(1), 147-158.
- Ramos, F. L., Krahne, J. S., & Kim, V. (2014). Clinical issues of mucus accumulation in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 9, 139-150. <https://doi.org/10.2147/copd.S38938>
- Ramos, M., Lamotte, M., Gerlier, L., Svangren, P., Miquel-Cases, A., & Haughney, J. (2019). Cost-effectiveness of physical activity in the management of COPD patients in the UK. *International Journal of Chronic Obstructive Pulmonary Disease*, 14, 227-239. <https://doi.org/10.2147/copd.S181194>
- Ramsey, K. A., Chen, A. C. H., Radicioni, G., Lourie, R., Martin, M., Broomfield, A., Sheng, Y. H., Hasnain, S. Z., Radford-Smith, G., Simms, L. A., Burr, L., Thornton, D. J., Bowler, S. D., Livengood, S., Ceppe, A., Knowles, M. R., Noone, P. G., Sr., Donaldson, S. H., Hill, D. B.,...McGuckin, M. A. (2020). Airway Mucus Hyperconcentration in Non-Cystic Fibrosis Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 201(6), 661-670. <https://doi.org/10.1164/rccm.201906-1219OC>
- Rebelo, P., Oliveira, A., Andrade, L., Valente, C., & Marques, A. (2020). Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Fatigue in Patients With COPD Following Pulmonary Rehabilitation. *CHEST*, 158(2), 550-561. <https://doi.org/10.1016/j.chest.2020.02.045>

RespirTech. (n.d). *HFCWO*. Retrieved 29/07/2024 from

<https://www.respirtech.com/conditions/cystic-fibrosis.html>

Reynolds, D., & Kollef, M. (2021). The Epidemiology and Pathogenesis and Treatment of *Pseudomonas aeruginosa* Infections: An Update. *Drugs*, 81(18), 2117-2131. <https://doi.org/10.1007/s40265-021-01635-6>

Riccelli, M. G., Goldoni, M., Poli, D., Mozzoni, P., Cavallo, D., & Corradi, M. (2020). Welding Fumes, a Risk Factor for Lung Diseases. *International Journal of Environmental Research and Public Health*, 17(7).
<https://doi.org/10.3390/ijerph17072552>

Ringshausen, F. C., de Roux, A., Diel, R., Hohmann, D., Welte, T., & Rademacher, J. (2015). Bronchiectasis in Germany: a population-based estimation of disease prevalence. *European Respiratory Journal*, 46(6), 1805-1807.
<https://doi.org/10.1183/13993003.00954-2015>

Robinson, O. C. (2014). Sampling in Interview-Based Qualitative Research: A Theoretical and Practical Guide. *Qualitative Research In Psychology*, 11(1), 25-41. <https://doi.org/10.1080/14780887.2013.801543>

Rodrigues, S. O., Cunha, C., Soares, G. M. V., Silva, P. L., Silva, A. R., & Gonçalves-de-Albuquerque, C. F. (2021). Mechanisms, Pathophysiology and Currently Proposed Treatments of Chronic Obstructive Pulmonary Disease. *Pharmaceuticals (Basel)*, 14(10).
<https://doi.org/10.3390/ph14100979>

Rogers, G. B., Zain, N. M., Bruce, K. D., Burr, L. D., Chen, A. C., Rivett, D. W., McGuckin, M. A., & Serisier, D. J. (2014). A novel microbiota stratification

system predicts future exacerbations in bronchiectasis. *Annals of the American Thoracic Society*, 11(4), 496-503.

<https://doi.org/10.1513/AnnalsATS.201310-335OC>

Rovina, N., Koutsoukou, A., & Koulouris, N. G. (2013). Inflammation and immune response in COPD: where do we stand? *Mediators Inflamm*, 2013, 413735.

<https://doi.org/10.1155/2013/413735>

Ryrsø, C. K., Godtfredsen, N. S., Kofod, L. M., Lavesen, M., Mogensen, L., Tobberup, R., Farver-Vestergaard, I., Callesen, H. E., Tendal, B., Lange, P., & Iepsen, U. W. (2018). Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulmonary Medicine*, 18(1), 154.

<https://doi.org/10.1186/s12890-018-0718-1>

Sahardin, B. (2021). *Impact of Aerobika® Oscillating Positive Expiratory Pressure (OPEP) in Improving Small Airway Disease and COPD Assessment Test (CAT) Score in Chronic Obstructive Pulmonary Disease (COPD)*. FF-2021-175 UNIVERSITI KEBANGSAAN MALAYSIA].

Sahardin, S. N., Jailaini, M. F. M., Abeed, N. N. N., Ban, A. Y., Hau, N. B., Azmel, A. A., Shah, S. A., & Hamid, M. F. A. (2023). Impact of Aerobika(®) oscillating positive expiratory pressure in improving small airway resistance, lung function, symptoms and exercise capacity in chronic obstructive pulmonary disease. *Frontiers in medicine*, 10, 1202380.

<https://doi.org/10.3389/fmed.2023.1202380>

- Sanderson, M. J., & Dirksen, E. R. (1986). Mechanosensitivity of cultured ciliated cells from the mammalian respiratory tract: implications for the regulation of mucociliary transport. *Proceedings of the National Academy of Sciences USA*, 83(19), 7302-7306. <https://doi.org/10.1073/pnas.83.19.7302>
- Sanderson, M. J., & Dirksen, E. R. (1989). Mechanosensitive and beta-adrenergic control of the ciliary beat frequency of mammalian respiratory tract cells in culture. *American Review of Respiratory Disease*, 139(2), 432-440. <https://doi.org/10.1164/ajrccm/139.2.432>
- Satir, P. (1999). The cilium as a biological nanomachine. *Faseb Journal*, 13 Suppl 2, S235-237. <https://doi.org/10.1096/fasebj.13.9002.s235>
- Satir, P., & Sleigh, M. A. (1990). The physiology of cilia and mucociliary interactions. *Annual review of physiology*, 52, 137-155. <https://doi.org/10.1146/annurev.ph.52.030190.001033>
- Schultz, K., Göhl, O., Stojanovic, D., Wittmann, M., Rudnik, J., & Schwarze, M. (2011). CAT (COPD assessment test) as outcome parameter of pulmonary rehabilitation (PR) in COPD. *European Respiratory Journal*, 38(Suppl 55), p3626.
- Scullion, J. E. (2007). The development of anticholinergics in the management of COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 2(1), 33-40. <https://doi.org/10.2147/copd.2007.2.1.33>
- Semwal, S., Mitra, S., & Singh, S. (2015). Autogenic Drainage Versus Acapella for Airway Clearance in Patients with Bronchiectasis: Randomized Crossover Trial. *International Journal of Health Sciences and Research*, 5, 323-327.

- Sen, D. (2014). Working with asbestos and the possible health risks. *Occupational Medicine*, 65(1), 6-14. <https://doi.org/10.1093/occmed/kqu175>
- Sethi, S. (2010). Infection as a comorbidity of COPD. *European Respiratory Journal*, 35(6), 1209-1215. <https://doi.org/10.1183/09031936.00081409>
- Shen, M., Li, Y., Xu, L., Shi, H., Ni, Y., Lin, H., & Li, F. (2021). Role of active cycle of breathing technique for patients with chronic obstructive pulmonary disease: A pragmatic, randomized clinical trial. *International Journal of Nursing Studies*, 117, 103880.
- Shimura, S., Andoh, Y., Haraguchi, M., & Shirato, K. (1996). Continuity of airway goblet cells and intraluminal mucus in the airways of patients with bronchial asthma. *European Respiratory Journal*, 9(7), 1395-1401. <https://erj.ersjournals.com/content/erj/9/7/1395.full.pdf>
- Shteinberg, M., Yaari, N., Stein, N., Bentur, L., Livnat, G., & Adir, Y. (2020). A randomized controlled trial of 4 weeks of airway clearance with oscillating positive end expiratory pressure device versus autogenic drainage in people with bronchiectasis. *European Respiratory Journal*, 56(suppl 64), 4103. <https://doi.org/10.1183/13993003.congress-2020.4103>
- Sibila, O., Suarez - Cuartin, G., Rodrigo - Troyano, A., Fardon, T. C., Finch, S., Mateus, E. F., Garcia - Bellmunt, L., Castillo, D., Vidal, S., & Sanchez - Reus, F. (2015). Secreted mucins and airway bacterial colonization in non - CF bronchiectasis. *Respirology*, 20(7), 1082-1088.

- Singh, D., Papi, A., Corradi, M., Pavlišová, I., Montagna, I., Francisco, C., Cohuet, G., Vezzoli, S., Scuri, M., & Vestbo, J. (2016). Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet*, 388(10048), 963-973.
[https://doi.org/10.1016/s0140-6736\(16\)31354-x](https://doi.org/10.1016/s0140-6736(16)31354-x)
- Singh, G., Acharya, S., Shukla, S., & Jain, D. (2023). Muco-Obstructive Lung Disease: A Systematic Review. *Cureus*, 15(10), e46866.
<https://doi.org/10.7759/cureus.46866>
- Smith, B., Benedetti, A., Allen, N. B., Bertoni, A., Hilpert, M., Jr., D. R. J., Kaufman, J. D., Lin, C.-L., Michos, E. D., Oelsner, E., Watson, K. E., Hoffman, E. A., & Barr, R. G. (2018). Late Breaking Abstract - Dysanapsis is a major determinant of airflow limitation among older adults. *European Respiratory Journal*, 52(suppl 62), PA2265. <https://doi.org/10.1183/13993003.congress-2018.PA2265>
- Smyth, A. R., Bell, S. C., Bojcin, S., Bryon, M., Duff, A., Flume, P., Kashirskaya, N., Munck, A., Ratjen, F., Schwarzenberg, S. J., Sermet-Gaudelus, I., Southern, K. W., Taccetti, G., Ullrich, G., Wolfe, S., & European Cystic Fibrosis, S. (2014). European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis*, 13 Suppl 1, S23-42.
<https://doi.org/10.1016/j.jcf.2014.03.010> (ECFS Standards of Care for Cystic Fibrosis: The 2014 Edition)

- Snell, N., Gibson, J., Jarrold, I., & Quint, J. K. (2019). Epidemiology of bronchiectasis in the UK: Findings from the British lung foundation's 'Respiratory health of the nation' project. *Respiratory Medicine*, 158, 21-23.
<https://doi.org/10.1016/j.rmed.2019.09.012>
- Sobala, R., & De Soyza, A. (2022). Bronchiectasis and chronic obstructive pulmonary disease overlap syndrome. *Clinics in Chest Medicine*, 43(1), 61-70.
- Song, D., Cahn, D., & Duncan, G. A. (2020). Mucin Biopolymers and Their Barrier Function at Airway Surfaces. *Langmuir*, 36(43), 12773-12783.
<https://doi.org/10.1021/acs.langmuir.0c02410>
- Spinou, A., Aliberti, S., Menendez, R., Blasi, F., Regis-Burgel, P., Ringshausen, F., De Soyza, A., Shteinberg, M., Shoemark, A., Vendrell, M., Polverino, E., Haworth, C., Dimakou, K., Loebinger, M. R., Torres, A., Welte, T., Elborn, S. J., Goeminne, P. C., Chalmers, J. D., & Herrero-Cortina, B. (2020). Airway clearance techniques in patients with bronchiectasis. Data from the EMBARC Registry. *European Respiratory Journal*, 56(suppl 64), 1263.
<https://doi.org/10.1183/13993003.congress-2020.1263>
- Spinou, A., Hererro-Cortina, B., Aliberti, S., Goeminne, P. C., Polverino, E., Dimakou, K., Haworth, C. S., Loebinger, M. R., De Soyza, A., Vendrell, M., Burgel, P. R., McDonnell, M., Sutharsan, S., Skrgat, S., Maiz-Carro, L., Sibila, O., Stolz, D., Kauppi, P., Bossios, A.,...Ringshausen, F. C. (2024). Airway clearance management in people with bronchiectasis: data from the

European Bronchiectasis Registry (EMBARC). *European Respiratory Journal*. <https://doi.org/10.1183/13993003.01689-2023>

Spruit, M. A., Singh, S. J., Garvey, C., ZuWallack, R., Nici, L., Rochester, C., Hill, K., Holland, A. E., Lareau, S. C., Man, W. D., Pitta, F., Sewell, L., Raskin, J., Bourbeau, J., Crouch, R., Franssen, F. M., Casaburi, R., Vercoulen, J. H., Vogiatzis, I.,...Wouters, E. F. (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*, 188(8), e13-64. <https://doi.org/10.1164/rccm.201309-1634ST>

Squillacioti, G., Bellisario, V., Ghelli, F., Marcon, A., Marchetti, P., Corsico, A. G., Pirina, P., Maio, S., Stafoggia, M., Verlato, G., & Bono, R. (2024). Air pollution and oxidative stress in adults suffering from airway diseases. Insights from the Gene Environment Interactions in Respiratory Diseases (GEIRD) multi-case control study. *Science of The Total Environment*, 909, 168601. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2023.168601>

Stolz, D., Mkorombindo, T., Schumann, D. M., Agusti, A., Ash, S. Y., Bafadhel, M., Bai, C., Chalmers, J. D., Criner, G. J., Dharmage, S. C., Franssen, F. M. E., Frey, U., Han, M., Hansel, N. N., Hawkins, N. M., Kalhan, R., Konigshoff, M., Ko, F. W., Parekh, T. M.,...Dransfield, M. T. (2022). Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet*, 400(10356), 921-972. [https://doi.org/10.1016/s0140-6736\(22\)01273-9](https://doi.org/10.1016/s0140-6736(22)01273-9)

- Stone, P. W., Hickman, K., Steiner, M. C., Roberts, C. M., Quint, J. K., & Singh, S. J. (2020). Predictors of referral to pulmonary rehabilitation from UK primary care. *International Journal of Chronic Obstructive Pulmonary Disease*, 2941-2952.
- Suggett, J. (2016). Review of Quality of Life Outcomes Following Use of an Oscillating Positive Expiratory Pressure (OPEP) Device for Chronic Obstructive Pulmonary Disease (COPD): 8 Weeks Field Study Using the COPD Assessment Test (CAT). In *D39. COPD: NON-PHARMACOLOGIC THERAPIES* (pp. A6888-A6888). https://doi.org/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A6888
- Suissa, S. (2019). Inhaled corticosteroids preventing pneumonia mortality: paradox or selection bias? *European Respiratory Journal*, 53(2). <https://doi.org/10.1183/13993003.02112-2018>
- Suissa, S. (2021). Perplexing mortality data from triple therapy trials in COPD. *The Lancet Respiratory Medicine*, 9(7), 684-685. [https://doi.org/10.1016/s2213-2600\(21\)00238-1](https://doi.org/10.1016/s2213-2600(21)00238-1)
- Suissa, S., Dell'Aniello, S., & Ernst, P. (2022a). Single-Inhaler Triple versus Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety. *International Journal of Chronic Obstructive Pulmonary Disease*, 17, 1975-1986. <https://doi.org/10.2147/copd.S378486>
- Suissa, S., Dell'Aniello, S., & Ernst, P. (2022b). Triple inhaler versus dual bronchodilator therapy in COPD: real-world effectiveness on mortality. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, 19(1), 1-9.

- Svenningsen, S., & Nair, P. (2022). Persistent Airway Plugs: A Call for Clinical Recognition and Novel Therapies. *American Journal of Respiratory and Critical Care Medicine*, 205(9), 977-978.
<https://doi.org/10.1164/rccm.202201-0147ED>
- Svenningsen, S., Paulin, G. A., Sheikh, K., Guo, F., Hasany, A., Kirby, M., Rezai, R. E., McCormack, D. G., & Parraga, G. (2016). Oscillatory Positive Expiratory Pressure in Chronic Obstructive Pulmonary Disease. *COPD*, 13(1), 66-74.
<https://doi.org/10.3109/15412555.2015.1043523>
- Tan, H.-L., Regamey, N., Brown, S., Bush, A., Lloyd, C. M., & Davies, J. C. (2011). The Th17 pathway in cystic fibrosis lung disease. *American Journal of Respiratory and Critical Care Medicine*, 184(2), 252-258.
- Tang, J. X., Wen, Q., Bennett, A., Kim, B., Sheils, C. A., Bucki, R., & Janmey, P. A. (2005). Anionic poly(amino acid)s dissolve F-actin and DNA bundles, enhance DNase activity, and reduce the viscosity of cystic fibrosis sputum. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 289(4), L599-605. <https://doi.org/10.1152/ajplung.00061.2005>
- Tashkin, D. P., Celli, B., Senn, S., Burkhart, D., Kesten, S., Menjoge, S., & Decramer, M. (2008). A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *New England Journal of Medicine*, 359(15), 1543-1554.
<https://doi.org/10.1056/NEJMoa0805800>
- Terry, P. B., & Traystman, R. J. (2016). The Clinical Significance of Collateral Ventilation. *Annals of the American Thoracic Society*, 13(12), 2251-2257.
<https://doi.org/10.1513/AnnalsATS.201606-448FR>

- Thanh, N. X., Jacobs, P., Suggett, J., McIvor, A., & Kaplan, A. (2019, 2019/01/10/). *Cost-Effectiveness of the Aerobika® Oscillating Positive Expiratory Pressure Device in the Management of Chronic Obstructive Pulmonary Disease Exacerbations in Canada*.
<https://www.hindawi.com/journals/crj/2019/9176504/>
- Thi, M. T. T., Wibowo, D., & Rehm, B. H. A. (2020). *Pseudomonas aeruginosa Biofilms*. *International Journal of Molecular Sciences*, 21(22).
<https://doi.org/10.3390/ijms21228671>
- Thornton, C. S., & Parkins, M. D. (2023). Microbial Epidemiology of the Cystic Fibrosis Airways: Past, Present, and Future. *Seminars in Respiratory and Critical Care Medicine*, 44(02), 269-286. <https://doi.org/10.1055/s-0042-1758732>
- Thornton, D. J., Rousseau, K., & McGuckin, M. A. (2008). Structure and function of the polymeric mucins in airways mucus. *Annual review of physiology*, 70, 459-486. <https://doi.org/10.1146/annurev.physiol.70.113006.100702>
- Tindall, L. (2009). J.A. Smith, P. Flower and M. Larkin (2009), Interpretative Phenomenological Analysis: Theory, Method and Research. *Qualitative Research In Psychology*, 6(4), 346-347.
<https://doi.org/10.1080/14780880903340091>
- Toumpanakis, D., & Usmani, O. S. (2023). Small airways disease in patients with alpha-1 antitrypsin deficiency. *Respiratory Medicine*, 211, 107222.
<https://doi.org/10.1016/j.rmed.2023.107222>

- Tran, B., Rafinejad-Farahani, B., Moodie, S., O'Hagan, R., & Glista, D. (2021). A Scoping Review of Virtual Focus Group Methods Used in Rehabilitation Sciences. *International Journal of Qualitative Methods*, 20, 16094069211042227. <https://doi.org/10.1177/16094069211042227>
- Trudell Medical International. (2021, June 28). *Aerobika Easy to follow instructions* [Video]. YouTube. <https://www.youtube.com/watch?v=PzwNDnre6Ng&t=66s>
- Tse, J., Wada, K., Wang, Y., Coppolo, D., Kushnarev, V., & Suggett, J. (2020). Impact of Oscillating Positive Expiratory Pressure Device Use on Post-Discharge Hospitalizations: A Retrospective Cohort Study Comparing Patients with COPD or Chronic Bronchitis Using the Aerobika® and Acapella® Devices. *International Journal of Chronic Obstructive Pulmonary Disease*, 15, 2527-2538. <https://www.dovepress.com/getfile.php?fileID=62662>
- Turner, R. D., & Birring, S. S. (2023). Measuring cough: what really matters? *Journal of Thoracic Disease*, 15(4), 2288-2299. <https://doi.org/10.21037/jtd-23-230>
- Üzmezoğlu, B., Altıay, G., Özdemir, L., Tuna, H., & Süt, N. (2018). The Efficacy of Flutter(®) and Active Cycle of Breathing Techniques in Patients with Bronchiectasis: A Prospective, Randomized, Comparative Study. *Turkish Thoracic Journal*, 19(3), 103-109. <https://doi.org/10.5152/TurkThoracJ.2018.17050>
- Van Allen, C., Lindskog, G., & Richter, H. (1931). Collateral respiration. Transfer of air collaterally between pulmonary lobules. *The Journal of Clinical Investigation*, 10(3), 559-590.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC435770/pdf/jcinvest00718-0133.pdf>

Van Fleet, H., Dunn, D. K., McNinch, N. L., & Volsko, T. A. (2017). Evaluation of Functional Characteristics of 4 Oscillatory Positive Pressure Devices in a Simulated Cystic Fibrosis Model. *Respiratory Care*, 62(4), 451-458.
<https://doi.org/10.4187/respcare.04570>

Vincken, W., van Noord, J. A., Greefhorst, A. P., Bantje, T. A., Kesten, S., Korducki, L., Cornelissen, P. J., & Dutch/Belgian Tiotropium Study, G. (2002). Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *European Respiratory Journal*, 19(2), 209-216.
<https://doi.org/10.1183/09031936.02.00238702>

Walker, H. K., Hall, W. D., & Hurst, J. W. (1990). Clinical methods: the history, physical, and laboratory examinations.

Walters, J. A., Tang, J. N., Poole, P., & Wood-Baker, R. (2017). Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, 1(1), Cd001390.
<https://doi.org/10.1002/14651858.CD001390.pub4>

Wang, J. B., Olgin, J. E., Nah, G., Vittinghoff, E., Cataldo, J. K., Pletcher, M. J., & Marcus, G. M. (2018). Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One*, 13(7), e0198681. <https://doi.org/10.1371/journal.pone.0198681>

Wang, Y., Xu, J., Meng, Y., Adcock, I. M., & Yao, X. (2018). Role of inflammatory cells in airway remodeling in COPD. *International Journal of Chronic*

Obstructive Pulmonary Disease, 13, 3341-3348.

<https://doi.org/10.2147/copd.S176122>

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*, 30(6), 473-483.

Warszawska, J. M., Gawish, R., Sharif, O., Sigel, S., Doninger, B., Lakovits, K., Mesteri, I., Nairz, M., Boon, L., & Spiel, A. (2013). Lipocalin 2 deactivates macrophages and worsens pneumococcal pneumonia outcomes. *The Journal of Clinical Investigation*, 123(8), 3363-3372.
<https://dm5migu4zj3pb.cloudfront.net/manuscripts/67000/67911/JCI67911.v2.pdf>

Wedzicha, J. A. (2015). Mechanisms of Chronic Obstructive Pulmonary Disease Exacerbations. *Annals of the American Thoracic Society*, 12(Supplement 2), S157-S159. <https://doi.org/10.1513/AnnalsATS.201507-427AW>

Wedzicha, J. A., Brill, S. E., Allinson, J. P., & Donaldson, G. C. (2013). Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. *BMC Medicine*, 11(1), 181. <https://doi.org/10.1186/1741-7015-11-181>

Whittaker, H. R., Torkpour, A., & Quint, J. (2024). Eligibility of patients with chronic obstructive pulmonary disease for inclusion in randomised control trials investigating triple therapy: a study using routinely collected data. *Respiratory Research*, 25(1), 43. [https://doi.org/10.1186/s12931-024-02672-](https://doi.org/10.1186/s12931-024-02672-x)

x

WHO. (2023, 16/03/2023). *Chronic obstructive pulmonary disease (COPD)*. World Health Organization [WHO]. Retrieved 29/6/2023 from [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))

Widdicombe, J. H., & Wine, J. J. (2015). Airway gland structure and function. *Physiological Reviews*, 95(4), 1241-1319.

Williams, D. M. (2018). Clinical Pharmacology of Corticosteroids. *Respiratory Care*, 63(6), 655-670. <https://doi.org/10.4187/respcare.06314>

Williams, P. J., Cumella, A., Philip, K. E. J., Lavery, A. A., & Hopkinson, N. S. (2022). Smoking and socioeconomic factors linked to acute exacerbations of COPD: analysis from an Asthma + Lung UK survey. *BMJ Open Respiratory Research*, 9(1), e001290. <https://doi.org/10.1136/bmjresp-2022-001290>

Wilson, S. R., Strub, P., Buist, A. S., Knowles, S. B., Lavori, P. W., Lapidus, J., & Vollmer, W. M. (2010). Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med*, 181(6), 566-577. <https://doi.org/10.1164/rccm.200906-0907OC>

Wing, K., Williamson, E., Carpenter, J. R., Wise, L., Schneeweiss, S., Smeeth, L., Quint, J. K., & Douglas, I. (2018). Real-world effects of medications for chronic obstructive pulmonary disease: protocol for a UK population-based non-interventional cohort study with validation against randomised trial results. *BMJ Open*, 8(3), e019475. <https://doi.org/10.1136/bmjopen-2017-019475>

- Wise, J. (2019). COPD: spirometry does not occur in 60% of admissions, audit shows. *Bmj*, 365, l2141. <https://doi.org/10.1136/bmj.l2141>
- Wong, C., Sullivan, C., & Jayaram, L. (2018). ELTGOL airway clearance in bronchiectasis: laying the bricks of evidence. *European Respiratory Journal*, 51(1), 1702232. <https://doi.org/10.1183/13993003.02232-2017>
- World-Medical-Association. (2013). World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA*, 310(20), 2191-2194. <https://doi.org/10.1001/jama.2013.281053>
- Wouters, E. F. M., Wouters, B. B. R. E. F., Augustin, I. M. L., Houben-Wilke, S., Vanfleteren, L. E. G. W., & Franssen, F. M. E. (2018). Personalised pulmonary rehabilitation in COPD. *European Respiratory Review*, 27(147), 170125. <https://doi.org/10.1183/16000617.0125-2017>
- Wu, Y.-K., Su, W.-L., Yang, M.-C., Chen, S.-Y., Wu, C.-W., & Lan, C.-C. (2021). Characterization Associated with the Frequent Severe Exacerbator Phenotype in COPD Patients. *International Journal of Chronic Obstructive Pulmonary Disease*, 16(null), 2475-2485. <https://doi.org/10.2147/COPD.S317177>
- Yamasaki, K., & Eeden, S. F. v. (2018). Lung Macrophage Phenotypes and Functional Responses: Role in the Pathogenesis of COPD. *International Journal of Molecular Sciences*, 19(2), 582. <https://www.mdpi.com/1422-0067/19/2/582>
- Yang, G. J., McDonald CF, McDonald V, Ordman R, Goodwin A, Smith B, McNamara R, Zwar N, Dabscheck E. The COPD-X Plan: Australian and

New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023. Version 2.73, December 2023. (2023). The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023. (Version 2.73).
<https://copdx.org.au/copd-x-plan/>

- Yang, I. A., Clarke, M. S., Sim, E. H., & Fong, K. M. (2012). Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(7).
- Young, R. L., Malcolm, K. C., Kret, J. E., Caceres, S. M., Poch, K. R., Nichols, D. P., Taylor-Cousar, J. L., Saavedra, M. T., Randell, S. H., & Vasil, M. L. (2011). Neutrophil extracellular trap (NET)-mediated killing of *Pseudomonas aeruginosa*: evidence of acquired resistance within the CF airway, independent of CFTR. *PLoS One*, 6(9), e23637.
- Yousuf, A., McAuley, H., Elneima, O., & Brightling, C. E. (2021). The different phenotypes of COPD. *British Medical Bulletin*, 137(1), 82-97.
<https://doi.org/10.1093/bmb/ldaa043>
- Yuan, S., Hollinger, M., Lachowicz-Scroggins, M. E., Kerr, S. C., Dunican, E. M., Daniel, B. M., Ghosh, S., Erzurum, S. C., Willard, B., & Hazen, S. L. (2015). Oxidation increases mucin polymer cross-links to stiffen airway mucus gels. *Science translational medicine*, 7(276), 276ra227-276ra227.
- Zahm, J., de Bentzmann, S. G., Deneuville, E., Perrot-Minnot, C., Dabadie, A., Pennaforte, F., Roussey, M., Shak, S., & Puchelle, E. (1995). Dose-dependent in vitro effect of recombinant human DNase on rheological and

transport properties of cystic fibrosis respiratory mucus. *European Respiratory Journal*, 8(3), 381-386.

Zanini, A., Aiello, M., Adamo, D., Cherubino, F., Zampogna, E., Sotgiu, G., Chetta, A., & Spanevello, A. (2015). Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of efficacy. *Respiration*, 89(6), 525-533.

Zhang, Y., Zheng, S. P., Hou, Y. F., Jie, X. Y., Wang, D., Da, H. J., Li, H. X., He, J., Zhao, H. Y., Liu, J. H., Ma, Y., Qiang, Z. H., Li, W., Zhang, M., Shan, H., Wu, Y. Y., Shi, H. Y., Zeng, L., Sun, X., & Liu, Y. (2023). A predictive model for frequent exacerbator phenotype of acute exacerbations of chronic obstructive pulmonary disease. *Journal of Thoracic Disease*, 15(12), 6502-6514. <https://doi.org/10.21037/jtd-23-931>

Zisi, D., Chryssanthopoulos, C., Nanas, S., & Philippou, A. (2022). The effectiveness of the active cycle of breathing technique in patients with chronic respiratory diseases: A systematic review. *Heart & Lung*, 53, 89-98.

AbdelHalim, H. A., AboElNaga, H. H., & Fathy, K. A. (2016). Comparison between active cycles of breathing with postural drainage versus conventional chest physiotherapy in subjects with bronchiectasis. *Egyptian Journal of Chest Diseases and Tuberculosis*, 65(1), 157-165.

<https://doi.org/https://doi.org/10.1016/j.ejcdt.2015.08.006>

Abelson, D., Di Michiel, J., Frater, C., Pearson, M., Russo, R., Wechselberger, M., Cottee, A., & Morgan, L. (2024). Mucus clears from the trachea in a helix: a new twist to understanding airway diseases. *Thorax*, 79(7), 607-614.

<https://doi.org/10.1136/thorax-2023-221052>

Abrami, M., Biasin, A., Tescione, F., Tierno, D., Dapas, B., Carbone, A., Grassi, G., Conese, M., Di Gioia, S., Larobina, D., & Grassi, M. (2024). Mucus Structure, Viscoelastic Properties, and Composition in Chronic Respiratory Diseases. *International Journal of Molecular Sciences*, 25(3).

<https://doi.org/10.3390/ijms25031933>

Adcock, I. M., Caramori, G., & Barnes, P. J. (2011). Chronic obstructive pulmonary disease and lung cancer: new molecular insights. *Respiration*, 81(4), 265-284. <https://karger.com/res/article-pdf/81/4/265/3904136/000324601.pdf>

Agustí, A., Celli, B. R., Criner, G. J., Halpin, D., Anzueto, A., Barnes, P., Bourbeau, J., Han, M. K., Martinez, F. J., Montes de Oca, M., Mortimer, K., Papi, A., Pavord, I., Roche, N., Salvi, S., Sin, D. D., Singh, D., Stockley, R., López Varela, M. V.,...Vogelmeier, C. F. (2023). Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Archivos de Bronconeumología*, 59(4), 232-248.

<https://doi.org/https://doi.org/10.1016/j.arbres.2023.02.009>

Agustí, A., & Hogg, J. C. (2019). Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, 381(13), 1248-1256.

<https://doi.org/10.1056/NEJMr1900475>

Agustí, A., Melén, E., DeMeo, D. L., Breyer-Kohansal, R., & Faner, R. (2022).

Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene–environment interactions across the lifespan. *The Lancet Respiratory Medicine*, 10(5), 512-524.

[https://doi.org/https://doi.org/10.1016/S2213-2600\(21\)00555-5](https://doi.org/https://doi.org/10.1016/S2213-2600(21)00555-5)

Aksamit, T., Bandel, T. J., Criollo, M., De Soyza, A., Elborn, J. S., Operschall, E.,

Polverino, E., Roth, K., Winthrop, K. L., & Wilson, R. (2017). The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. *Contemporary Clinical Trials*, 58, 78-85.

<https://doi.org/10.1016/j.cct.2017.05.007>

Aksamit, T., O'Donnell, A. E., Barker, A., Olivier, K. N., Winthrop, K. L., Daniels, M.

L. A., Johnson, M., Eden, E., Griffith, D., Knowles, M., Metersky, M., Salathe, M., Thomashow, B., Tino, G., Turino, G., Carretta, B., & Daley, C. L. (2017). Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. *CHEST*, 151(5), 982-992.

<https://doi.org/10.1016/j.chest.2016.10.055>

Albert, R. K., Connett, J., Bailey, W. C., Casaburi, R., Cooper, J. A., Jr., Criner, G. J.,

Curtis, J. L., Dransfield, M. T., Han, M. K., Lazarus, S. C., Make, B., Marchetti, N., Martinez, F. J., Madinger, N. E., McEvoy, C., Niewoehner, D. E., Porsasz, J., Price, C. S., Reilly, J.,...Network, C. C. R. (2011). Azithromycin for prevention of exacerbations of COPD. *New England*

Journal of Medicine, 365(8), 689-698.

<https://doi.org/10.1056/NEJMoa1104623>

Alderwick, H., & Dixon, J. (2019). The NHS long term plan. *Bmj*, 364, l84.

<https://doi.org/10.1136/bmj.l84>

Alghamdi, S. M., Alsulayyim, A. S., Alasmari, A. M., Philip, K. E. J., Buttery, S. C., Banya, W. A. S., Polkey, M. I., Birring, S. S., & Hopkinson, N. S. (2023). Oscillatory positive expiratory pressure therapy in COPD (O-COPD): a randomised controlled trial. *Thorax*, 78(2), 136-143.

<https://doi.org/10.1136/thorax-2022-219077>

Alghamdi, S. M., Alzahrani, A., Alshahrani, Y. M., Al Ruwaithi, A. A., Aldhahir, A. M., Alsulayyim, A. S., Siraj, R. A., Almansour, A. H., Alasmari, A. M., Alqahtani, J. S., Alanazi, A. M., Jaishi, S. T., Allehyani, B. A., & Hopkinson, N. S. (2023). Perception and clinical practice regarding mucus clearance devices with chronic obstructive pulmonary disease: a cross-sectional study of healthcare providers in Saudi Arabia. *BMJ Open*, 13(9), e074849.

<https://doi.org/10.1136/bmjopen-2023-074849>

Alghamdi, S. M., Barker, R. E., Alsulayyim, A. S. S., Alasmari, A. M., Banya, W. A. S., Polkey, M. I., Birring, S. S., & Hopkinson, N. S. (2020). Use of oscillatory positive expiratory pressure (OPEP) devices to augment sputum clearance in COPD: a systematic review and meta-analysis. *Thorax*, 75(10), 855-863.

<https://doi.org/10.1136/thoraxjnl-2019-214360>

Aliberti, S., Goeminne, P. C., O'Donnell, A. E., Aksamit, T. R., Al-Jahdali, H., Barker, A. F., Blasi, F., Boersma, W. G., Crichton, M. L., & De Soyza, A. (2022). Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. *The Lancet Respiratory Medicine*, 10(3), 298-306.

Aliberti, S., Ringshausen, F. C., Dhar, R., Haworth, C. S., Loebinger, M. R., Dimakou, K., Crichton, M. L., De Soyza, A., Vendrell, M., Burgel, P. R., McDonnell, M., Skrgat, S., Maiz Carro, L., de Roux, A., Sibila, O., Bossios, A., van der Eerden, M., Kauppi, P., Wilson, R.,...Chalmers, J. D. (2024). Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). *European Respiratory Journal*, 63(4).

<https://doi.org/10.1183/13993003.01554-2023>

Andreeva, E., Pokhaznikova, M., Lebedev, A., Moiseeva, I., Kuznetsova, O., & Degryse, J.-M. (2017). Spirometry is not enough to diagnose COPD in epidemiological studies: a follow-up study. *npj Primary Care Respiratory Medicine*, 27(1), 62. <https://doi.org/10.1038/s41533-017-0062-6>

Antunes, M. B., & Cohen, N. A. (2007). Mucociliary clearance—a critical upper airway host defense mechanism and methods of assessment. *Current opinion in allergy and clinical immunology*, 7(1), 5-10.

ASH. (2018). 10-years-of-smoking-ban. <https://ash.wales/wp-content/uploads/2018/05/10-years-of-smoking-ban-1.pdf>

ASH. (2024). *Position statement on Vaping*Blog.

<https://ash.wales/campaign/electronic-cigarettes/>

ASH, C. (2022). *National Campaign Helps School to Safeguard Against Illegal*

Tobacco [https://noifs-nobutts.co.uk/national-campaign-helps-school-to-](https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community)

[safeguard-against-illegal-](https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community)

[tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20](https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community)

[by%20the%20tobacco%20control%20organisation,health%2C%20and%20t](https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community)

[he%20wider%20community](https://noifs-nobutts.co.uk/national-campaign-helps-school-to-safeguard-against-illegal-tobacco/#:~:text=The%20campaign%20has%20been%20spearheaded%20by%20the%20tobacco%20control%20organisation,health%2C%20and%20the%20wider%20community)

Asthma-Lung-UK. (2024). *saving-your-breath-how-better-lung-health-benefits-us-all-*

us-wales-english (1).pdf>. [https://www.asthmaandlung.org.uk/saving-your-](https://www.asthmaandlung.org.uk/saving-your-breath-how-better-lung-health-benefits-us-all-us-wales-english)

[breath-how-better-lung-health-benefits-us-all-us-wales-english](https://www.asthmaandlung.org.uk/saving-your-breath-how-better-lung-health-benefits-us-all-us-wales-english)

Asthma Australia. (2022, June 6). *'Huff'* [Video]. YouTube.

<https://www.youtube.com/watch?v=wBxxhAmfxTw>

Avci, E., Sarvari, P., Savai, R., Seeger, W., & Pullamsetti, S. S. (2022). Epigenetic

Mechanisms in Parenchymal Lung Diseases: Bystanders or Therapeutic

Targets? *International Journal of Molecular Sciences*, 23(1).

<https://doi.org/10.3390/ijms23010546>

Bafeta, A., Dechartres, A., Trinquart, L., Yavchitz, A., Boutron, I., & Ravaud, P.

(2012). Impact of single centre status on estimates of intervention effects in

trials with continuous outcomes: meta-epidemiological study. *Bmj*, 344,

e813. <https://doi.org/10.1136/bmj.e813>

- Bailey, K. L., LeVan, T. D., Yanov, D. A., Pavlik, J. A., DeVasure, J. M., Sisson, J. H., & Wyatt, T. A. (2012). Non-typeable *Haemophilus influenzae* decreases cilia beating via protein kinase C epsilon. *Respiratory Research*, 13, 1-8.
- Bansal, A., Patel, K., & Katakwar, M. (2023). *Assessment of the Clinical Value of an Oscillating Positive Expiratory Pressure (OPEP) Device for Chronic Obstructive Pulmonary Disease (COPD) Patients in India: A 6 Week Field Study Using the COPD Assessment Test (CAT) C27*. OPTIMIZING THE INTERVENTIONS AND PROGRAM MODELS OF PULMONARY REHABILITATION, https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A4681
- Barker, R., Lavery, A. A., & Hopkinson, N. S. (2017). Adjuncts for sputum clearance in COPD: clinical consensus versus actual use. *BMJ Open Respiratory Research*, 4(1), e000226. <https://doi.org/10.1136/bmjresp-2017-000226>
- Barnes, P. (1994). *Therapeutics in respiratory disease / Peter J. Barnes ... [et al.], with contribution by Robert F. Miller*. New York : Churchill Livingstone.
- Barnes, P. J. (2009). The cytokine network in chronic obstructive pulmonary disease. *American journal of respiratory cell and molecular biology*, 41(6), 631-638.
- Barnes, P. J. (2022). Oxidative Stress in Chronic Obstructive Pulmonary Disease. *Antioxidants (Basel)*, 11(5). <https://doi.org/10.3390/antiox11050965>
- Barnes, P. J., Shapiro, S. D., & Pauwels, R. A. (2003). Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *European*

Respiratory Journal, 22(4), 672-688.

<https://doi.org/10.1183/09031936.03.00040703>

Bartlett, J. A., Fischer, A. J., & Paul Jr, B. (2008). Innate immune functions of the airway epithelium. *Trends in Innate Immunity*, 15, 147-163.

Barto, T. L., Maselli, D. J., Daignault, S., Stiglich, J., Porter, J., Kraemer, C., & Hansen, G. (2020). Real-life experience with high-frequency chest wall oscillation vest therapy in adults with non-cystic fibrosis bronchiectasis.

Therapeutic Advances in Respiratory Disease, 14, 1753466620932508.

<https://doi.org/10.1177/1753466620932508>

Basavaraj, A., Choate, R., Addrizzo-Harris, D., Aksamit, T. R., Barker, A., Daley, C. L., Anne Daniels, M. L., Eden, E., DiMango, A., Fennelly, K., Griffith, D. E., Johnson, M. M., Knowles, M. R., Metersky, M. L., Noone, P. G., O'Donnell, A. E., Olivier, K. N., Salathe, M. A., Schmid, A.,...Winthrop, K. L. (2020). Airway Clearance Techniques in Bronchiectasis: Analysis From the United States Bronchiectasis and Non-TB Mycobacteria Research Registry. *CHEST*, 158(4), 1376-1384.

<https://doi.org/https://doi.org/10.1016/j.chest.2020.06.050>

Basavaraj, A., Choate, R., Becker, B. C., Aksamit, T. R., & Metersky, M. L. (2024). Severity of bronchiectasis predicts use of and adherence to high frequency chest wall oscillation therapy - Analysis from the United States Bronchiectasis and NTM research registry. *Respiratory Medicine*, 223, 107555. <https://doi.org/10.1016/j.rmed.2024.107555>

Bedi, P., Cartlidge, M. K., Zhang, Y., Turnbull, K., Donaldson, S., Clarke, A., Crowe, J., Campbell, K., Graham, C., Franguylan, R., Rossi, A. G., & Hill, A. T. (2021). Feasibility of shortening intravenous antibiotic therapy for bronchiectasis based on bacterial load: a proof-of-concept randomised controlled trial. *European Respiratory Journal*, 58(6), 2004388.
<https://doi.org/10.1183/13993003.04388-2020>

Belli, S., Prince, I., Savio, G., Paracchini, E., Cattaneo, D., Bianchi, M., Masocco, F., Bellanti, M. T., & Balbi, B. (2021). Airway Clearance Techniques: The Right Choice for the Right Patient. *Frontiers in medicine*, 8, 544826-544826.
<https://doi.org/10.3389/fmed.2021.544826>

Bellomo, R., Warrillow, S. J., & Reade, M. C. (2009). Why we should be wary of single-center trials. *Critical care medicine*, 37(12), 3114-3119.
<https://doi.org/10.1097/CCM.0b013e3181bc7bd5>

Bennett, W. D., Foster, W. M., & Chapman, W. F. (1990). Cough-enhanced mucus clearance in the normal lung. *Journal of Applied Physiology*, 69(5), 1670-1675.

Bennett, W. D., Wu, J., Fuller, F., Balcazar, J. R., Zeman, K. L., Duckworth, H., Donn, K., O'Riordan, T. G., Boucher, R. C., & Donaldson, S. H. (2015). Duration of action of hypertonic saline on mucociliary clearance in the normal lung. *Journal of Applied Physiology*, 118(12), 1483-1490.

Benzo, R. (2011). Lung volume reduction surgery: nonpharmacological approach.

Current Opinion in Anesthesiology, 24(1), 44-48.

<https://doi.org/10.1097/ACO.0b013e3283420608>

Berkhof, F. F., Boom, L. N., Ten Hertog, N. E., Uil, S. M., Kerstjens, H. A., & Van

Den Berg, J. W. (2012). The validity and precision of the leicester cough questionnaire in COPD patients with chronic cough. *Health and quality of life outcomes*, 10(1), 4.

<https://doi.org/10.1186/1477-7525-10-4>

Berner-Rodoreda, A., Bärnighausen, T., Kennedy, C., Brinkmann, S., Sarker, M.,

Wikler, D., Eyal, N., & McMahon, S. A. (2020). From doxastic to epistemic: A typology and critique of qualitative interview styles. *Qualitative inquiry*, 26(3-4), 291-305.

Bilton, D., Tino, G., Barker, A. F., Chambers, D. C., Soyza, A. D., Dupont, L. J. A.,

O'Dochartaigh, C., Haren, E. H. J. v., Vidal, L. O., Welte, T., Fox, H. G., Wu, J., & Charlton, B. (2014). Inhaled mannitol for non-cystic fibrosis

bronchiectasis: a randomised, controlled trial. *Thorax*, 69(12), 1073-1079.

<https://doi.org/10.1136/thoraxjnl-2014-205587>

Birring, S. S. (2003). Development of a symptom specific health status measure for

patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*,

58(4), 339-343. <https://doi.org/10.1136/thorax.58.4.339>

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the

Hospital Anxiety and Depression Scale. An updated literature review.

Journal of psychosomatic research, 52(2), 69-77.

[https://doi.org/10.1016/s0022-3999\(01\)00296-3](https://doi.org/10.1016/s0022-3999(01)00296-3)

Blanco-Aparicio, M., Saleta Canosa, J. L., Valiño López, P., Martín Egaña, M. T., Vidal García, I., & Montero Martínez, C. (2019). Eradication of *Pseudomonas aeruginosa* with inhaled colistin in adults with non-cystic fibrosis bronchiectasis. *Chronic Respiratory Disease*, 16, 1479973119872513. <https://doi.org/10.1177/1479973119872513>

Blanco, I., Bueno, P., Diego, I., Pérez-Holanda, S., Casas-Maldonado, F., Esquinas, C., & Miravittles, M. (2017). Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 561-569.

<https://doi.org/10.2147/copd.S125389>

Blanco, I., Diego, I., Bueno, P., Casas-Maldonado, F., & Miravittles, M. (2019). Geographic distribution of COPD prevalence in the world displayed by Geographic Information System maps. *European Respiratory Journal*, 54(1), 1900610. <https://doi.org/10.1183/13993003.00610-2019>

BLF. (2023). *Chronic obstructive pulmonary disease (COPD) statistics*. British Lung Foundation. Retrieved 29/6/2023 from <https://statistics.blf.org.uk/copd>

Bolton, C. E., Singh, S. J., Walker, P. P., & Group, B. T. S. P. R. G. (2013). Commentary: the British Thoracic Society guideline on pulmonary rehabilitation in adults. *Thorax*, 68(9), 887-888.

<https://thorax.bmj.com/content/thoraxjnl/68/9/887.full.pdf>

Borgerding, M., & Klus, H. (2005). Analysis of complex mixtures--cigarette smoke.

Experimental and Toxicologic Pathology, 57 Suppl 1, 43-73.

<https://doi.org/10.1016/j.etp.2005.05.010>

Bose, S., Pascoe, C., & McEvoy, C. (2023). Lifetime lung function trajectories and

COPD: when the train derails. *The Lancet Respiratory Medicine*, 11(3), 221-

222. [https://doi.org/10.1016/s2213-2600\(22\)00391-5](https://doi.org/10.1016/s2213-2600(22)00391-5)

Bourbeau, J., Bafadhel, M., Barnes, N. C., Compton, C., Di Boscio, V., Lipson, D. A.,

Jones, P. W., Martin, N., Weiss, G., & Halpin, D. M. G. (2021). Benefit/Risk

Profile of Single-Inhaler Triple Therapy in COPD. *International Journal of*

Chronic Obstructive Pulmonary Disease, 16, 499-517.

<https://doi.org/10.2147/copd.S291967>

Bracey, A., Suggett, J., & Conway, J. (2019). A national audit of the Aerobika*

Oscillatory Positive Pressure (OPEP) device when used to assist airway

clearance for those with cystic fibrosis, bronchiectasis and COPD. *European*

Respiratory Journal, 54(suppl 63), PA5267.

<https://doi.org/10.1183/13993003.congress-2019.PA5267>

Brasch, F., Johnen, G., Winn-Brasch, A., Guttentag, S. H., Schmiedl, A., Kapp, N.,

Suzuki, Y., Muller, K. M., Richter, J., & Hawgood, S. (2004). Surfactant

protein B in type II pneumocytes and intra-alveolar surfactant forms of

human lungs. *American journal of respiratory cell and molecular biology*,

30(4), 449-458.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology.

Qualitative Research In Psychology, 3(2), 77-101.

<https://doi.org/10.1191/1478088706qp063oa>

Braun, V., & Clarke, V. (2014). What can "thematic analysis" offer health and wellbeing researchers? *International journal of qualitative studies on health and well-being*, 9, 26152. <https://doi.org/10.3402/qhw.v9.26152>

Braun, V., & Clarke, V. (2019). Reflecting on reflexive thematic analysis. *Qualitative research in sport, exercise and health*, 11(4), 589-597.

Bridges, C., Carter, H., Ketchell, R., Lau, D., & Duckers, J. (2018). EPS6. 01 Shaking it up: a look at our centre experience with high frequency chest wall oscillation (HFCWO). *Journal of Cystic Fibrosis*, 17, S48.

Bridges, C., Graham-Wollard, L., Morris, H., Annandale, J., & Lewis, K. (2023). S56 A feasibility randomised control trial (RCT) of OPEP verses active cycle of breathing technique (ACBT) in people with chronic obstructive pulmonary disease (COPD). *Thorax*, 78(Suppl 4), A43-A44.
<https://doi.org/10.1136/thorax-2023-BTSabstracts.62>

Bridges, C., Suggett, J., & Lewis, K. (2024). Assessment of the Clinical Value of an Oscillating Positive Expiratory Pressure (OPEP) Device and Active Cycle of Breathing Technique (ACBT) for Chronic Obstructive Pulmonary Disease (COPD) Post Exacerbation: A 12 Week Prospective, Randomized Study Using the Leicester Cough Questionnaire (LCQ) and COPD Assessment Test (CAT). In *D29. INSIGHTS INTO MECHANISMS AND*

EFFECTIVENESS OF DIFFERENT COMPONENTS OF PULMONARY REHABILITATION (pp. A7169-A7169). American Thoracic Society.

https://doi.org/doi:10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A7169

Brill, S. E., Patel, A. R., Singh, R., Mackay, A. J., Brown, J. S., & Hurst, J. R. (2015).

Lung function, symptoms and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study.

Respiratory Research, 16(1), 1-9.

Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D. S.,

Weinrauch, Y., & Zychlinsky, A. (2004). Neutrophil extracellular traps kill bacteria. *science*, 303(5663), 1532-1535.

<https://www.nature.com/articles/nri1340.pdf>

Bronchiectasis Toolbox. (n.d). *Autogenic Drainage*.

<https://bronchiectasis.com.au/resources/videos/autogenic-drainage>

Buhl, R., Criée, C. P., Kardos, P., Vogelmeier, C. F., Kostikas, K., Lossi, N. S., &

Worth, H. (2018). Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. *International Journal of Chronic Obstructive*

Pulmonary Disease, 13, 2557-2568. <https://doi.org/10.2147/copd.S169958>

Burgel, P.-R., Nesme-Meyer, P., Chanez, P., Caillaud, D., Carré, P., Perez, T., &

Roche, N. (2009). Cough and Sputum Production Are Associated With Frequent Exacerbations and Hospitalizations in COPD Subjects. *CHEST*,

135(4), 975-982. <https://doi.org/10.1378/chest.08-2062>

Burholt, V., & Nash, P. (2011). Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. *Journal of Public Health*, 33(4), 587-603.

<https://doi.org/10.1093/pubmed/fdr006>

Burnham, P., Stanford, G., & Stewart, R. (2021). Autogenic drainage for airway clearance in cystic fibrosis. *The Cochrane Database of Systematic Reviews*, 12(12), Cd009595. <https://doi.org/10.1002/14651858.CD009595.pub3>

Burudpakdee, C., Seetasith, A., Dunne, P., Kauffman, G., Carlin, B., Coppolo, D., & Suggett, J. (2017). A Real-World Study of 30-Day Exacerbation Outcomes in Chronic Obstructive Pulmonary Disease (COPD) Patients Managed with Aerobika OPEP. *Pulmonary Therapy*, 3(1), 163-171.

<https://doi.org/10.1007/s41030-017-0027-5>

Bush, A., Payne, D., Pike, S., Jenkins, G., Henke, M. O., & Rubin, B. K. (2006). Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. *CHEST*, 129(1), 118-123.

Buss, P., Howson, H., O'Neill, C., & Berwick, D. (2022). 'Values to value' for recovery and renewal: prudent healthcare the key to transforming the health and care system. *Journal of the Royal Society of Medicine*, 115(12), 482-483.

<https://doi.org/10.1177/01410768221142026>

Button, B., Cai, L.-H., Ehre, C., Kesimer, M., Hill, D. B., Sheehan, J. K., Boucher, R. C., & Rubinstein, M. (2012). A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia. *science*, 337(6097), 937-941.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633213/pdf/nihms407560.p
df](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633213/pdf/nihms407560.pdf)

Button, B., Heine, R., Catto - Smith, A., & Phelan, P. (1998). Postural drainage in cystic fibrosis: is there a link with gastro - oesophageal reflux? *Journal of paediatrics and child health*, 34(4), 330-334.

Cazzola, M., & Molimard, M. (2010). The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulmonary pharmacology & therapeutics*, 23(4), 257-267.

<https://doi.org/10.1016/j.pupt.2010.03.003>

Cazzola, M., Santangelo, G., Piccolo, A., Salzillo, A., Matera, M. G., D'Amato, G., & Rossi, F. (1994). Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease. *Pulmonary Pharmacology*, 7(2), 103-107.

<https://doi.org/10.1006/pulp.1994.1012>

Celli, B., Fabbri, L., Criner, G., Martinez, F. J., Mannino, D., Vogelmeier, C., Montes de Oca, M., Papi, A., Sin, D. D., & Han, M. K. (2022). Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *American Journal of Respiratory and Critical Care Medicine*, 206(11), 1317-1325.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9746870/pdf/rccm.202204-
0671PP.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9746870/pdf/rccm.202204-0671PP.pdf)

Celli, B., Fabbri, L., Criner, G., Martinez, F. J., Mannino, D., Vogelmeier, C., Montes de Oca, M., Papi, A., Sin, D. D., Han, M. K., & Agusti, A. (2022). Definition

and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. *American Journal of Respiratory and Critical Care Medicine*, 206(11), 1317-1325. <https://doi.org/10.1164/rccm.202204-0671PP>

Celli, B. R., Fabbri, L. M., Aaron, S. D., Agusti, A., Brook, R., Criner, G. J., Franssen, F. M. E., Humbert, M., Hurst, J. R., O'Donnell, D., Pantoni, L., Papi, A., Rodriguez-Roisin, R., Sethi, S., Torres, A., Vogelmeier, C. F., & Wedzicha, J. A. (2021). An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *American Journal of Respiratory and Critical Care Medicine*, 204(11), 1251-1258. <https://doi.org/10.1164/rccm.202108-1819PP>

Celli, B. R., Fabbri, L. M., Aaron, S. D., Agusti, A., Brook, R. D., Criner, G. J., Franssen, F. M. E., Humbert, M., Hurst, J. R., Montes de Oca, M., Pantoni, L., Papi, A., Rodriguez-Roisin, R., Sethi, S., Stolz, D., Torres, A., Vogelmeier, C. F., & Wedzicha, J. A. (2023). Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting: Best Practice. *American Journal of Respiratory and Critical Care Medicine*, 207(9), 1134-1144. <https://doi.org/10.1164/rccm.202209-1795CI>

Chalmers, J. D. (2017). Macrolide resistance in *Pseudomonas aeruginosa*: implications for practice. *European Respiratory Journal*, 49(5). <https://doi.org/10.1183/13993003.00689-2017>

Chalmers, J. D., Aliberti, S., & Blasi, F. (2015). Management of bronchiectasis in adults. In *European Respiratory Journal* (Vol. 45, pp. 1446-1462): European Respiratory Society (ERS).

Chalmers, J. D., Aliberti, S., Filonenko, A., Shteinberg, M., Goeminne, P. C., Hill, A. T., Fardon, T. C., Obradovic, D., Gerlinger, C., Sotgiu, G., Operschall, E., Rutherford, R. M., Dimakou, K., Polverino, E., De Soyza, A., & McDonnell, M. J. (2018). Characterization of the “Frequent Exacerbator Phenotype” in Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 197(11), 1410-1420. <https://doi.org/10.1164/rccm.201711-2202oc>

Chalmers, J. D., Boersma, W., Lonergan, M., Jayaram, L., Crichton, M. L., Karalus, N., Taylor, S. L., Martin, M. L., Burr, L. D., & Wong, C. (2019). Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. *The Lancet Respiratory Medicine*, 7(10), 845-854.

Chalmers, J. D., Goeminne, P., Aliberti, S., McDonnell, M. J., Lonni, S., Davidson, J., Poppelwell, L., Salih, W., Pesci, A., Dupont, L. J., Fardon, T. C., De Soyza, A., & Hill, A. T. (2014). The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*, 189(5), 576-585. <https://doi.org/10.1164/rccm.201309-1575OC>

Chalmers, J. D., Haworth, C. S., Metersky, M. L., Loebinger, M. R., Blasi, F., Sibila, O., O'Donnell, A. E., Sullivan, E. J., Mange, K. C., & Fernandez, C. (2020). Phase 2 trial of the DPP-1 inhibitor brensocatib in bronchiectasis. *New England Journal of Medicine*, 383(22), 2127-2137.

Chalmers, J. D., Moffitt, K. L., Suarez-Cuartin, G., Sibila, O., Finch, S., Furrie, E., Dicker, A., Wrobel, K., Elborn, J. S., & Walker, B. (2017). Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 195(10), 1384-1393.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443898/pdf/rccm.201605-1027OC.pdf>

Chalmers, J. D., Polverino, E., Crichton, M. L., Ringshausen, F. C., De Soyza, A., Vendrell, M., Burgel, P. R., Haworth, C. S., Loebinger, M. R., & Dimakou, K. (2023). Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). *The Lancet Respiratory Medicine*.

Chalmers, J. D., Smith, M. P., McHugh, B. J., Doherty, C., Govan, J. R., & Hill, A. T. (2012). Short-and long-term antibiotic treatment reduces airway and systemic inflammation in non–cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 186(7), 657-665.

Chalmers, J. D., Elborn, S., & Greene, C. M. (2023). Basic, translational and clinical aspects of bronchiectasis in adults. *European Respiratory Review*, 32(168), 230015. <https://doi.org/10.1183/16000617.0015-2023>

Chang, A. B., Bell, S. C., Torzillo, P. J., King, P. T., Maguire, G. P., Byrnes, C. A., Holland, A. E., O'Mara, P., & Grimwood, K. (2015). Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Medical*

Journal of Australia, 202(1), 21-23.

https://core.ac.uk/reader/47206145?utm_source=linkout

Chatterjee, M., van Putten, J. P., & Strijbis, K. (2020). Defensive properties of mucin glycoproteins during respiratory infections—relevance for SARS-CoV-2. *MBio*, 11(6), 10.1128/mbio.02374-02320.

Chatwin. (2008). How to use a mechanical insufflator–exsufflator “cough assist machine”. *Breathe*, 4(4), 320-329.

<https://breathe.ersjournals.com/content/breathe/4/4/320.full.pdf>

Chatwin, M., Ross, E., Hart, N., Nickol, A., Polkey, M., & Simonds, A. (2003). Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. *European Respiratory Journal*, 21(3), 502-508.

Chatwin, M., & Wakeman, R. H. (2023). Mechanical Insufflation-Exsufflation: Considerations for Improving Clinical Practice. *Journal of Clinical Medicine*, 12(7), 2626. <https://www.mdpi.com/2077-0383/12/7/2626>

Chen, P., Abacherli, L. E., Nadler, S. T., Wang, Y., Li, Q., & Parks, W. C. (2009). MMP7 shedding of syndecan-1 facilitates re-epithelialization by affecting $\alpha 2\beta 1$ integrin activation. *PLoS One*, 4(8), e6565. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719060/pdf/pone.0006565.p
df](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719060/pdf/pone.0006565.pdf)

Cheyne, L., Irvin - Sellers, M. J., & White, J. (2015). Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(9). <https://doi.org/10.1002/14651858.CD009552.pub3>

- Chisholm, J. F., Shenoy, S. K., Shade, J. K., Kim, V., Putcha, N., Carson, K. A., Wise, R., Hansel, N. N., Hanes, J. S., & Suk, J. S. (2019). Nanoparticle diffusion in spontaneously expectorated sputum as a biophysical tool to probe disease severity in COPD. *European Respiratory Journal*, 54(2).
- Choi, H., Yang, B., Kim, Y. J., Sin, S., Jo, Y. S., Kim, Y., Park, H. Y., Ra, S. W., Oh, Y. M., Chung, S. J., Yeo, Y., Park, D. W., Park, T. S., Moon, J. Y., Kim, S. H., Kim, T. H., Yoon, H. J., Sohn, J. W., & Lee, H. (2021). Increased mortality in patients with non cystic fibrosis bronchiectasis with respiratory comorbidities. *Scientific reports*, 11(1), 7126. <https://doi.org/10.1038/s41598-021-86407-8>
- Chung, K. F., & Adcock, I. M. (2008). Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *European Respiratory Journal*, 31(6), 1334-1356. <https://doi.org/10.1183/09031936.00018908>
- Cloonan, S. M., Kim, K., Esteves, P., Trian, T., & Barnes, P. J. (2020). Mitochondrial dysfunction in lung ageing and disease. *European Respiratory Review*, 29(157).
- Cole, P. J. (1986). Inflammation: a two-edged sword--the model of bronchiectasis. *European Journal Respiratory Diseases*, 147, 6-15.
- Comer, D. M., Kidney, J. C., Ennis, M., & Elborn, J. S. (2013). Airway epithelial cell apoptosis and inflammation in COPD, smokers and nonsmokers. *European*

Respiratory Journal, 41(5), 1058-1067.

<https://doi.org/10.1183/09031936.00063112>

Coppolo, D. P., Schloss, J., Suggett, J. A., & Mitchell, J. P. (2022). Non-Pharmaceutical Techniques for Obstructive Airway Clearance Focusing on the Role of Oscillating Positive Expiratory Pressure (OPEP): A Narrative Review. *Pulmonary Therapy*, 8(1), 1-41. <https://doi.org/10.1007/s41030-021-00178-1>

Cosio, B. G., Soriano, J. B., Lopez-Campos, J. L., Calle, M., Soler, J. J., de-Torres, J. P., Marin, J. M., Martinez, C., de Lucas, P., Mir, I., Peces-Barba, G., Feu-Collado, N., Solanes, I., Alfageme, I., & study, C. (2016). Distribution and Outcomes of a Phenotype-Based Approach to Guide COPD Management: Results from the CHAIN Cohort. *PLoS One*, 11(9), e0160770. <https://doi.org/10.1371/journal.pone.0160770>

Costa, J. C., Machado, J. N., Ferreira, C., Gama, J., & Rodrigues, C. (2018). The Bronchiectasis Severity Index and FACED score for assessment of the severity of bronchiectasis. *Pulmonology*, 24(3), 149-154. <https://doi.org/https://doi.org/10.1016/j.rppnen.2017.08.009>

Cox, M. J., Turek, E. M., Hennessy, C., Mirza, G. K., James, P. L., Coleman, M., Jones, A., Wilson, R., Bilton, D., & Cookson, W. O. (2017). Longitudinal assessment of sputum microbiome by sequencing of the 16S rRNA gene in non-cystic fibrosis bronchiectasis patients. *PLoS One*, 12(2), e0170622. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5295668/pdf/pone.0170622.p
df](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5295668/pdf/pone.0170622.pdf)

Cranston, J. M., Crockett, A. J., Moss, J. R., & Alpers, J. H. (2005). Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(4), CD001744.

<https://doi.org/10.1002/14651858.CD001744.pub2>

Creswell, J. W., & Poth, C. N. (2017). *Qualitative Inquiry and Research Design: Choosing Among Five Approaches*. SAGE Publications.

<https://books.google.co.uk/books?id=Pz5RvgAACAAJ>

Daviskas, E., Anderson, S. D., Gomes, K., Briffa, P., Cochrane, B., CHAN, H. K., Young, I. H., & Rubin, B. K. (2005). Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. *Respirology*, 10(1), 46-56.

Davison, J., Robinson-Barella, A., Davies, G., Campos-Hinojosa, M., Collins, C., Husband, A., Okeowo, D., Hester, K. L., Lee, R., Rapley, T., & Soyza, A. D. (2023). Patient attitudes to nebulised antibiotics in the treatment of bronchiectasis: a mixed-methods study. *ERJ Open Research*, 00735-02022.

<https://doi.org/10.1183/23120541.00735-2022>

Dawson, M., Wirtz, D., & Hanes, J. (2003). Enhanced viscoelasticity of human cystic fibrotic sputum correlates with increasing microheterogeneity in particle transport. *Journal of Biological Chemistry*, 278(50), 50393-50401.

de la Rosa-Carrillo, D., Suárez-Cuartín, G., Golpe, R., Máiz Carro, L., & Martinez-García, M. A. (2022). Inhaled Colistimethate Sodium in the Management of Patients with Bronchiectasis Infected by *Pseudomonas aeruginosa*: A

Narrative Review of Current Evidence. *Infection and Drug Resistance*, 15(null), 7271-7292. <https://doi.org/10.2147/IDR.S318173>

De Rose, V., Molloy, K., Gohy, S., Pilette, C., & Greene, C. M. (2018). Airway epithelium dysfunction in cystic fibrosis and COPD. *Mediators of inflammation*, 2018.

De Soyza, A., Aksamit, T., Bandel, T. J., Criollo, M., Elborn, J. S., Operschall, E., Polverino, E., Roth, K., Winthrop, K. L., & Wilson, R. (2018). RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*, 51(1). <https://doi.org/10.1183/13993003.02052-2017>

Demchuk, A. M., & Chatburn, R. L. (2021). Performance Characteristics of Positive Expiratory Pressure Devices. *Respiratory Care*, 66(3), 482-493. <https://doi.org/10.4187/respcare.08150>

DeSoyza, A., Bradley, J., Moloney, S., Butler, J., & McCallion, P. (2022). A systematic review to determine the presence and effectiveness of shared decision making interventions for airway clearance techniques in adults with bronchiectasis. *Journal of the Association of Chartered Physiotherapists in Respiratory Care. Volume 54. Issue 2. 2022.*, 54(2), 60-91. <https://www.acprc.org.uk/publications/acprc-journal/2022-journal-vol-54-issue-2/a-systematic-review-to-determine-the-presence-and-effectiveness-of-shared-decision-making-interventions-for-airway-clearance-techniques-in-adults-with-bronchiectasis/>

DeSoyza, A., Mawson, P., Hill, A. T., Elborn, S., Bradley, J. M., Haworth, C. S., Floto, R. A., Wilson, R., Loebinger, M. R., Carroll, M., Crichton, M., Chalmers, J. D., Sullivan, A., Brown, J., Hurst, J. R., Duckers, J., Kelly, M., Steer, J., Gatheral, T.,... McNally, R. (2021). BronchUK: protocol for an observational cohort study and biobank in bronchiectasis. *ERJ Open Research*, 7(2), 00775-02020. <https://doi.org/10.1183/23120541.00775-2020>

Dey, S., Eapen, M. S., Chia, C., Gaikwad, A. V., Wark, P. A. B., & Sohal, S. S. (2022). Pathogenesis, clinical features of asthma COPD overlap, and therapeutic modalities. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 322(1), L64-L83. <https://doi.org/10.1152/ajplung.00121.2021>

DHSC, M. T. (2024, 15/04/2024). <https://healthmedia.blog.gov.uk/2024/04/15/creating-a-smokefree-generation-and-tackling-youth-vaping-what-you-need-to-know/>

Diaz, A. A., Orejas, J. L., Grumley, S., Nath, H. P., Wang, W., Dolliver, W. R., Yen, A., Kligerman, S. J., Jacobs, K., Manapragada, P. P., Abozeed, M., Aziz, M. U., Zahid, M., Ahmed, A. N., Terry, N. L., San José Estépar, R., Kim, V., Make, B. J., Han, M. K.,... San José Estépar, R. (2023). Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease. *JAMA*, 329(21), 1832-1839. <https://doi.org/10.1001/jama.2023.2065>

Dicker, A. J., Lonergan, M., Keir, H. R., Smith, A. H., Pollock, J., Finch, S., Cassidy, A. J., Huang, J. T., & Chalmers, J. D. (2021). The sputum microbiome and

clinical outcomes in patients with bronchiectasis: a prospective observational study. *The Lancet Respiratory Medicine*, 9(8), 885-896.

Diver, W. R., Jacobs, E. J., & Gapstur, S. M. (2018). Secondhand Smoke Exposure in Childhood and Adulthood in Relation to Adult Mortality Among Never Smokers. *American journal of preventive medicine*, 55(3), 345-352.

<https://doi.org/10.1016/j.amepre.2018.05.005>

Doe, G., Taylor, S. J., Topalovic, M., Russell, R., Evans, R. A., Maes, J., Orshovon, K. V., Sunjaya, A., Scott, D., Prevost, A. T., El-Emir, E., Harvey, J., Hopkinson, N. S., Kon, S. S., Patel, S., Jarrold, I., Spain, N., Man, W. D.-C., & Hutchinson, A. (2023). Spirometry services in England post-pandemic and the potential role of AI support software: a qualitative study of challenges and opportunities. *British Journal of General Practice*, 73(737), e915-e923.

<https://doi.org/10.3399/bjgp.2022.0608>

Dubin, R., Robinson, S., & Widdicombe, J. (2004). Secretion of lactoferrin and lysozyme by cultures of human airway epithelium. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 286(4), L750-L755.

Dunican, E. M., Elicker, B. M., Gierada, D. S., Nagle, S. K., Schiebler, M. L., Newell, J. D., Raymond, W. W., Lachowicz-Scroggins, M. E., Di Maio, S., Hoffman, E. A., Castro, M., Fain, S. B., Jarjour, N. N., Israel, E., Levy, B. D., Erzurum, S. C., Wenzel, S. E., Meyers, D. A., Bleecker, E. R.,...Fahy, J. V. (2018). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *The Journal of Clinical Investigation*, 128(3), 997-1009.

<https://doi.org/10.1172/jci95693>

Eaton, T., Young, P., Zeng, I., & Kolbe, J. (2007). A randomized evaluation of the acute efficacy, acceptability and tolerability of flutter and active cycle of breathing with and without postural drainage in non-cystic fibrosis bronchiectasis. *Chronic Respiratory Disease*, 4(1), 23-30.

<https://doi.org/10.1177/1479972306074481>

Elkins, M., & Dentice, R. (2020). Timing of hypertonic saline inhalation for cystic fibrosis. *Cochrane Database of Systematic Reviews*, 2(2), Cd008816.

<https://doi.org/10.1002/14651858.CD008816.pub4>

Everaerts, S., Vandervelde, C. M., Shah, P., Slebos, D. J., & Ceulemans, L. J. (2023). Surgical and bronchoscopic pulmonary function-improving procedures in lung emphysema. *European Respiratory Review*, 32(170).

<https://doi.org/10.1183/16000617.0004-2023>

Fabbri, L. M., Romagnoli, M., Corbetta, L., Casoni, G., Busljetic, K., Turato, G., Ligabue, G., Ciaccia, A., Saetta, M., & Papi, A. (2003). Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, 167(3), 418-424.

<https://doi.org/10.1164/rccm.200203-183OC>

Faner, R., Sibila, O., Agustí, A., Bernasconi, E., Chalmers, J. D., Huffnagle, G. B., Manichanh, C., Molyneaux, P. L., Paredes, R., & Brocal, V. P. (2017). The microbiome in respiratory medicine: current challenges and future perspectives. *European Respiratory Journal*, 49(4).

Feng, T., Sun, Y., Shi, Y., Ma, J., Feng, C., & Chen, Z. (2024). Air pollution control policies and impacts: A review. *Renewable and Sustainable Energy Reviews*, 191, 114071.

<https://doi.org/https://doi.org/10.1016/j.rser.2023.114071>

Fernandez, E., De Santi, C., De Rose, V., & Greene, C. M. (2018). CFTR dysfunction in cystic fibrosis and chronic obstructive pulmonary disease. *Expert Review of Respiratory Medicine*, 12(6), 483-492.

Ferreira de Camillis, M. L., Savi, A., Goulart Rosa, R., Figueiredo, M., Wickert, R., Borges, L. G. A., Galant, L., & Teixeira, C. (2018). Effects of Mechanical Insufflation-Exsufflation on Airway Mucus Clearance Among Mechanically Ventilated ICU Subjects. *Respiratory Care*, 63(12), 1471-1477.

<https://doi.org/10.4187/respcare.06253>

Fishman, A., Fessler, H., Martinez, F., McKenna, R. J., Jr., Naunheim, K., Piantadosi, S., Weinmann, G., & Wise, R. (2001). Patients at high risk of death after lung-volume-reduction surgery. *New England Journal of Medicine*, 345(15), 1075-1083. <https://doi.org/10.1056/NEJMoa11798>

Flume, P. A., Chalmers, J. D., & Olivier, K. N. (2018). Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *The Lancet*, 392(10150), 880-890.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6173801/pdf/nihms-1506383.pdf>

- Fortis, S., Shannon, Z. K., Garcia, C. J., Guillet, R. V., Aloe, A. M., Schweizer, M. L., Kim, V., & Nair, R. (2022). Association of nonobstructive chronic bronchitis with all-cause mortality: a systematic literature review and meta-analysis. *CHEST*, 162(1), 92-100.
- Franks, L. J., Walsh, J. R., Hall, K., Jacuinde, G., Yerkovich, S., & Morris, N. R. (2019). Comparing the Performance Characteristics of Different Positive Expiratory Pressure Devices. *Respiratory Care*, 64(4), 434-444.
<https://doi.org/10.4187/respcare.06410>
- Franks, L. J., Walsh, J. R., Hall, K., & Morris, N. R. (2020). Measuring airway clearance outcomes in bronchiectasis: a review. *European Respiratory Review*, 29(156), 190161. <https://doi.org/10.1183/16000617.0161-2019>
- Gao, Y. H., Guan, W. J., Xu, G., Tang, Y., Gao, Y., Lin, Z. Y., Lin, Z. M., Zhong, N. S., & Chen, R. C. (2014). Macrolide therapy in adults and children with non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *PLoS One*, 9(3), e90047. <https://doi.org/10.1371/journal.pone.0090047>
- GBD Collaborators, Forouzanfar, M., Alexander, L., Bachman, V., Biryukov, S., Brauer, M., Casey, D., Coates, M., Delwiche, K., & Estep, K. (2015). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, 386(10010), 2287-2323.

- Gertsberg, I., Hellman, V., Fainshtein, M., Weil, S., Silberberg, S. D., Danilenko, M., & Priel, Z. (2004). Intracellular Ca²⁺ regulates the phosphorylation and the dephosphorylation of ciliary proteins via the NO pathway. *The Journal of General Physiology*, 124(5), 527-540. <https://doi.org/10.1085/jgp.200409153>
- Glasgow, A. M., & Greene, C. M. (2022). Epithelial damage in the cystic fibrosis lung: the role of host and microbial factors. *Expert Review of Respiratory Medicine*, 16(7), 737-748.
- Goeminne, P. C., Hernandez, F., Diel, R., Filonenko, A., Hughes, R., Juelich, F., Solomon, G. M., Upton, A., Wichmann, K., & Xu, W. (2019). The economic burden of bronchiectasis—known and unknown: a systematic review. *BMC Pulmonary Medicine*, 19(1), 1-11.
- Goeminne, P. C., Nawrot, T. S., Ruttens, D., Seys, S., & Dupont, L. J. (2014). Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respiratory Medicine*, 108(2), 287-296. <https://doi.org/10.1016/j.rmed.2013.12.015>
- GOLD. (2023). *Global Strategy for the diagnosis, management and prevention of COPD* (2023). https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf
- GOLD. (2024a). 2024 Report: GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: . <https://goldcopd.org/2024-gold-report/>

GOLD. (2024b). *GOLD TEACHING SLIDE SET*. <https://goldcopd.org/2024-gold-report/>

Gordon, C. S., Waller, J. W., Cook, R. M., Cavallera, S. L., Lim, W. T., & Osadnik, C. R. (2019). Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *CHEST*, 156(1), 80-91. <https://doi.org/10.1016/j.chest.2019.04.009>

Gordon, M., Duffy, S., & Criner, G. J. (2018). Lung volume reduction surgery or bronchoscopic lung volume reduction: is there an algorithm for allocation? *Journal of Thoracic Disease*, S2816-S2823. <https://jtd.amegroups.org/article/view/21533>

Government, W. (2022). *A-smoke-free-wales-our-long-term-tobacco-control-strategy-for-wales-and-towards-a-smoke-free-wales-delivery-plan-2022-to-2024*. Retrieved from <https://www.gov.wales/sites/default/files/consultations/2022-07/a-smoke-free-wales-our-long-term-tobacco-control-strategy-for-wales-and-towards-a-smoke-free-wales-delivery-plan-2022-to-2024.pdf>

Greenhalgh, T., Wherton, J., Papoutsis, C., Lynch, J., Hughes, G., A'Court, C., Hinder, S., Fahy, N., Procter, R., & Shaw, S. (2017). Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies [Original Paper]. *J Med Internet Res*, 19(11), e367. <https://doi.org/10.2196/jmir.8775>

- Griffiths, T. L., Burr, M. L., Campbell, I. A., Lewis-Jenkins, V., Mullins, J., Shiels, K., Turner-Lawlor, P. J., Payne, N., Newcombe, R. G., Ionescu, A. A., Thomas, J., & Tunbridge, J. (2000). Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet*, 355(9201), 362-368. [https://doi.org/10.1016/s0140-6736\(99\)07042-7](https://doi.org/10.1016/s0140-6736(99)07042-7)
- Guan, W.-J., Gao, Y.-H., Xu, G., Li, H.-M., Yuan, J.-J., Zheng, J.-P., Chen, R.-C., & Zhong, N.-S. (2016). Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. *Journal of Thoracic Disease*, 8(1), 14.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740118/pdf/jtd-08-01-014.pdf>
- Guo, M., Pegoraro, A. F., Mao, A., Zhou, E. H., Arany, P. R., Han, Y., Burnette, D. T., Jensen, M. H., Kasza, K. E., & Moore, J. R. (2017). Cell volume change through water efflux impacts cell stiffness and stem cell fate. *Proceedings of the National Academy of Sciences*, 114(41), E8618-E8627.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642688/pdf/pnas.201705179.pdf>
- Gupta, N., Pinto, L. M., Morogan, A., & Bourbeau, J. (2014). The COPD assessment test: a systematic review. *European Respiratory Journal*, 44(4), 873-884.
<https://doi.org/10.1183/09031936.00025214>
- Halpin, D. M. G., Kerkhof, M., Soriano, J. B., Mikkelsen, H., & Price, D. B. (2016). Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-

acting bronchodilator therapy. *Respiratory Research*, 17(1), 120.

<https://doi.org/10.1186/s12931-016-0433-5>

Hardinge, M., Annandale, J., Bourne, S., Cooper, B., Evans, A., Freeman, D., Green, A., Hippolyte, S., Knowles, V., MacNee, W., McDonnell, L., Pye, K., Suntharalingam, J., Vora, V., Wilkinson, T., British Thoracic Society Home Oxygen Guideline Development, G., & British Thoracic Society Standards of Care, C. (2015). British Thoracic Society guidelines for home oxygen use in adults. *Thorax*, 70 Suppl 1, i1-43. <https://doi.org/10.1136/thoraxjnl-2015-206865>

Hasani, A., Pavia, D., Agnew, J., & Clarke, S. (1994). Regional lung clearance during cough and forced expiration technique (FET): effects of flow and viscoelasticity. *Thorax*, 49(6), 557-561. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC474944/pdf/thorax00298-0037.pdf>

Haworth, C. S., Bilton, D., Chalmers, J. D., Davis, A. M., Froehlich, J., Gonda, I., Thompson, B., Wanner, A., & O'Donnell, A. E. (2019). Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. *The Lancet Respiratory Medicine*, 7(3), 213-226. [https://doi.org/10.1016/s2213-2600\(18\)30427-2](https://doi.org/10.1016/s2213-2600(18)30427-2)

Haworth, C. S., Bilton, D., & Elborn, J. S. (2014). Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. *Respiratory Medicine*, 108(10), 1397-1408. <https://doi.org/10.1016/j.rmed.2014.09.005>

Health Technology, W. (2020). *Oscillating positive expiratory pressure devices for airway clearance in chronic hypersecretory lung conditions.*

<https://www.healthtechnology.wales/wp-content/uploads/2020/07/EAR023-Oscillating-positive-expiratory-pressure-devices.pdf>

Henkle, E., Aksamit, T. R., Barker, A. F., Curtis, J. R., Daley, C. L., Anne Daniels, M. L., DiMango, A., Eden, E., Fennelly, K., Griffith, D. E., Johnson, M., Knowles, M. R., Leitman, A., Leitman, P., Malanga, E., Metersky, M. L., Noone, P. G., O'Donnell, A. E., Olivier, K. N.,...Winthrop, K. L. (2017). Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *CHEST*, 152(6), 1120-1127.

<https://doi.org/10.1016/j.chest.2017.04.167>

Henkle, E., Aksamit, T. R., Daley, C. L., Griffith, D. E., O'Donnell, A. E., Quittner, A. L., Malanga, E., Prieto, D., Leitman, A., & Winthrop, K. L. (2018). US Patient-Centered Research Priorities and Roadmap for Bronchiectasis. *CHEST*, 154(5), 1016-1023. <https://doi.org/10.1016/j.chest.2018.06.032>

Henkle, E., Chan, B., Curtis, J. R., Aksamit, T. R., Daley, C. L., & Winthrop, K. L. (2018). Characteristics and health-care utilization history of patients with bronchiectasis in US Medicare enrollees with prescription drug plans, 2006 to 2014. *CHEST*, 154(6), 1311-1320.

Herrero-Cortina, B., Lee, A. L., Oliveira, A., O'Neill, B., Jácome, C., Dal Corso, S., Poncin, W., Muñoz, G., Inal-Ince, D., Alcaraz-Serrano, V., Reyhler, G., Bellofiore, A., Tonia, T., Chalmers, J. D., & Spinou, A. (2023). European

Respiratory Society statement on airway clearance techniques in adults with bronchiectasis. *European Respiratory Journal*, 2202053.

<https://doi.org/10.1183/13993003.02053-2022>

Herrero-Cortina, B., Vilaró, J., Martí, D., Torres, A., San Miguel-Pagola, M., Alcaraz, V., & Polverino, E. (2016). Short-term effects of three slow expiratory airway clearance techniques in patients with bronchiectasis: a randomised crossover trial. *Physiotherapy*, 102(4), 357-364.

<https://doi.org/10.1016/j.physio.2015.07.005>

Herrero Cortina, B., Aliberti, S., & Blasi, F. (2017). Chest physiotherapy in European patients with bronchiectasis: Data from the EMBARC registry. *European Respiratory Journal*, 50, PA4071.

Hill, Button, B., Rubinstein, M., & Boucher, R. C. (2022). Physiology and pathophysiology of human airway mucus. *Physiological Reviews*, 102(4), 1757-1836. <https://doi.org/10.1152/physrev.00004.2021>

Hill, A. T., Grillo, L., Gruffydd-Jones, K., Payne, K., Souto, M., Sullivan, A., Wildgoose, J., & Loebinger, M. R. (2022). British Thoracic Society Quality Standard for Clinically Significant Bronchiectasis in Adults 2022. *BMJ Open Respiratory Research*, 9(1), e001369. <https://doi.org/10.1136/bmjresp-2022-001369>

Hill, A. T., Haworth, C. S., Aliberti, S., Barker, A., Blasi, F., Boersma, W., Chalmers, J. D., Soyza, A. D., Dimakou, K., Elborn, J. S., Feldman, C., Flume, P., Goeminne, P. C., Loebinger, M. R., Menendez, R., Morgan, L., Murriss, M.,

- Polverino, E., Quittner, A.,...Aksamit, T. (2017). Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *European Respiratory Journal*, 49(6), 1700051. <https://doi.org/10.1183/13993003.00051-2017>
- Hill, A. T., Routh, C., & Welham, S. (2014). National BTS bronchiectasis audit 2012: is the quality standard being adhered to in adult secondary care? *Thorax*, 69(3), 292-294. <https://doi.org/10.1136/thoraxjnl-2013-203739>
- Hill, A. T., Sullivan, A. L., Chalmers, J. D., De Soyza, A., Elborn, J. S., Floto, R. A., Grillo, L., Gruffydd-Jones, K., Harvey, A., & Haworth, C. S. (2019). British Thoracic Society Guideline for bronchiectasis in adults. *Thorax*, 74(Suppl 1), 1-69. https://thorax.bmj.com/content/thoraxjnl/74/Suppl_1/1.full.pdf
- Hill, A. T., Sullivan, A. L., Chalmers, J. D., De Soyza, A., Elborn, J. S., Floto, R. A., Grillo, L., Gruffydd-Jones, K., Harvey, A., Haworth, C. S., Hiscocks, E., Hurst, J. R., Johnson, C., Kelleher, W. P., Bedi, P., Payne, K., Saleh, H., Screaton, N. J., Smith, M.,...Loebinger, M. R. (2018). British Thoracic Society guideline for bronchiectasis in adults. *BMJ Open Respiratory Research*, 5(1), e000348. <https://doi.org/10.1136/bmjresp-2018-000348>
- Hill, D. B., Vasquez, P. A., Mellnik, J., McKinley, S. A., Vose, A., Mu, F., Henderson, A. G., Donaldson, S. H., Alexis, N. E., & Boucher, R. C. (2014). A biophysical basis for mucus solids concentration as a candidate biomarker for airways disease. *PLoS One*, 9(2), e87681. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928107/pdf/pone.0087681.p
df](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928107/pdf/pone.0087681.pdf)

- Hoesterey, D., Das, N., Janssens, W., Buhr, R. G., Martinez, F. J., Cooper, C. B., Tashkin, D. P., & Barjaktarevic, I. (2019). Spirometric indices of early airflow impairment in individuals at risk of developing COPD: Spirometry beyond FEV1/FVC. *Respiratory Medicine*, 156, 58-68.
<https://doi.org/https://doi.org/10.1016/j.rmed.2019.08.004>
- Honkoop, P., Usmani, O., & Bonini, M. (2022). The Current and Future Role of Technology in Respiratory Care. *Pulmonary Therapy*, 8(2), 167-179.
<https://doi.org/10.1007/s41030-022-00191-y>
- Hopkinson, N. S., Molyneux, A., Pink, J., & Harrisingh, M. C. (2019). Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. *Bmj*, 366, l4486. <https://doi.org/10.1136/bmj.l4486>
- Hosseini, M., Almasi-Hashiani, A., Sepidarkish, M., & Maroufizadeh, S. (2019). Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respiratory Research*, 20(1), 1-10.
- Houtmeyers, E., Gosselink, R., Gayan-Ramirez, G., & Decramer, M. (1999). Regulation of mucociliary clearance in health and disease. *European Respiratory Journal*, 13(5), 1177-1188. <https://doi.org/10.1034/j.1399-3003.1999.13e39.x>
- Hov, B., Andersen, T., Toussaint, M., Mikalsen, I. B., Vollsæter, M., Markussen, H., Indrekvam, S., & Hovland, V. (2023). User - perceived impact of long - term

mechanical assisted cough in paediatric neurodisability. *Developmental Medicine & Child Neurology*, 65(5), 655-663.

Hoy, R. F., & Chambers, D. C. (2020). Silica-related diseases in the modern world. *Allergy*, 75(11), 2805-2817. <https://doi.org/10.1111/all.14202>

HRA. (2023). *UK Policy Framework for Health and Social Care*. N. H. R. Authority. <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/uk-policy-framework-health-and-social-care-research/>

<http://img.medscapestatic.com/>. (2023). *Proposed synergy of LABA and inhaled CS*.

Retrieved 31.01.2023 from

<http://img.medscapestatic.com/fullsize/migrated/editorial/cmeline/2007/6294/images/slide20.gif>

i.pinimg.com. (2023). *The distribution of beta receptors in the body*. Retrieved 31.01.2023 from

<https://i.pinimg.com/originals/a6/e2/e4/a6e2e403fd20cec1f4aaaa23a2508c08.png>

Jabbar, A. (2016). *Introduction to Human Physiology*.

Jaffé, A., & Bush, A. (2001). Anti - inflammatory effects of macrolides in lung disease. *Pediatr Pulmonol*, 31(6), 464-473.

<https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.1076?sid=nlm%3Apubmed>

<https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/ppul.1076?download=true>

- Jain, B., Rubinstein, I., Robbins, R. A., Leise, K. L., & Sisson, J. H. (1993).
Modulation of airway epithelial cell ciliary beat frequency by nitric oxide.
Biochem Biophys Res Commun, 191(1), 83-88.
<https://doi.org/10.1006/bbrc.1993.1187>
- Janjua, S., Fortescue, R., & Poole, P. (2020). Phosphodiesterase - 4 inhibitors for
chronic obstructive pulmonary disease. *Cochrane Database of Systematic
Reviews*(5).
- Johns, D. P., Walters, J. A., & Walters, E. H. (2014). Diagnosis and early detection of
COPD using spirometry. *Journal of Thoracic Disease*, 6(11), 1557-1569.
<https://doi.org/10.3978/j.issn.2072-1439.2014.08.18>
- Johnson, A., Paul, C., Duckers, J., & Bridges, C. (2020). P329 To evaluate
adherence to NIV for airways clearance at the All Wales Adult Cystic
Fibrosis Centre (AWACFC). *Journal of Cystic Fibrosis*, 19, S148.
[https://doi.org/10.1016/S1569-1993\(20\)30658-5](https://doi.org/10.1016/S1569-1993(20)30658-5)
- Jones, P. W., Harding, G., Berry, P., Wiklund, I., Chen, W. H., & Kline Leidy, N.
(2009). Development and first validation of the COPD Assessment Test.
European Respiratory Journal, 34(3), 648-654.
<https://doi.org/10.1183/09031936.00102509>
- Jones, P. W., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., & Leidy, N. K.
(2012). Tests of the responsiveness of the COPD assessment test following
acute exacerbation and pulmonary rehabilitation. *CHEST*, 142(1), 134-140.
<https://doi.org/10.1378/chest.11-0309>

- Jones, P. W., Tabberer, M., & Chen, W.-H. (2011). Creating scenarios of the impact of copd and their relationship to copd assessment test (CAT™) scores. *BMC Pulmonary Medicine*, 11(1), 42. <https://doi.org/10.1186/1471-2466-11-42>
- Kanazawa, H., Tochino, Y., Asai, K., Ichimaru, Y., Watanabe, T., & Hirata, K. (2012). Validity of HMGB1 measurement in epithelial lining fluid in patients with COPD. *European journal of clinical investigation*, 42(4), 419-426.
- Karabis, A., Lindner, L., Mocarski, M., Huisman, E., & Greening, A. (2013). Comparative efficacy of acclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease*, 8, 405-423. <https://doi.org/10.2147/copd.S48967>
- Kavanaugh, J. S., Flack, C. E., Lister, J., Ricker, E. B., Ibberson, C. B., Jenul, C., Moormeier, D. E., Delmain, E. A., Bayles, K. W., & Horswill, A. R. (2019). Identification of extracellular DNA-binding proteins in the biofilm matrix. *MBio*, 10(3), 10.1128/mbio.01137-01119.
- KC, R., Shukla, S. D., Gautam, S. S., Hansbro, P. M., & O'Toole, R. F. (2018). The role of environmental exposure to non-cigarette smoke in lung disease. *Clinical and Translational Medicine*, 7(1), 39. <https://doi.org/10.1186/s40169-018-0217-2>

- Keir, H. R., & Chalmers, J. D. (2021). Pathophysiology of Bronchiectasis. *Seminars in Respiratory and Critical Care Medicine*, 42(4), 499-512.
<https://doi.org/10.1055/s-0041-1730891>
- Kendrick, A. H. (2007). Airway clearance techniques in cystic fibrosis: physiology, devices and the future. *Journal of the Royal Society of Medicine (Supplement)*, 100(47).
- Khan, Q., Ismail, M., Haider, I., & Ali, Z. (2019). Prevalence of the risk factors for QT prolongation and associated drug-drug interactions in a cohort of medical inpatients. *Journal of the Formosan Medical Association*, 118(1 Pt 1), 109-115. <https://doi.org/10.1016/j.jfma.2018.01.016>
- Khoudigian-Sinani, S., Kowal, S., Suggett, J. A., & Coppolo, D. P. (2017). Cost-effectiveness of the Aerobika* oscillating positive expiratory pressure device in the management of COPD exacerbations. *International Journal of Chronic Obstructive Pulmonary Disease*, 12(null), 3065-3073.
<https://doi.org/10.2147/COPD.S143334>
- Kim, S. R., Kim, S. H., Kim, G. H., Cho, J. Y., Choi, H., Lee, H., Ra, S. W., Lee, K. M., Choe, K. H., Oh, Y. M., Shin, Y. M., & Yang, B. (2023). Effectiveness of the use of an oscillating positive expiratory pressure device in bronchiectasis with frequent exacerbations: a single-arm pilot study. *Frontiers in medicine (Lausanne)*, 10, 1159227. <https://doi.org/10.3389/fmed.2023.1159227>
- Kirkham, S., Sheehan, J. K., Knight, D., Richardson, P. S., & Thornton, D. J. (2002). Heterogeneity of airways mucus: variations in the amounts and glycoforms

- of the major oligomeric mucins MUC5AC and MUC5B. *Biochem J*, 361(Pt 3), 537-546. <https://doi.org/10.1042/0264-6021:3610537>
- Kite, J., & Phongsavan, P. (2017). Insights for conducting real-time focus groups online using a web conferencing service. *F1000Research*, 6.
- Knowles, M. R., & Boucher, R. C. (2002). Mucus clearance as a primary innate defense mechanism for mammalian airways. *The Journal of Clinical Investigation*, 109(5), 571-577. <https://doi.org/10.1172/JCI15217>
- Knowles, M. R., Zariwala, M., & Leigh, M. (2016). Primary ciliary dyskinesia. *Clinics in Chest Medicine*, 37(3), 449-461.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988337/pdf/nihms-800827.pdf>
- Knox, L., Gemine, R., Rees, S., Bowen, S., Groom, P., Taylor, D., Bond, I., Rosser, W., & Lewis, K. (2021). Using the Technology Acceptance Model to conceptualise experiences of the usability and acceptability of a self-management app (COPD.Pal®) for Chronic Obstructive Pulmonary Disease. *Health and Technology*, 11(1), 111-117. <https://doi.org/10.1007/s12553-020-00494-7>
- Kon, S. S., Canavan, J. L., Jones, S. E., Nolan, C. M., Clark, A. L., Dickson, M. J., Haselden, B. M., Polkey, M. I., & Man, W. D. (2014). Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *The Lancet Respiratory Medicine*, 2(3), 195-203.

Kopsaftis, Z., Wood-Baker, R., & Poole, P. (2018). Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*, 6(6), Cd002733.

<https://doi.org/10.1002/14651858.CD002733.pub3>

Kourliouros, A., Hogg, R., Mehew, J., Al-Aloul, M., Carby, M., Lordan, J. L., Thompson, R. D., Tsui, S., & Parmar, J. (2018). Patient outcomes from time of listing for lung transplantation in the UK: are there disease-specific differences? *Thorax*, thoraxjnl-2018-211731.

Krishnan, J. K., & Calverley, P. M. A. (2022). Understanding the People Excluded from Chronic Obstructive Pulmonary Disease Clinical Trials. *American Journal of Respiratory and Critical Care Medicine*, 206(3), 235-236.

<https://doi.org/10.1164/rccm.202204-0688ED>

Krueger, R. A. (2014). *Focus groups: A practical guide for applied research*. Sage publications.

Landrigan, P. J., Fuller, R., Acosta, N. J. R., Adeyi, O., Arnold, R., Basu, N., Baldé, A. B., Bertollini, R., Bose-O'Reilly, S., Boufford, J. I., Breysse, P. N., Chiles, T., Mahidol, C., Coll-Seck, A. M., Cropper, M. L., Fobil, J., Fuster, V., Greenstone, M., Haines, A.,...Zhong, M. (2018). The Lancet Commission on pollution and health. *The Lancet*, 391(10119), 462-512.

[https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)32345-0](https://doi.org/https://doi.org/10.1016/S0140-6736(17)32345-0)

- Laney, A. S., & Weissman, D. N. (2014). Respiratory diseases caused by coal mine dust. *Journal of Occupational and Environmental Medicine*, 56 Suppl 10(0 10), S18-22. <https://doi.org/10.1097/jom.0000000000000260>
- Lapin, C. D. (2002). Airway physiology, autogenic drainage, and active cycle of breathing. *Respiratory Care*, 47(7), 778-785.
- Laska, I. F., & Chalmers, J. D. (2019). Treatment to prevent exacerbations in bronchiectasis: macrolides as first line? *European Respiratory Journal*, 54(1), 1901213. <https://doi.org/10.1183/13993003.01213-2019>
- Lathen, L., & Laestadius, L. (2021). Reflections on online focus group research with low socio-economic status African American adults during COVID-19. *International Journal of Qualitative Methods*, 20, 16094069211021713.
- Le Rouzic, O., Roche, N., Cortot, A. B., Tillie-Leblond, I., Masure, F., Perez, T., Boucot, I., Hamouti, L., Ostinelli, J., Pribil, C., Poutchnine, C., Schück, S., Pouriel, M., & Housset, B. (2018). Defining the "Frequent Exacerbator" Phenotype in COPD: A Hypothesis-Free Approach. *CHEST*, 153(5), 1106-1115. <https://doi.org/10.1016/j.chest.2017.10.009>
- Lee, A. L. (2023). Physiotherapy management of bronchiectasis in adults. *Journal of Physiotherapy*, 69(1), 7-14. <https://doi.org/https://doi.org/10.1016/j.jphys.2022.11.013>
- Lee, A. L., Baenziger, S., Louey, A., Jennings, S., Solin, P., & Hoy, R. (2021). A review of physiotherapy practice for people with bronchiectasis. *ERJ Open Research*, 7(2), 00569-02020. <https://doi.org/10.1183/23120541.00569-2020>

Lee, A. L., Burge, A. T., & Holland, A. E. (2017). Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis. *Cochrane Database of Systematic Reviews*(9).

<https://doi.org/10.1002/14651858.CD011699.pub2>

Lee, J.-W., Chun, W., Lee, H. J., Min, J.-H., Kim, S.-M., Seo, J.-Y., Ahn, K.-S., & Oh, S.-R. (2021). The role of macrophages in the development of acute and chronic inflammatory lung diseases. *Cells*, 10(4), 897.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8070705/pdf/cells-10-00897.pdf>

Leonard-Nimoy. (2015). X. Retrieved 25/08/2024 from

Lewis, A., Cave, P., Stern, M., Welch, L., Taylor, K., Russell, J., Doyle, A. M., Russell, A. M., McKee, H., Clift, S., Bott, J., & Hopkinson, N. S. (2016). Singing for Lung Health-a systematic review of the literature and consensus statement. *npj Primary Care Respiratory Medicine*, 26, 16080.

<https://doi.org/10.1038/npjpcrm.2016.80>

Lewis, A., & Osadnik, C. R. (2023). Changing practice by changing pressures: a role for oscillating positive expiratory pressure in chronic obstructive pulmonary disease. *Thorax*, 78(2), 113-115. [https://doi.org/10.1136/thorax-2022-](https://doi.org/10.1136/thorax-2022-219451)

[219451](https://doi.org/10.1136/thorax-2022-219451)

Lewis, A., Philip, K. E. J., Lound, A., Cave, P., Russell, J., & Hopkinson, N. S. (2021). The physiology of singing and implications for 'Singing for Lung Health' as a therapy for individuals with chronic obstructive pulmonary

disease. *BMJ Open Respiratory Research*, 8(1).

<https://doi.org/10.1136/bmjresp-2021-000996>

Lewis, L. K., Williams, M. T., & Olds, T. S. (2012). The active cycle of breathing technique: A systematic review and meta-analysis. *Respiratory Medicine*, 106(2), 155-172. <https://doi.org/10.1016/j.rmed.2011.10.014>

Li, L. S., Paquet, C., Johnston, K., & Williams, M. T. (2017). "What are my chances of developing COPD if one of my parents has the disease?" A systematic review and meta-analysis of prevalence of co-occurrence of COPD diagnosis in parents and offspring. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 403-415.

<https://doi.org/10.2147/copd.S123933>

Lillehoj, E. P., Kato, K., Lu, W., & Kim, K. C. (2013). Cellular and molecular biology of airway mucins. *International review of cell and molecular biology*, 303, 139-202. <https://doi.org/10.1016/b978-0-12-407697-6.00004-0>

Lipson, D. A., Barnhart, F., Brealey, N., Brooks, J., Criner, G. J., Day, N. C., Dransfield, M. T., Halpin David, M. G., Han, M. K., Elaine, J. C., Kilbride, S., Lange, P., Lomas, D. A., Martinez, F. J., Singh, D., Tabberer, M., Wise, R. A., & Pascoe, S. J. (2018). Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*, 378(18), 1671-1680.

<https://doi.org/https://doi.org/10.1056/NEJMoa1713901>

Livnat, G., Yaari, N., Stein, N., Bentur, L., Hanna, M., Harel, M., Adir, Y., & Shteinberg, M. (2021). 4-week daily airway clearance using oscillating

- positive-end expiratory pressure versus autogenic drainage in bronchiectasis patients: a randomised controlled trial. *ERJ Open Research*, 7(4), 00426-02021. <https://doi.org/10.1183/23120541.00426-2021>
- Loebinger, M. R., Wells, A. U., Hansell, D. M., Chinyanganya, N., Devaraj, A., Meister, M., & Wilson, R. (2009). Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *European Respiratory Journal*, 34(4), 843-849. <https://doi.org/10.1183/09031936.00003709>
- Long, M. B., Chotirmall, S. H., Shteinberg, M., & Chalmers, J. D. (2024). Rethinking bronchiectasis as an inflammatory disease. *The Lancet Respiratory Medicine*. [https://doi.org/10.1016/S2213-2600\(24\)00176-0](https://doi.org/10.1016/S2213-2600(24)00176-0)
- Mac Aogáin, M., Chandrasekaran, R., Lim, A. Y. H., Low, T. B., Tan, G. L., Hassan, T., Ong, T. H., Ng, A. H. Q., Bertrand, D., & Koh, J. Y. (2018). Immunological corollary of the pulmonary mycobiome in bronchiectasis: the CAMEB study. *European Respiratory Journal*, 52(1).
- Machin, M., Amaral, A. F., Wielscher, M., Rezwan, F. I., Imboden, M., Jarvelin, M.-R., Adcock, I. M., Probst-Hensch, N., Holloway, J. W., & Jarvis, D. L. (2017). Systematic review of lung function and COPD with peripheral blood DNA methylation in population based studies. *BMC Pulmonary Medicine*, 17, 1-10.
- Mackay, A. J., Donaldson, G. C., Patel, A. R., Jones, P. W., Hurst, J. R., & Wedzicha, J. A. (2012). Usefulness of the chronic obstructive pulmonary disease assessment test to evaluate severity of COPD exacerbations.

American Journal of Respiratory and Critical Care Medicine, 185(11), 1218-1224.

Magge, A., Ashraf, S., Quittner, A. L., & Metersky, M. L. (2019). Quality of life in patients with bronchiectasis: a 2-year longitudinal study. *Annals of Internal Medicine*, 7(14), 334. <https://doi.org/10.21037/atm.2019.06.62>

Mahler, D. A., & Mackowiak, J. I. (1995). Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. *CHEST*, 107(6), 1585-1589. <https://doi.org/10.1378/chest.107.6.1585>

Man, W., Chaplin, E., Daynes, E., Drummond, A., Evans, R. A., Greening, N. J., Nolan, C., Pavitt, M. J., Roberts, N. J., Vogiatzis, I., & Singh, S. J. (2023). British Thoracic Society Clinical Statement on pulmonary rehabilitation. *Thorax*, 78(Suppl 5), s2-s15. <https://doi.org/10.1136/thorax-2023-220439>

Mandour, M. A., Helmi, A. M., El-Sheikh, M. M., El-Garem, F., & El-Ghazzawi, E. (1977). Effect of tympanic neurectomy on human parotid salivary gland: histopathologic, histochemical, and clinical study. *Archives of Otolaryngology*, 103(6), 338-341.

Mark, S. C. v. d., Hoek, R. A. S., & Hellemons, M. E. (2020). Developments in lung transplantation over the past decade. *European Respiratory Review*, 29(157), 190132. <https://doi.org/10.1183/16000617.0132-2019>

Marmor, M., & McShane, P. J. (2024). Mind the gap: challenges to overcome in airway clearance. *European Respiratory Journal*, 63(6). <https://doi.org/10.1183/13993003.00687-2024>

- Martínez-García, M., Oscullo, G., García-Ortega, A., Matera, M. G., Rogliani, P., & Cazzola, M. (2022). Rationale and Clinical Use of Bronchodilators in Adults with Bronchiectasis. *Drugs*, 82(1), 1-13. <https://doi.org/10.1007/s40265-021-01646-3>
- Matera, M. G., Page, C. P., Calzetta, L., Rogliani, P., & Cazzola, M. (2020). Pharmacology and Therapeutics of Bronchodilators Revisited. *Pharmacological reviews*, 72(1), 218-252. <https://doi.org/10.1124/pr.119.018150>
- Matthews, L. W., Doershuk, C. F., Wise, M., Eddy, G., Nudelman, H., & Spector, S. (1964). A therapeutic regimen for patients with cystic fibrosis. *The Journal of pediatrics*, 65(4), 558-575.
- McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(2). <https://doi.org/10.1002/14651858.CD003793.pub3>
- McCullough, A. R., Ryan, C., O'Neill, B., Bradley, J. M., Elborn, J. S., & Hughes, C. M. (2015). Defining the content and delivery of an intervention to Change Adherence to treatment in Bronchiectasis (CAN-BE): a qualitative approach incorporating the Theoretical Domains Framework, behavioural change techniques and stakeholder expert panels. *BMC Health Services Research*, 15, 342. <https://doi.org/10.1186/s12913-015-1004-z>

- McCullough, A. R., Tunney, M. M., Elborn, J. S., Bradley, J. M., & Hughes, C. M. (2015). Predictors of adherence to treatment in bronchiectasis. *Respiratory Medicine*, 109(7), 838-845.
- McCullough, A. R., Tunney, M. M., Quittner, A. L., Elborn, J. S., Bradley, J. M., & Hughes, C. M. (2014). Treatment adherence and health outcomes in patients with bronchiectasis [Article]. *BMC Pulmonary Medicine*, 14(1), Article 107. <https://doi.org/10.1186/1471-2466-14-107>
- McDonnell, M., Aliberti, S., Goeminne, P. a., Dimakou, K., Zucchetti, S., Davidson, J., Ward, C., Laffey, J., Finch, S., & Pesci, A. (2016). Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax*, thoraxjnl-2016-208481.
- McGarvey, L. P., Birring, S. S., Morice, A. H., Dicpinigaitis, P. V., Pavord, I. D., Schelfhout, J., Nguyen, A. M., Li, Q., Tzontcheva, A., Iskold, B., Green, S. A., Rosa, C., Muccino, D. R., & Smith, J. A. (2022). Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet*, 399(10328), 909-923. [https://doi.org/10.1016/s0140-6736\(21\)02348-5](https://doi.org/10.1016/s0140-6736(21)02348-5)
- McIlwaine, M., Bradley, J., Elborn, J. S., & Moran, F. (2017). Personalising airway clearance in chronic lung disease. *European Respiratory Review*, 26(143). <https://doi.org/10.1183/16000617.0086-2016>

McIlwaine, M., Button, B., & Nevitt, S. J. (2019). Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *Cochrane Database of Systematic Reviews*(11).

<https://doi.org/10.1002/14651858.CD003147.pub5>

McIlwaine, M. P., Alarie, N., Davidson, G. F., Lands, L. C., Ratjen, F., Milner, R., Owen, B., & Agnew, J. L. (2013). Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. *Thorax*, 68(8), 746-751.

<https://doi.org/10.1136/thoraxjnl-2012-202915>

McLeese, R. H., O'Neill, K., O'Neill, B., Chalmers, J. D., Boyd, J., De Soyza, A., McChrystal, R., Crichton, M. L., & Bradley, J. M. (2023). Airway clearance treatments in bronchiectasis: feasibility of linking survey results to registry data and a survey of patients' and physiotherapists' practices. *ERJ Open Research*, 9(2), 00540-02022. <https://doi.org/10.1183/23120541.00540-2022>

McNamara, R. J., Epsley, C., Coren, E., & McKeough, Z. J. (2017). Singing for adults with chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*, 12(12), Cd012296.

<https://doi.org/10.1002/14651858.CD012296.pub2>

McShane, A., Bath, J., Jaramillo, A. M., Ridley, C., Walsh, A. A., Evans, C. M., Thornton, D. J., & Ribbeck, K. (2021). Mucus. *Current Biology*, 31(15), R938-R945.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8759706/pdf/nihms-1769811.pdf>

- McShane, A., Philley, J. V., Prieto, D. A., & Aksamit, T. R. (2021). Global Attitudes of Health Care Providers About Aerosolized Airway Clearance Therapy in Bronchiectasis Patients During the Coronavirus Disease 2019 Pandemic. *Chronic Obstructive Pulmonary Diseases*, 8(3), 319-325.
<https://doi.org/10.15326/jcopdf.2021.0214>
- Mead, J., Turner, J. M., Macklem, P. T., & Little, J. B. (1967). Significance of the relationship between lung recoil and maximum expiratory flow. *Journal of Applied Physiology*, 22(1), 95-108.
- Merton, R. K. (1987). The focussed interview and focus groups: Continuities and discontinuities. *The Public opinion quarterly*, 51(4), 550-566.
- Metersky, M. L., Choate, R., Addrizzo-Harris, D., Aksamit, T. R., Barker, A., Basavaraj, A., Daley, C. L., Daniels, M. L. A., Eden, E., & DiMango, A. (2021). The association of long-term macrolide therapy and nontuberculous mycobacterial culture positivity in patients with bronchiectasis. *CHEST*, 160(2), 466-469.
- Mettler., S. K., Sonavane., S., Grumley., S., Nath., H. P., Yen., A. C., Pistenmaa., C., Nardelli., P., Estepar., R. S. J., Cho., M. H., & Diaz., A. A. (2024). Airway-occluding Mucus Plugs and Cause-specific Mortality in COPD. *American Journal of Respiratory and Critical Care Medicine*, 0(ja), null.
<https://doi.org/10.1164/rccm.202401-0121LE>
- Mikami, M., Llewellyn-Jones, C. G., Bayley, D., Hill, S. L., & Stockley, R. A. (1998). The chemotactic activity of sputum from patients with bronchiectasis.

American Journal of Respiratory and Critical Care Medicine, 157(3), 723-728.

Milan, S., Bondalapati, P., Megally, M., Patel, E., Vaghasia, P., Gross, L., Bachman, E. M., Chadha, P., & Weingarten, J. A. (2019). Positive Expiratory Pressure Therapy With And Without Oscillation And Hospital Length Of Stay For Acute Exacerbation Of Chronic Obstructive Pulmonary Disease.

International Journal of Chronic Obstructive Pulmonary Disease, 14, 2553-2561. <https://doi.org/10.2147/copd.S213546>

Miravittles, M., & Ribera, A. (2017). Understanding the impact of symptoms on the burden of COPD. *Respiratory Research*, 18(1), 67.

<https://doi.org/10.1186/s12931-017-0548-3>

Mirra, V., Werner, C., & Santamaria, F. (2017). Primary ciliary dyskinesia: an update on clinical aspects, genetics, diagnosis, and future treatment strategies.

Frontiers in pediatrics, 5, 135.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465251/pdf/fped-05-00135.pdf>

Monteagudo, M., Rodríguez-Blanco, T., Barrecheguren, M., Simonet, P., &

Miravittles, M. (2016). Prevalence and incidence of bronchiectasis in Catalonia, Spain: A population-based study. *Respiratory Medicine*, 121, 26-

31. <https://doi.org/10.1016/j.rmed.2016.10.014>

- Morgan, K. T., Jiang, X.-Z., Patterson, D. L., & Gross, E. A. (1984). The nasal mucociliary apparatus: correlation of structure and function in the rat. *American Review of Respiratory Disease*, 130(2), 275-281.
- Morgan, S. E., Mosakowski, S., Giles, B. L., Naureckas, E., & Tung, A. (2019). Variability in expiratory flow requirements among oscillatory positive expiratory pressure. *Canadian Journal of Respiratory Therapy*, 56, 7-10.
<https://doi.org/10.29390/cjrt-2019-025>
- Morrison, C. B., Markovetz, M. R., & Ehre, C. (2019). Mucus, mucins, and cystic fibrosis. *Pediatr Pulmonol*, 54(S3), S84-S96.
<https://doi.org/https://doi.org/10.1002/ppul.24530>
- Muñoz, G., De Gracia, J., Buxó, M., Alvarez, A., & Vendrell, M. (2018). Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. *European Respiratory Journal*, 51(1), 1701926.
<https://doi.org/10.1183/13993003.01926-2017>
- Murgia, N., & Gambelunghe, A. (2022). Occupational COPD-The most under-recognized occupational lung disease? *Respirology*, 27(6), 399-410.
<https://doi.org/10.1111/resp.14272>
- Murray, M. P., Pentland, J. L., & Hill, A. T. (2009). A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*, 34(5), 1086-1092.
<https://doi.org/10.1183/09031936.00055509>

- Mwimbi, X. K., Muimo, R., Green, M. W., & Mehta, A. (2003). Making human nasal cilia beat in the cold: a real time assay for cell signalling. *Cell Signal*, 15(4), 395-402. [https://doi.org/10.1016/s0898-6568\(02\)00143-2](https://doi.org/10.1016/s0898-6568(02)00143-2)
- Nair, C., Shoemark, A., Chan, M., Ollosson, S., Dixon, M., Hogg, C., Alton, E. W., Davies, J. C., & Williams, H. D. (2014). Cyanide levels found in infected cystic fibrosis sputum inhibit airway ciliary function. *European Respiratory Journal*, 44(5), 1253-1261. <https://erj.ersjournals.com/content/erj/44/5/1253.full.pdf>
- Naraparaju, S., Vaishali, K., Venkatesan, P., & Acharya, V. (2010). A comparison of the Acapella and a threshold inspiratory muscle trainer for sputum clearance in bronchiectasis-A pilot study. *Physiotherapy Theory and Practice*, 26(6), 353-357. <https://doi.org/10.3109/09593981003596616>
- Nayak, M. K., Alaparthi, G. K., Krishnan, K. S., Anand, R., & Acharya, V. (2018). Level of Patient Satisfaction with Chest Physiotherapy Airway Clearance Techniques in Bronchiectasis-A Survey. *Indian Journal of Public Health Research and Development*, 9, 90-95.
- Nettle, C. J., Jenkins, L., Curtis, D., Badiei, N., Lewis, K., Williams, P. R., & Daniels, D. R. (2018). Linear rheology as a potential monitoring tool for sputum in patients with Chronic Obstructive Pulmonary Disease (COPD). *Biorheology*, 54, 67-80. <https://doi.org/10.3233/BIR-17141>
- Nguyen, A. M., Schelfhout, J., Muccino, D., Bacci, E. D., La Rosa, C., Vernon, M., & Birring, S. S. (2022). Leicester Cough Questionnaire validation and clinically

important thresholds for change in refractory or unexplained chronic cough.

Therapeutic Advances in Respiratory Disease, 16, 17534666221099737.

<https://doi.org/10.1177/17534666221099737>

NICE. (2016). Motor neurone disease: assessment and management. In: National institute for clinical health and care excellence.

NICE. (2018). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 69.

<https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245>

NICE. (2023). <Diagnosis - COPD _ Diagnosis _ Chronic obstructive pulmonary disease _ CKS _ NICE.pdf>. Retrieved 04/05/2024 from

<https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/diagnosis/diagnosis-copd/>

Nichol, K. L., Margolis, K. L., Wuorenma, J., & Von Sternberg, T. (1994). The Efficacy and Cost Effectiveness of Vaccination against Influenza among Elderly Persons Living in the Community. *New England Journal of Medicine*, 331(12), 778-784. <https://doi.org/10.1056/nejm199409223311206>

NIH. (2020). *Marvels of Mucus and Phlegm. The Slime That Keeps You Healthy*.

National Institutes of Health. Retrieved 26/08/2024 from

<https://newsinhealth.nih.gov/2020/08/marvels-mucus-phlegm>

Nikolaou, V., Massaro, S., Fakhimi, M., Stergioulas, L., & Price, D. (2020). COPD phenotypes and machine learning cluster analysis: A systematic review and future research agenda. *Respiratory Medicine*, 171, 106093.

<https://doi.org/https://doi.org/10.1016/j.rmed.2020.106093>

O'Donnell, A. E. (2022). Airway Clearance and Mucoactive Therapies in Bronchiectasis. *Clinics in Chest Medicine*, 43(1), 157-163.

<https://doi.org/10.1016/j.ccm.2021.12.004>

O'Neill, K., O'donnell, A. E., & Bradley, J. (2019). Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. *Respirology*, 24, 227 - 237.

Oba, Y., Keeney, E., Ghatehorde, N., & Dias, S. (2018). Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD) : A systematic review and network meta-analysis.

<https://doi.org/10.1002/14651858.CD012620.pub2>

Okuda, K., Chen, G., Subramani, D. B., Wolf, M., Gilmore, R. C., Kato, T., Radicioni, G., Kesimer, M., Chua, M., & Dang, H. (2019). Localization of secretory mucins MUC5AC and MUC5B in normal/healthy human airways. *American Journal of Respiratory and Critical Care Medicine*, 199(6), 715-727.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6423099/pdf/rccm.201804-0734OC.pdf>

Olsén, M. F., Olofsson, P., Frejd, P., Lannefors, L., & Westerdahl, E. (2021).

Technical aspects of devices and equipment for positive expiratory pressure with and without oscillation. *Respiratory Care*, 66(5), 862-877.

Osadnik, C. R., McDonald, C. F., Miller, B. R., Hill, C. J., Tarrant, B., Steward, R.,

Chao, C., Stodden, N., Oliveira, C. C., Gagliardi, N., & Holland, A. E. (2014).

The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. *Thorax*, 69(2), 137-143.

<https://doi.org/10.1136/thoraxjnl-2013-203425>

Osei, A. D., Mirbolouk, M., Orimoloye, O. A., Dzaye, O., Uddin, S. M. I., Benjamin, E.

J., Hall, M. E., DeFilippis, A. P., Bhatnagar, A., Biswal, S. S., & Blaha, M. J.

(2020). Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. *American journal of preventive medicine*, 58(3), 336-342. <https://doi.org/10.1016/j.amepre.2019.10.014>

Osman, L. P., Roughton, M., Hodson, M. E., & Pryor, J. A. (2010). Short-term

comparative study of high frequency chest wall oscillation and European airway clearance techniques in patients with cystic fibrosis. *Thorax*, 65(3), 196-200. <https://doi.org/10.1136/thx.2008.111492>

Otis, A. B., McKerrow, C. B., Bartlett, R. A., Mead, J., McIlroy, M., Selverstone, N., &

Radford Jr, E. (1956). Mechanical factors in distribution of pulmonary ventilation. *Journal of Applied Physiology*, 8(4), 427-443.

Ottewill, C., Gleeson, M., Kerr, P., Hale, E. M., & Costello, R. W. (2024). Digital health delivery in respiratory medicine: adjunct, replacement or cause for division? *European Respiratory Review*, 33(173), 230251.

<https://doi.org/10.1183/16000617.0251-2023>

Ouaalaya, E. H., Falque, L., Dupis, J. M., Sabatini, M., Bernady, A., Nguyen, L., Ozier, A., Nocent-Ejnaini, C., Le Guillou, F., Molimard, M., Zysman, M., & Raherison-Semjen, C. (2020). Susceptibility to frequent exacerbation in COPD patients: Impact of the exacerbations history, vaccinations and comorbidities? *Respiratory Medicine*, 169, 106018.

<https://doi.org/https://doi.org/10.1016/j.rmed.2020.106018>

Paff, T., Omran, H., Nielsen, K. G., & Haarman, E. G. (2021). Current and Future Treatments in Primary Ciliary Dyskinesia. *International Journal of Molecular Sciences*, 22(18). <https://doi.org/10.3390/ijms22189834>

Pan, C.-X., Shi, M.-X., & Guan, W.-J. (2023). Airway clearance technique in the modern era of bronchiectasis management. In (Vol. 9): Eur Respiratory Soc.

Papi, A., Vestbo, J., Fabbri, L., Corradi, M., Prunier, H., Cohuet, G., Guasconi, A., Montagna, I., Vezzoli, S., Petruzzelli, S., Scuri, M., Roche, N., & Singh, D. (2018). Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet*, 391(10125), 1076-1084.

[https://doi.org/10.1016/s0140-6736\(18\)30206-x](https://doi.org/10.1016/s0140-6736(18)30206-x)

- Park, J. A., Crotty Alexander, L. E., & Christiani, D. C. (2022). Vaping and Lung Inflammation and Injury. *Annual review of physiology*, 84, 611-629.
<https://doi.org/10.1146/annurev-physiol-061121-040014>
- Pathak, U., Gupta, N. C., & Suri, J. C. (2020). Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. *International Journal of Environmental Health Research*, 30(1), 75-88.
<https://doi.org/10.1080/09603123.2019.1575951>
- Patterson, J. E., Bradley, J. M., & Elborn, J. S. (2004). Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques (incorporating postural drainage and vibration) versus test of incremental respiratory endurance. *Chronic Respiratory Disease*, 1(3), 127-130. <https://doi.org/10.1191/1479972304cd034oa>
- Patterson, J. E., Bradley, J. M., Hewitt, O., Bradbury, I., & Elborn, J. S. (2005). Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques versus Acapella. *Respiration*, 72(3), 239-242.
<https://doi.org/10.1159/000085363>
- Peng, C., Yan, Y., Li, Z., Jiang, Y., & Cai, Y. (2020). Chronic obstructive pulmonary disease caused by inhalation of dust: A meta-analysis. *Medicine (Baltimore)*, 99(34), e21908. <https://doi.org/10.1097/md.00000000000021908>
- Philip, K. E. J., Buttery, S. C., Bowen, S., Lewis, A., Jeffery, E., Alghamdi, S. M., Williams, P., Alasmari, A. M., Alsulayyim, A. S., Orton, C. M., Conway, F., Chan, L., Vijayakumar, B., Tana, A., Tonkin, J., Perkins, A., Garner, J. L.,

- Srikanthan, K., Sadaka, A.,...Hopkinson, N. S. (2024). Singing for lung health in COPD: a multicentre randomised controlled trial of online delivery. *BMJ Open Respiratory Research*, 11(1), e002365.
<https://doi.org/10.1136/bmjresp-2024-002365>
- Phillips, J., Hing, W., Pope, R., Canov, A., Harley, N., & Lee, A. L. (2023). Active cycle of breathing technique versus oscillating PEP therapy versus walking with huffing during an acute exacerbation of bronchiectasis: a randomised, controlled trial protocol. *BMC Pulmonary Medicine*, 23(1).
<https://doi.org/10.1186/s12890-023-02324-8>
- Phillips, J., Lee, A., Pope, R., & Hing, W. (2021). Physiotherapists' use of airway clearance techniques during an acute exacerbation of bronchiectasis: a survey study. *Archives of physiotherapy*, 11, 1-11.
- PHW. (2018). *UK smoking prevalence, age-standardised percentage, persons aged 18+, UK constituent countries, 2018*. Retrieved from
<https://publichealthwales.shinyapps.io/smokinginwales/>
- PHW. (2020). *Smoking-attributable admissions, EASR per 100,000, males and females aged 35+, Wales by deprivation fifth, 2008/09-2010/11 to 2016/17-2018/19*. Retrieved from
<https://publichealthwales.shinyapps.io/smokinginwales/>
- Pleasants, R. A., Riley, I. L., & Mannino, D. M. (2016). Defining and targeting health disparities in chronic obstructive pulmonary disease. *International Journal of*

Chronic Obstructive Pulmonary Disease, 11, 2475-2496.

<https://doi.org/10.2147/copd.S79077>

Polverino, E., Dimakou, K., Traversi, L., Bossios, A., Haworth, C. S., Loebinger, M. R., De Soyza, A., Vendrell, M., Burgel, P.-R., Mertsch, P., McDonnell, M., Škrgat, S., Carro, L. M., Sibila, O., van der Eerden, M., Kauppi, P., Hill, A. T., Wilson, R., Milenkovic, B.,...Goeminne, P. C. (2024). Bronchiectasis and asthma: Data from The European Bronchiectasis Registry (EMBARC). *Journal of Allergy and Clinical Immunology*.

<https://doi.org/https://doi.org/10.1016/j.jaci.2024.01.027>

Polverino, E., Goeminne, P. C., McDonnell, M. J., Aliberti, S., Marshall, S. E., Loebinger, M. R., Murris, M., Cantón, R., Torres, A., Dimakou, K., De Soyza, A., Hill, A. T., Haworth, C. S., Vendrell, M., Ringshausen, F. C., Subotic, D., Wilson, R., Vilaró, J., Stallberg, B.,...Chalmers, D., James. (2017). European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal*, 50(3), 1700629.

<https://doi.org/10.1183/13993003.00629-2017>

Poncin, W., Reyhler, G., Leeuwerck, N., Bauwens, N., Aubriot, A.-S., Nader, C., Liistro, G., & Gohy, S. (2017). Short-term effect of autogenic drainage on ventilation inhomogeneity in adult subjects with stable non-cystic fibrosis bronchiectasis. *Respiratory Care*, 62(5), 524-531.

Poncin, W., Reyhler, G., Liistro, M., & Liistro, G. (2020). Comparison of 6 Oscillatory Positive Expiratory Pressure Devices During Active Expiratory

Flow. *Respiratory Care*, 65(4), 492-499.

<https://doi.org/10.4187/respcare.07271>

Price, D., Brusselle, G., Roche, N., Freeman, D., & Chisholm, A. (2015). Real-world research and its importance in respiratory medicine. *Breathe (Sheff)*, 11(1), 26-38. <https://doi.org/10.1183/20734735.015414>

Pryor, J. A. (2016). Active cycle of breathing techniques. *International Physiotherapy Group for Cystic Fibrosis Blue Booklet on Physiotherapy Techniques*. www.ecfs.eu/ipg_cf/booklet Date last accessed: October, 20.

Public-Health-England. (2018). The 2nd Atlas of variation in risk factors and healthcare for respiratory in England, 2019. In. NHS England.

Pumar, M. I., Gray, C. R., Walsh, J. R., Yang, I. A., Rolls, T. A., & Ward, D. L. (2014). Anxiety and depression-Important psychological comorbidities of COPD. *Journal of Thoracic Disease*, 6(11), 1615-1631. <https://doi.org/10.3978/j.issn.2072-1439.2014.09.28>

Quint, J. K., Millett, E. R. C., Joshi, M., Navaratnam, V., Thomas, S. L., Hurst, J. R., Smeeth, L., & Brown, J. S. (2016). Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal*, 47(1), 186-193. <https://doi.org/10.1183/13993003.01033-2015>

Quittner, A. L., O'Donnell, A. E., Salathe, M. A., Lewis, S. A., Li, X., Montgomery, A. B., O'Riordan, T. G., & Barker, A. F. (2015). Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal

important difference scores. *Thorax*, 70(1), 12-20.

<https://doi.org/10.1136/thoraxjnl-2014-205918>

Rabe, K. F. (2011). Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *British journal of pharmacology*, 163(1), 53-67.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085868/pdf/bph0163-0053.pdf>

Rabe, K. F., Martinez, F. J., Ferguson, G. T., Wang, C., Singh, D., Wedzicha, J. A., Trivedi, R., St Rose, E., Ballal, S., McLaren, J., Darken, P., Aurivillius, M., Reisner, C., & Dorinsky, P. (2020). Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *New England Journal of Medicine*, 383(1), 35-48. <https://doi.org/10.1056/NEJMoa1916046>

Raju, S. V., Solomon, G. M., Dransfield, M. T., & Rowe, S. M. (2016). Acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis and other diseases of mucus clearance. *Clinics in Chest Medicine*, 37(1), 147-158.

Ramos, F. L., Krahne, J. S., & Kim, V. (2014). Clinical issues of mucus accumulation in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 9, 139-150. <https://doi.org/10.2147/copd.S38938>

Ramos, M., Lamotte, M., Gerlier, L., Svargren, P., Miquel-Cases, A., & Haughney, J. (2019). Cost-effectiveness of physical activity in the management of COPD

patients in the UK. *International Journal of Chronic Obstructive Pulmonary Disease*, 14, 227-239. <https://doi.org/10.2147/copd.S181194>

- Ramsey, K. A., Chen, A. C. H., Radicioni, G., Lourie, R., Martin, M., Broomfield, A., Sheng, Y. H., Hasnain, S. Z., Radford-Smith, G., Simms, L. A., Burr, L., Thornton, D. J., Bowler, S. D., Livengood, S., Ceppe, A., Knowles, M. R., Noone, P. G., Sr., Donaldson, S. H., Hill, D. B.,...McGuckin, M. A. (2020). Airway Mucus Hyperconcentration in Non-Cystic Fibrosis Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, 201(6), 661-670. <https://doi.org/10.1164/rccm.201906-1219OC>
- Rebelo, P., Oliveira, A., Andrade, L., Valente, C., & Marques, A. (2020). Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Fatigue in Patients With COPD Following Pulmonary Rehabilitation. *CHEST*, 158(2), 550-561. <https://doi.org/10.1016/j.chest.2020.02.045>
- RespirTech. (n.d). *HFCWO*. Retrieved 29/07/2024 from <https://www.respirtech.com/conditions/cystic-fibrosis.html>
- Reynolds, D., & Kollef, M. (2021). The Epidemiology and Pathogenesis and Treatment of *Pseudomonas aeruginosa* Infections: An Update. *Drugs*, 81(18), 2117-2131. <https://doi.org/10.1007/s40265-021-01635-6>
- Riccelli, M. G., Goldoni, M., Poli, D., Mozzoni, P., Cavallo, D., & Corradi, M. (2020). Welding Fumes, a Risk Factor for Lung Diseases. *International Journal of Environmental Research and Public Health*, 17(7). <https://doi.org/10.3390/ijerph17072552>

- Ringshausen, F. C., de Roux, A., Diel, R., Hohmann, D., Welte, T., & Rademacher, J. (2015). Bronchiectasis in Germany: a population-based estimation of disease prevalence. *European Respiratory Journal*, 46(6), 1805-1807.
<https://doi.org/10.1183/13993003.00954-2015>
- Robinson, O. C. (2014). Sampling in Interview-Based Qualitative Research: A Theoretical and Practical Guide. *Qualitative Research In Psychology*, 11(1), 25-41. <https://doi.org/10.1080/14780887.2013.801543>
- Rodrigues, S. O., Cunha, C., Soares, G. M. V., Silva, P. L., Silva, A. R., & Gonçalves-de-Albuquerque, C. F. (2021). Mechanisms, Pathophysiology and Currently Proposed Treatments of Chronic Obstructive Pulmonary Disease. *Pharmaceuticals (Basel)*, 14(10).
<https://doi.org/10.3390/ph14100979>
- Rogers, G. B., Zain, N. M., Bruce, K. D., Burr, L. D., Chen, A. C., Rivett, D. W., McGuckin, M. A., & Serisier, D. J. (2014). A novel microbiota stratification system predicts future exacerbations in bronchiectasis. *Annals of the American Thoracic Society*, 11(4), 496-503.
<https://doi.org/10.1513/AnnalsATS.201310-335OC>
- Rovina, N., Koutsoukou, A., & Koulouris, N. G. (2013). Inflammation and immune response in COPD: where do we stand? *Mediators Inflamm*, 2013, 413735.
<https://doi.org/10.1155/2013/413735>
- Ryrsø, C. K., Godtfredsen, N. S., Kofod, L. M., Lavesen, M., Mogensen, L., Tobberup, R., Farver-Vestergaard, I., Callesen, H. E., Tendal, B., Lange, P.,

& Iepson, U. W. (2018). Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulmonary Medicine*, 18(1), 154.

<https://doi.org/10.1186/s12890-018-0718-1>

Sahardin, B. (2021). *Impact of Aerobika® Oscillating Positive Expiratory Pressure (OPEP) in Improving Small Airway Disease and COPD Assessment Test (CAT) Score in Chronic Obstructive Pulmonary Disease (COPD)*. FF-2021-175 UNIVERSITI KEBANGSAAN MALAYSIA].

Sahardin, S. N., Jailaini, M. F. M., Abeed, N. N. N., Ban, A. Y., Hau, N. B., Azmel, A. A., Shah, S. A., & Hamid, M. F. A. (2023). Impact of Aerobika(®) oscillating positive expiratory pressure in improving small airway resistance, lung function, symptoms and exercise capacity in chronic obstructive pulmonary disease. *Frontiers in medicine*, 10, 1202380.

<https://doi.org/10.3389/fmed.2023.1202380>

Sanderson, M. J., & Dirksen, E. R. (1986). Mechanosensitivity of cultured ciliated cells from the mammalian respiratory tract: implications for the regulation of mucociliary transport. *Proceedings of the National Academy of Sciences USA*, 83(19), 7302-7306. <https://doi.org/10.1073/pnas.83.19.7302>

Sanderson, M. J., & Dirksen, E. R. (1989). Mechanosensitive and beta-adrenergic control of the ciliary beat frequency of mammalian respiratory tract cells in culture. *American Review of Respiratory Disease*, 139(2), 432-440.

<https://doi.org/10.1164/ajrccm/139.2.432>

- Satir, P. (1999). The cilium as a biological nanomachine. *Faseb Journal*, 13 Suppl 2, S235-237. <https://doi.org/10.1096/fasebj.13.9002.s235>
- Satir, P., & Sleigh, M. A. (1990). The physiology of cilia and mucociliary interactions. *Annual review of physiology*, 52, 137-155. <https://doi.org/10.1146/annurev.ph.52.030190.001033>
- Schultz, K., Göhl, O., Stojanovic, D., Wittmann, M., Rudnik, J., & Schwarze, M. (2011). CAT (COPD assessment test) as outcome parameter of pulmonary rehabilitation (PR) in COPD. *European Respiratory Journal*, 38(Suppl 55), p3626.
- Scullion, J. E. (2007). The development of anticholinergics in the management of COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 2(1), 33-40. <https://doi.org/10.2147/copd.2007.2.1.33>
- Semwal, S., Mitra, S., & Singh, S. (2015). Autogenic Drainage Versus Acapella for Airway Clearance in Patients with Bronchiectasis: Randomized Crossover Trial. *International Journal of Health Sciences and Research*, 5, 323-327.
- Sen, D. (2014). Working with asbestos and the possible health risks. *Occupational Medicine*, 65(1), 6-14. <https://doi.org/10.1093/occmed/kqu175>
- Sethi, S. (2010). Infection as a comorbidity of COPD. *European Respiratory Journal*, 35(6), 1209-1215. <https://doi.org/10.1183/09031936.00081409>
- Shen, M., Li, Y., Xu, L., Shi, H., Ni, Y., Lin, H., & Li, F. (2021). Role of active cycle of breathing technique for patients with chronic obstructive pulmonary disease:

A pragmatic, randomized clinical trial. *International Journal of Nursing Studies*, 117, 103880.

Shimura, S., Andoh, Y., Haraguchi, M., & Shirato, K. (1996). Continuity of airway goblet cells and intraluminal mucus in the airways of patients with bronchial asthma. *European Respiratory Journal*, 9(7), 1395-1401.

<https://erj.ersjournals.com/content/erj/9/7/1395.full.pdf>

Shteinberg, M., Yaari, N., Stein, N., Bentur, L., Livnat, G., & Adir, Y. (2020). A randomized controlled trial of 4 weeks of airway clearance with oscillating positive end expiratory pressure device versus autogenic drainage in people with bronchiectasis. *European Respiratory Journal*, 56(suppl 64), 4103.

<https://doi.org/10.1183/13993003.congress-2020.4103>

Sibila, O., Suarez - Cuartin, G., Rodrigo - Troyano, A., Fardon, T. C., Finch, S., Mateus, E. F., Garcia - Bellmunt, L., Castillo, D., Vidal, S., & Sanchez - Reus, F. (2015). Secreted mucins and airway bacterial colonization in non - CF bronchiectasis. *Respirology*, 20(7), 1082-1088.

Singh, D., Papi, A., Corradi, M., Pavlišová, I., Montagna, I., Francisco, C., Cohuet, G., Vezzoli, S., Scuri, M., & Vestbo, J. (2016). Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet*, 388(10048), 963-973.

[https://doi.org/10.1016/s0140-6736\(16\)31354-x](https://doi.org/10.1016/s0140-6736(16)31354-x)

Singh, G., Acharya, S., Shukla, S., & Jain, D. (2023). Muco-Obstructive Lung Disease: A Systematic Review. *Cureus*, 15(10), e46866.

<https://doi.org/10.7759/cureus.46866>

Smith, B., Benedetti, A., Allen, N. B., Bertoni, A., Hilpert, M., Jr., D. R. J., Kaufman, J. D., Lin, C.-L., Michos, E. D., Oelsner, E., Watson, K. E., Hoffman, E. A., & Barr, R. G. (2018). Late Breaking Abstract - Dysanapsis is a major determinant of airflow limitation among older adults. *European Respiratory Journal*, 52(suppl 62), PA2265. <https://doi.org/10.1183/13993003.congress-2018.PA2265>

Smyth, A. R., Bell, S. C., Bojcin, S., Bryon, M., Duff, A., Flume, P., Kashirskaya, N., Munck, A., Ratjen, F., Schwarzenberg, S. J., Sermet-Gaudelus, I., Southern, K. W., Taccetti, G., Ullrich, G., Wolfe, S., & European Cystic Fibrosis, S. (2014). European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis*, 13 Suppl 1, S23-42. <https://doi.org/10.1016/j.jcf.2014.03.010> (ECFS Standards of Care for Cystic Fibrosis: The 2014 Edition)

Snell, N., Gibson, J., Jarrold, I., & Quint, J. K. (2019). Epidemiology of bronchiectasis in the UK: Findings from the British lung foundation's 'Respiratory health of the nation' project. *Respiratory Medicine*, 158, 21-23. <https://doi.org/10.1016/j.rmed.2019.09.012>

Sobala, R., & De Soyza, A. (2022). Bronchiectasis and chronic obstructive pulmonary disease overlap syndrome. *Clinics in Chest Medicine*, 43(1), 61-70.

Song, D., Cahn, D., & Duncan, G. A. (2020). Mucin Biopolymers and Their Barrier Function at Airway Surfaces. *Langmuir*, 36(43), 12773-12783.

<https://doi.org/10.1021/acs.langmuir.0c02410>

Spinou, A., Aliberti, S., Menendez, R., Blasi, F., Regis-Burgel, P., Ringshausen, F., De Soyza, A., Shteinberg, M., Shoemark, A., Vendrell, M., Polverino, E., Haworth, C., Dimakou, K., Loebinger, M. R., Torres, A., Welte, T., Elborn, S. J., Goeminne, P. C., Chalmers, J. D., & Herrero-Cortina, B. (2020). Airway clearance techniques in patients with bronchiectasis. Data from the EMBARC Registry. *European Respiratory Journal*, 56(suppl 64), 1263.

<https://doi.org/10.1183/13993003.congress-2020.1263>

Spinou, A., Hererro-Cortina, B., Aliberti, S., Goeminne, P. C., Polverino, E., Dimakou, K., Haworth, C. S., Loebinger, M. R., De Soyza, A., Vendrell, M., Burgel, P. R., McDonnell, M., Sutharsan, S., Skrgat, S., Maiz-Carro, L., Sibila, O., Stolz, D., Kauppi, P., Bossios, A.,...Ringshausen, F. C. (2024). Airway clearance management in people with bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). *European Respiratory Journal*. <https://doi.org/10.1183/13993003.01689-2023>

Spruit, M. A., Singh, S. J., Garvey, C., ZuWallack, R., Nici, L., Rochester, C., Hill, K., Holland, A. E., Lareau, S. C., Man, W. D., Pitta, F., Sewell, L., Raskin, J., Bourbeau, J., Crouch, R., Franssen, F. M., Casaburi, R., Vercoulen, J. H., Vogiatzis, I.,...Wouters, E. F. (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and*

Critical Care Medicine, 188(8), e13-64. <https://doi.org/10.1164/rccm.201309-1634ST>

- Squillacioti, G., Bellisario, V., Ghelli, F., Marcon, A., Marchetti, P., Corsico, A. G., Pirina, P., Maio, S., Stafoggia, M., Verlato, G., & Bono, R. (2024). Air pollution and oxidative stress in adults suffering from airway diseases. Insights from the Gene Environment Interactions in Respiratory Diseases (GEIRD) multi-case control study. *Science of The Total Environment*, 909, 168601. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2023.168601>
- Steele Gray, C., Ramachandran, M., Brinton, C., Forte, M., Loganathan, M., Walsh, R., Callaghan, J., Upshur, R., & Wiljer, D. (2024). Digitally mediated relationships: How social representation in technology influences the therapeutic relationship in primary care. *Social Science & Medicine*, 353, 116962. <https://doi.org/https://doi.org/10.1016/j.socscimed.2024.116962>
- Stolz, D., Mkorombindo, T., Schumann, D. M., Agusti, A., Ash, S. Y., Bafadhel, M., Bai, C., Chalmers, J. D., Criner, G. J., Dharmage, S. C., Franssen, F. M. E., Frey, U., Han, M., Hansel, N. N., Hawkins, N. M., Kalhan, R., Konigshoff, M., Ko, F. W., Parekh, T. M., ... Dransfield, M. T. (2022). Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet*, 400(10356), 921-972. [https://doi.org/10.1016/s0140-6736\(22\)01273-9](https://doi.org/10.1016/s0140-6736(22)01273-9)
- Stone, P. W., Hickman, K., Steiner, M. C., Roberts, C. M., Quint, J. K., & Singh, S. J. (2020). Predictors of referral to pulmonary rehabilitation from UK primary care. *International Journal of Chronic Obstructive Pulmonary Disease*, 2941-2952.

- Suggett, J. (2016). Review of Quality of Life Outcomes Following Use of an Oscillating Positive Expiratory Pressure (OPEP) Device for Chronic Obstructive Pulmonary Disease (COPD): 8 Weeks Field Study Using the COPD Assessment Test (CAT). In *D39. COPD: NON-PHARMACOLOGIC THERAPIES* (pp. A6888-A6888). https://doi.org/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A6888
- Suissa, S. (2019). Inhaled corticosteroids preventing pneumonia mortality: paradox or selection bias? *European Respiratory Journal*, 53(2). <https://doi.org/10.1183/13993003.02112-2018>
- Suissa, S. (2021). Perplexing mortality data from triple therapy trials in COPD. *The Lancet Respiratory Medicine*, 9(7), 684-685. [https://doi.org/10.1016/s2213-2600\(21\)00238-1](https://doi.org/10.1016/s2213-2600(21)00238-1)
- Suissa, S., Dell'Aniello, S., & Ernst, P. (2022a). Single-Inhaler Triple versus Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety. *International Journal of Chronic Obstructive Pulmonary Disease*, 17, 1975-1986. <https://doi.org/10.2147/copd.S378486>
- Suissa, S., Dell'Aniello, S., & Ernst, P. (2022b). Triple inhaler versus dual bronchodilator therapy in COPD: real-world effectiveness on mortality. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, 19(1), 1-9.
- Svenningsen, S., & Nair, P. (2022). Persistent Airway Plugs: A Call for Clinical Recognition and Novel Therapies. *American Journal of Respiratory and*

Critical Care Medicine, 205(9), 977-978.

<https://doi.org/10.1164/rccm.202201-0147ED>

Svenningsen, S., Paulin, G. A., Sheikh, K., Guo, F., Hasany, A., Kirby, M., Rezai, R. E., McCormack, D. G., & Parraga, G. (2016). Oscillatory Positive Expiratory Pressure in Chronic Obstructive Pulmonary Disease. *COPD*, 13(1), 66-74.

<https://doi.org/10.3109/15412555.2015.1043523>

Tan, H.-L., Regamey, N., Brown, S., Bush, A., Lloyd, C. M., & Davies, J. C. (2011). The Th17 pathway in cystic fibrosis lung disease. *American Journal of Respiratory and Critical Care Medicine*, 184(2), 252-258.

Tang, J. X., Wen, Q., Bennett, A., Kim, B., Sheils, C. A., Bucki, R., & Janmey, P. A. (2005). Anionic poly(amino acid)s dissolve F-actin and DNA bundles, enhance DNase activity, and reduce the viscosity of cystic fibrosis sputum. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 289(4), L599-605. <https://doi.org/10.1152/ajplung.00061.2005>

Tashkin, D. P., Celli, B., Senn, S., Burkhart, D., Kesten, S., Menjoge, S., & Decramer, M. (2008). A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *New England Journal of Medicine*, 359(15), 1543-1554.

<https://doi.org/10.1056/NEJMoa0805800>

Terry, P. B., & Traystman, R. J. (2016). The Clinical Significance of Collateral Ventilation. *Annals of the American Thoracic Society*, 13(12), 2251-2257.

<https://doi.org/10.1513/AnnalsATS.201606-448FR>

- Thanh, N. X., Jacobs, P., Suggett, J., McIvor, A., & Kaplan, A. (2019, 2019/01/10/). *Cost-Effectiveness of the Aerobika® Oscillating Positive Expiratory Pressure Device in the Management of Chronic Obstructive Pulmonary Disease Exacerbations in Canada*.
<https://www.hindawi.com/journals/crj/2019/9176504/>
- Thi, M. T. T., Wibowo, D., & Rehm, B. H. A. (2020). *Pseudomonas aeruginosa Biofilms*. *International Journal of Molecular Sciences*, 21(22).
<https://doi.org/10.3390/ijms21228671>
- Thornton, C. S., & Parkins, M. D. (2023). Microbial Epidemiology of the Cystic Fibrosis Airways: Past, Present, and Future. *Seminars in Respiratory and Critical Care Medicine*, 44(02), 269-286. <https://doi.org/10.1055/s-0042-1758732>
- Thornton, D. J., Rousseau, K., & McGuckin, M. A. (2008). Structure and function of the polymeric mucins in airways mucus. *Annual review of physiology*, 70, 459-486. <https://doi.org/10.1146/annurev.physiol.70.113006.100702>
- Tindall, L. (2009). J.A. Smith, P. Flower and M. Larkin (2009), Interpretative Phenomenological Analysis: Theory, Method and Research. *Qualitative Research In Psychology*, 6(4), 346-347.
<https://doi.org/10.1080/14780880903340091>
- Toumpanakis, D., & Usmani, O. S. (2023). Small airways disease in patients with alpha-1 antitrypsin deficiency. *Respiratory Medicine*, 211, 107222.
<https://doi.org/10.1016/j.rmed.2023.107222>

- Tran, B., Rafinejad-Farahani, B., Moodie, S., O'Hagan, R., & Glista, D. (2021). A Scoping Review of Virtual Focus Group Methods Used in Rehabilitation Sciences. *International Journal of Qualitative Methods*, 20, 16094069211042227. <https://doi.org/10.1177/16094069211042227>
- Trudell Medical International. (2021, June 28). *Aerobika Easy to follow instructions* [Video]. YouTube. <https://www.youtube.com/watch?v=PzwNDnre6Ng&t=66s>
- Tse, J., Wada, K., Wang, Y., Coppolo, D., Kushnarev, V., & Suggett, J. (2020). Impact of Oscillating Positive Expiratory Pressure Device Use on Post-Discharge Hospitalizations: A Retrospective Cohort Study Comparing Patients with COPD or Chronic Bronchitis Using the Aerobika® and Acapella® Devices. *International Journal of Chronic Obstructive Pulmonary Disease*, 15, 2527-2538. <https://www.dovepress.com/getfile.php?fileID=62662>
- Turner, R. D., & Birring, S. S. (2023). Measuring cough: what really matters? *Journal of Thoracic Disease*, 15(4), 2288-2299. <https://doi.org/10.21037/jtd-23-230>
- Üzmezoğlu, B., Altıay, G., Özdemir, L., Tuna, H., & Süt, N. (2018). The Efficacy of Flutter(®) and Active Cycle of Breathing Techniques in Patients with Bronchiectasis: A Prospective, Randomized, Comparative Study. *Turkish Thoracic Journal*, 19(3), 103-109. <https://doi.org/10.5152/TurkThoracJ.2018.17050>
- Van Allen, C., Lindskog, G., & Richter, H. (1931). Collateral respiration. Transfer of air collaterally between pulmonary lobules. *The Journal of Clinical*

Investigation, 10(3), 559-590.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC435770/pdf/jcinvest00718-0133.pdf>

Van Fleet, H., Dunn, D. K., McNinch, N. L., & Volsko, T. A. (2017). Evaluation of Functional Characteristics of 4 Oscillatory Positive Pressure Devices in a Simulated Cystic Fibrosis Model. *Respiratory Care*, 62(4), 451-458.

<https://doi.org/10.4187/respcare.04570>

Vincken, W., van Noord, J. A., Greefhorst, A. P., Bantje, T. A., Kesten, S., Korducki, L., Cornelissen, P. J., & Dutch/Belgian Tiotropium Study, G. (2002). Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *European Respiratory Journal*, 19(2), 209-216.

<https://doi.org/10.1183/09031936.02.00238702>

Walker, H. K., Hall, W. D., & Hurst, J. W. (1990). Clinical methods: the history, physical, and laboratory examinations.

Walters, J. A., Tang, J. N., Poole, P., & Wood-Baker, R. (2017). Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, 1(1), Cd001390.

<https://doi.org/10.1002/14651858.CD001390.pub4>

Wang, J. B., Olgin, J. E., Nah, G., Vittinghoff, E., Cataldo, J. K., Pletcher, M. J., & Marcus, G. M. (2018). Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One*, 13(7), e0198681. <https://doi.org/10.1371/journal.pone.0198681>

Wang, Y., Xu, J., Meng, Y., Adcock, I. M., & Yao, X. (2018). Role of inflammatory cells in airway remodeling in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 13, 3341-3348.

<https://doi.org/10.2147/copd.S176122>

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*, 30(6), 473-483.

Warszawska, J. M., Gawish, R., Sharif, O., Sigel, S., Doninger, B., Lakovits, K., Mesteri, I., Nairz, M., Boon, L., & Spiel, A. (2013). Lipocalin 2 deactivates macrophages and worsens pneumococcal pneumonia outcomes. *The Journal of Clinical Investigation*, 123(8), 3363-3372.

<https://dm5migu4zj3pb.cloudfront.net/manuscripts/67000/67911/JCI67911.v2.pdf>

Wedzicha, J. A. (2015). Mechanisms of Chronic Obstructive Pulmonary Disease Exacerbations. *Annals of the American Thoracic Society*, 12(Supplement 2), S157-S159. <https://doi.org/10.1513/AnnalsATS.201507-427AW>

Wedzicha, J. A., Brill, S. E., Allinson, J. P., & Donaldson, G. C. (2013). Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. *BMC Medicine*, 11(1), 181. <https://doi.org/10.1186/1741-7015-11-181>

Whittaker, H. R., Torkpour, A., & Quint, J. (2024). Eligibility of patients with chronic obstructive pulmonary disease for inclusion in randomised control trials

investigating triple therapy: a study using routinely collected data.

Respiratory Research, 25(1), 43. [https://doi.org/10.1186/s12931-024-02672-](https://doi.org/10.1186/s12931-024-02672-x)

[x](#)

WHO. (2023, 16/03/2023). *Chronic obstructive pulmonary disease (COPD)*. World

Health Organization [WHO]. Retrieved 29/6/2023 from

[https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))

Widdicombe, J. H., & Wine, J. J. (2015). Airway gland structure and function.

Physiological Reviews, 95(4), 1241-1319.

Williams, D. M. (2018). Clinical Pharmacology of Corticosteroids. *Respiratory Care*,

63(6), 655-670. <https://doi.org/10.4187/respcare.06314>

Williams, P. J., Cumella, A., Philip, K. E. J., Lavery, A. A., & Hopkinson, N. S.

(2022). Smoking and socioeconomic factors linked to acute exacerbations of

COPD: analysis from an Asthma + Lung UK survey. *BMJ Open Respiratory*

Research, 9(1), e001290. <https://doi.org/10.1136/bmjresp-2022-001290>

Wilson, S. R., Strub, P., Buist, A. S., Knowles, S. B., Lavori, P. W., Lapidus, J., &

Vollmer, W. M. (2010). Shared treatment decision making improves

adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care*

Med, 181(6), 566-577. <https://doi.org/10.1164/rccm.200906-0907OC>

Wing, K., Williamson, E., Carpenter, J. R., Wise, L., Schneeweiss, S., Smeeth, L.,

Quint, J. K., & Douglas, I. (2018). Real-world effects of medications for

chronic obstructive pulmonary disease: protocol for a UK population-based

- non-interventional cohort study with validation against randomised trial results. *BMJ Open*, 8(3), e019475. <https://doi.org/10.1136/bmjopen-2017-019475>
- Wise, J. (2019). COPD: spirometry does not occur in 60% of admissions, audit shows. *Bmj*, 365, l2141. <https://doi.org/10.1136/bmj.l2141>
- Wong, C., Sullivan, C., & Jayaram, L. (2018). ELTGOL airway clearance in bronchiectasis: laying the bricks of evidence. *European Respiratory Journal*, 51(1), 1702232. <https://doi.org/10.1183/13993003.02232-2017>
- World-Medical-Association. (2013). World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA*, 310(20), 2191-2194. <https://doi.org/10.1001/jama.2013.281053>
- Wouters, E. F. M., Wouters, B. B. R. E. F., Augustin, I. M. L., Houben-Wilke, S., Vanfleteren, L. E. G. W., & Franssen, F. M. E. (2018). Personalised pulmonary rehabilitation in COPD. *European Respiratory Review*, 27(147), 170125. <https://doi.org/10.1183/16000617.0125-2017>
- Wu, Y.-K., Su, W.-L., Yang, M.-C., Chen, S.-Y., Wu, C.-W., & Lan, C.-C. (2021). Characterization Associated with the Frequent Severe Exacerbator Phenotype in COPD Patients. *International Journal of Chronic Obstructive Pulmonary Disease*, 16(null), 2475-2485. <https://doi.org/10.2147/COPD.S317177>
- Yamasaki, K., & Eeden, S. F. v. (2018). Lung Macrophage Phenotypes and Functional Responses: Role in the Pathogenesis of COPD. *International*

Journal of Molecular Sciences, 19(2), 582. <https://www.mdpi.com/1422-0067/19/2/582>

Yang, G. J., McDonald CF, McDonald V, Ordman R, Goodwin A, Smith B, McNamara R, Zwar N, Dabscheck E. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023. Version 2.73, December 2023. (2023). The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023. (Version 2.73).

<https://copdx.org.au/copd-x-plan/>

Yang, I. A., Clarke, M. S., Sim, E. H., & Fong, K. M. (2012). Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(7).

Young, R. L., Malcolm, K. C., Kret, J. E., Caceres, S. M., Poch, K. R., Nichols, D. P., Taylor-Cousar, J. L., Saavedra, M. T., Randell, S. H., & Vasil, M. L. (2011). Neutrophil extracellular trap (NET)-mediated killing of *Pseudomonas aeruginosa*: evidence of acquired resistance within the CF airway, independent of CFTR. *PLoS One*, 6(9), e23637.

Yousuf, A., McAuley, H., Elneima, O., & Brightling, C. E. (2021). The different phenotypes of COPD. *British Medical Bulletin*, 137(1), 82-97.

<https://doi.org/10.1093/bmb/ldaa043>

Yuan, S., Hollinger, M., Lachowicz-Scroggins, M. E., Kerr, S. C., Dunican, E. M., Daniel, B. M., Ghosh, S., Erzurum, S. C., Willard, B., & Hazen, S. L. (2015).

Oxidation increases mucin polymer cross-links to stiffen airway mucus gels.

Science translational medicine, 7(276), 276ra227-276ra227.

Zahm, J., de Bentzmann, S. G., Deneuville, E., Perrot-Minnot, C., Dabadie, A., Pennaforte, F., Roussey, M., Shak, S., & Puchelle, E. (1995). Dose-dependent in vitro effect of recombinant human DNase on rheological and transport properties of cystic fibrosis respiratory mucus. *European Respiratory Journal*, 8(3), 381-386.

Zanini, A., Aiello, M., Adamo, D., Cherubino, F., Zampogna, E., Sotgiu, G., Chetta, A., & Spanevello, A. (2015). Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of efficacy. *Respiration*, 89(6), 525-533.

Zhang, Y., Zheng, S. P., Hou, Y. F., Jie, X. Y., Wang, D., Da, H. J., Li, H. X., He, J., Zhao, H. Y., Liu, J. H., Ma, Y., Qiang, Z. H., Li, W., Zhang, M., Shan, H., Wu, Y. Y., Shi, H. Y., Zeng, L., Sun, X., & Liu, Y. (2023). A predictive model for frequent exacerbator phenotype of acute exacerbations of chronic obstructive pulmonary disease. *Journal of Thoracic Disease*, 15(12), 6502-6514. <https://doi.org/10.21037/jtd-23-931>

Zisi, D., Chryssanthopoulos, C., Nanas, S., & Philippou, A. (2022). The effectiveness of the active cycle of breathing technique in patients with chronic respiratory diseases: A systematic review. *Heart & Lung*, 53, 89-98.