Comparison of respiratory pathogen colonization and antimicrobial susceptibility in people with cystic fibrosis versus non cystic fibrosis bronchiectasis: A systematic review

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Protocol

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Abstract

Background

Both cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis are characterized by permanent bronchial dilation, leading to impaired mucociliary clearance and development of chronic infections. Although the core airway microbiota in both CF and non-CF bronchiectasis may be similar, particular satellite microbes are associated with specific conditions. Moreover, there are several factors, which may be responsible for the disparity in antibiotic susceptibility profile between the CF and non-CF populations. Hence comparing the microbiota and antibiotic susceptibility pattern in CF bronchiectasis with non-CF bronchiectasis would aid in improved management of both the conditions.

Methods

Two authors will independently search the electronic databases PubMed and EMBASE for studies reporting bacterial colonization of the respiratory tract determined by examination of any respiratory tract specimen, by conventional bacterial culture or specialized techniques; and/or antimicrobial susceptibility testing in adults and children diagnosed with bronchiectasis in either CF subjects or non-CF subjects. The authors will independently assess the risk of bias for each included study using the Newcastle Ottawa Scale (NOS). We will present the data with descriptive statistics and provide pooled estimates of outcome parameters, wherever it is feasible to perform meta-analysis using a random effects model. Heterogeneity in studies will be explored by visual inspection of forest plot as well as using the Higgins and Thompson I^2 method. We will contact the corresponding authors of studies where data is/are missing and try to obtain the missing data.

Discussion

To date, there are no locally applicable evidence-based guidelines for antimicrobial treatment of non-CF bronchiectasis patients. In general, treatment in non-CF bronchiectasis is based on extrapolation of clinical trials done in subjects with CF bronchiectasis. An insight into the microbiota and antimicrobial susceptibility patterns against specific organisms in both the conditions would facilitate appropriate rather than empiric therapy, and hopefully reduce the burden of antimicrobial resistance created by rampant usage of antibiotics. Therefore, this systematic review is being undertaken to compare the respiratory tract colonization and antibacterial susceptibility pattern in people with cystic fibrosis versus non-cystic fibrosis bronchiectasis.

Systematic review registration:

The protocol was submitted for publication in PROSPERO on June 26, 2020 (PROSPERO ID: 193859).

Background

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene, which regulates the activity of sodium and chloride channels across the epithelial cells, thereby facilitating appropriate hydration of mucins and effective mucociliary clearance in various organs of the body (1). Impaired secretion of chloride and bicarbonate ions due to CFTR mutation leads to the formation of mucus, which is too thick to be cleared (2). This predisposes CF patients to pulmonary bacterial infections caused by *Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae* or *Burkholderia cepacia* complex (Bcc) (3). The inflammatory response of the body to these recurrent infections eventually leads to bronchiectasis, characterized by permanent bronchial dilation, leading to impaired mucociliary clearance allowing bacterial adherence, increased bacterial load and the development of chronic infection. The bacteria gradually adapt to these conditions by forming biofilms, which ensures protection from phagocytic attack as well as antibiotics (4).

Besides CF, bronchiectasis is associated with various other conditions such as immunodeficiency disorders, autoimmune diseases, ciliary abnormalities, connective tissue diseases, airway injury, malignancy, inflammatory bowel disease, alpha-1 antitrypsin deficiency or hypersensitivity (allergic bronchopulmonary aspergillosis). These are collectively termed as non-CF bronchiectasis (5).

There are many similarities between CF and non-CF bronchiectasis. Both are associated with exacerbations and severe inflammation, progress to complications, are associated with impaired mucociliary function leading to mucus obstruction and reduced lung function, predispose to microbial infections, and can cause permanent damage (6, 7). However, there are also many differences between the two. These include the differences in the etiology, age, and lung predominance. Bronchiectasis in CF patients is associated with mutations in the CFTR gene while non-CF bronchiectasis is associated with various underlying conditions like immunodeficiency disorders, ciliary dyskinesis or demonstrates post-infectious etiology. Non-CF bronchiectasis affects mainly older population (age > 60 years) unlike CF patients, which is a genetic disorder thereby manifesting in both children and adults. Furthermore, non-CF bronchiectasis is associated with lower lung lobe predominance as compared to upper lung lobe predominance in CF (7).

Although the core airway microbiota is similar in both CF and non-CF bronchiectasis, particular satellite microbes are associated with specific conditions. Sputum is the preferred specimen for culturing the bacterial organisms, and is also tested for acid-fast bacilli in case of non-CF bronchiectasis (5). However, bronchioalveolar lavage (BAL) is reserved for patients who are unable to produce sputum or whose CT (computed tomography) scan indicates microbial infection but sputum culture is negative. In case of CF bronchiectasis, culture of sputum or BAL or epithelial lining fluid (ELF) guides the antimicrobial therapy. *Staphylococcus aureus*, *Pseudomonas aeruginosa, Burkholderia cepacia* complex, *Haemophilus influenzae*, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* are commonly associated with CF bronchiectasis (8) while *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella*

catarrhalis, *or non-tuburculous mycobacteria* (NTM) are the predominant bacterial species associated with non-CF bronchiectasis (5, 9). Gram-positive bacteria including *Streptococcus pneumoniae* and *Staphylococcus aureus* are rarely associated with non-CF bronchiectasis unlike CF bronchiectasis (10). Interestingly, the core microbiota in both the conditions is similar in childhood and eventually diverges by adulthood (6, 11).

Antibiotics are the mainstay of treatment of bronchiectasis in both CF and non-CF patients, the choice of which is based on the understanding of the predominant respiratory tract colonizers as well as the results of local antimicrobial susceptibility testing (AST). The use of antibiotics is associated with substantially less devastating pulmonary disease in these patients, thereby improving their survival (12).

AST is used to predict the success or failure of an antibiotic by sorting out the resistant bacteria from the susceptible ones on the basis of Minimal Inhibitory Concentration (MIC) breakpoints, which are determined by breakpoint committees like European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical & Laboratory Standards Institute (CLSI). However, the epidemiological cut-off is determined using the susceptibility data from the wild-type population and does not take into consideration any mutant strains (13), which are commonly encountered for the bacteria to survive in the mucus obstructed airways of the CF patients and to combat the antibiotic treatment, which is often given for longer duration in CF patients and at doses higher than those in non-CF patients (14). So clinicians cannot rely only on such data for prescribing empirical therapy to the CF patients. Besides this there are several other factors, which may be responsible for the disparity in antibiotic susceptibility profile between the CF and non-CF populations. For instance, in response to the oxygen or nutrient deficit conditions in CF lungs, the bacteria adapt by slowing down their growth rate or by altering their metabolism (4), which fosters resistance to several antibiotics among these microorganisms (e.g. the cell-wall acting antibiotics might not be effective in eradicating such bacteria, which are not actively dividing or are growing slowly) or the bacteria form biofilms, which likewise is responsible for antibiotic resistance (15). In addition to this, different colonial types of bacteria such as small colony variants (SCVs) are observed in the respiratory samples of the CF patients (16)(17), which are often missed in the routine laboratory testing. A single sample from CF patients may contain a mixed population of the same organism with varied antibiotic susceptibility profile thereby requiring utmost caution while culturing the microorganisms and testing for antibiotic susceptibility (18).

Therefore, a detailed insight into the comparison of respiratory pathogen colonization in both the conditions would pave way for improved management strategies of bronchiectasis in both the CF and non-CF populations.

Study Aim and Objectives

This systematic review aims to compare the microbiota and antimicrobial susceptibility profile in CF and non-CF bronchiectasis. We propose to undertake a systematic review of literature to address the following research questions:

1. What are the bacteria colonizing the respiratory tract in patients with cystic fibrosis bronchiectasis compared to non cystic fibrosis bronchiectasis?
2. How does the antibiotic susceptibility profile of specific bacteria, differ between CF bronchiectasis and non-CF bronchiectasis patients?

Methods/design

Types of studies

The data required for this review could be available in Observational studies including cohort studies or case-control studies (case arm), one or other arm of controlled clinical trials (randomized or non-randomized) or case series.

Types of participants

Adults and children diagnosed with bronchiectasis in either CF subjects or non-CF subjects.

Inclusion criteria

Studies reporting bacterial colonization of the respiratory tract (upper or lower) determined by examination of any respiratory tract specimen, by conventional bacterial culture or specialized techniques; and/or antimicrobial susceptibility testing by any method.

Exclusion criteria

We will exclude the below mentioned studies:

1. Those in which include patients with CF or non-CF, but patients do not have bronchiectasis.
2. Those in which data of patients with and without bronchiectasis cannot be distinguished.
3. Those in which the underlying cause(s) of bronchiectasis cannot be distinguished as CF or non-CF
4. Those in which non-standard culture methods were used to identify organisms.
5. Those wherein multiple clinical conditions have been studied, and it is not possible to separately analyze the data for CF and non-CF or retrospective microbiology studies wherein the underlying clinical condition(s) are not specified.
6. Case series with less than 10 participants.
7. Studies conducted in animals or animal models or studies wherein already identified organisms were evaluated further for genotypic or phenotypic characteristics will be excluded.

Comparisons considered in this review

1. Clinical or microbiological studies of any design (observational, controlled clinical trials or case series), reporting bacterial colonization of the respiratory tract (from any type of biological specimen), and/or antimicrobial susceptibility in both types of patients *i.e.* CF and non-CF. Such studies will be considered direct comparisons.
2. Clinical or microbiological studies of any design (observational, controlled clinical trials or case series), reporting bacterial colonization of the respiratory tract, and/or antimicrobial susceptibility in either CF or non-CF patients, if they are within a three-year period. Such studies will be considered indirect comparisons.
3. Clinical or microbiological studies of any design (observational, controlled clinical trials or case series), reporting bacterial colonization of the respiratory tract, and/or antimicrobial susceptibility in either CF or non-CF patients, within any time period, if they are from the same institution. Such studies will also be considered indirect comparisons.

Types of outcome measures

1. List of bacteria identified in the respiratory tract in patients with CF versus non-CF bronchiectasis.
2. Relative proportion of various bacterial species identified in the respiratory tract in patients with CF versus non-CF bronchiectasis.
3. Number of bacterial species identified per patient with CF versus non-CF bronchiectasis.
4. Proportion of specific bacterial species susceptible to specific antimicrobial agents.
5. Proportion of specific bacterial species resistant to specific antimicrobial agents.
6. Proportion of specific bacterial species with intermediate susceptibility to specific antimicrobial agents.
7. Time-trend of antimicrobial sensitivity patterns in 10-year epochs.

Search methods for identification of studies

Two authors will independently search the electronic database PubMed and EMBASE using search MeSH terms for the below mentioned keywords:

1. Bronchiectasis AND Cystic fibrosis AND non-cystic fibrosis AND (antibiotic OR antimicrobial) AND (susceptibility OR sensitivity OR resistance)
2. Cystic fibrosis AND bronchiectasis AND (antibiotic OR antimicrobial) AND (susceptibility OR sensitivity OR resistance)
3. Non-cystic fibrosis AND bronchiectasis AND (antibiotic OR antimicrobial) AND (susceptibility OR sensitivity OR resistance)
4. Pulmonary exacerbation AND (antibiotic OR antimicrobial) AND (susceptibility OR sensitivity OR resistance)
5. Bronchiectasis AND Cystic fibrosis AND non-cystic fibrosis AND (microbiota OR pathogens OR colonizers OR bacteria OR microbiology)
6. Cystic fibrosis AND bronchiectasis AND (microbiota OR pathogens OR colonizers OR bacteria OR microbiology)
7. Non-cystic fibrosis AND bronchiectasis AND (microbiota OR pathogens OR colonizers OR bacteria OR microbiology)

Data collection and analysis

Studies will be screened by study titles and abstracts. Those identified as potentially relevant will be retrieved and full text examined. The studies will be evaluated for eligibility to be included in the review. Manual search of the reference lists of the retrieved studies will also be performed. In case of disagreements/ discrepancies, the senior author will do arbitration.

Data extraction and management

A special data extraction form will be prepared, for the following data. Data will be independently extracted by two reviewers, and analyzed by the joint team.

From each included study, information regarding the following will be extracted: Identification data (Author, year), study design, institution, country or countries, time-period of study, whether clinical or microbiological analysis, inclusion criteria of patients (CF and non-CF), age of patients, clinical state of patients (stable, acute exacerbation, surveillance culture etc.), underlying clinical condition, duration of illness if known, presence of co-morbidity, specimen tested, specimen collection method, whether already on antibiotics, microorganisms identified, bacteriological method used for identification (culture, biochemical tests, MALDI-TOF, PCR, other), quantification if any, biofilm formation, antibiotic therapy, antimicrobial susceptibility profile, method of testing antimicrobial susceptibility, definition of sensitivity, and clinical/bacteriological outcome (Tables 1 and 2).

Table 1
Respiratory pathogen colonization in people with cystic fibrosis versus non cystic fibrosis bronchiectasis

Data extracted by		
Reference	Author & year	
	Citation	
	Country/Countries	
	Institution/s	
Study design		
Clinical/ Microbiology study		
• Observational study		
• Clinical trial		
• Case series with ≥ 10 cases		
• Case series with ≤ 9 case		
Time period		
Participants	• CF bronchiectasis	
	• Non-CF bronchiectasis	
	• Mixed	
	• Other	
Study group (CF bronchiectasis)	No.	
	Age	
	• Adults ≥ 18 years	
	• Children < 18 years	
	• Mixed (not possible to separate)	
	Sex	
	Respiratory pathogens	**no. (%)**
	Staphylococcus aureus (MSSA)	
	Staphylococcus aureus (MRSA)	
	Pseudomonas aeruginosa	
	Burkholderia cepacia complex	
	Haemophilus influenzae	
	Stenotrophomonas maltophilia	
	Achromobacter xylosoxidans	
	NTM	
	Streptococcus	
	Veillonella	
	Prevotella	
	Others	
	Inclusion/Exclusion criteria	
	Sample type (sputum/BAL/ELF)	
	Upper respiratory specimen	
	• Nasal specimen	
	• Nasopharyngeal specimen	
	• Oropharyngeal specimen	
	• Other	

Data extracted by	
	Lower respiratory specimen
	• Sputum
	• Induced sputum
	• BAL
	• Lung aspirate
	• Other
	Antibiotic therapy
	• Already on antibiotic(s)
	• Not on antibiotic(s)
	• Unclear
	Method of identifying species
	• Culture
	• PCR
	• Other
	Antimicrobial resistance
	Yes/No
Comparison group (non-CF bronchiectasis)	No.
	Age
	Adults ≥ 18 years
	Children < 18 years
	Mixed (not possible to separate)
	Sex
	Respiratory pathogens **no. (%)**
	Haemophilus influenzae
	Pseudomonas aeruginosa
	Moraxella catarrhalis
	NTM
	Staphylococcus aureus
	Streptococcus
	Veillonella
	Prevotella
	Others
	Inclusion/Exclusion criteria
	Sample type (sputum/BAL/ELF)
	Upper respiratory specimen
	• Nasal specimen
	• Nasopharyngeal specimen
	• Oropharyngeal specimen
	• Other
	Lower respiratory specimen
	• Sputum
	• Induced sputum

Data extracted by	
	• BAL
	• Lung aspirate
	• Other
	Antibiotic therapy
	• Already on antibiotic(s)
	• Not on antibiotic(s)
	• Unclear
	Method of identifying species
	• Culture
	• PCR
	• Other
	Clinical state
	• Acute pulmonary exacerbation
	• Surveillance culture
	Antimicrobial resistance
	Yes/No
Remarks	

Table 2
Antibiotic susceptibility profile in people with cystic fibrosis versus non cystic fibrosis bronchiectasis

Data extracted by								
Reference	Author & year							
	Citation							
	Country/Countries							
	Institution/s							
Study design								
	Clinical/ Microbiology study							
	Observational study							
	Clinical trial							
	Case series with > 10 cases							
	Case series with < 9 case							
Time period								
Participants	• CF bronchiectasis							
	• Non CF bronchiectasis							
	• Mixed							
	• Other							
Study group (CF bronchiectasis)	No.							
	Age							
	• Adults > 18 years							
	• Children < 18 years							
	• Mixed (not possible to separate)							
	Sex							
	AST method							
	• AST definition							
	• Ability to detect mutants							
	• Advantages							
	• Disadvantages							
	Antibiotic susceptibility (S/I/R; MIC)							
Microorganism		Tobramycin	Azythromycin	Carbenicillin	Ceftazidime	Gentamycin	Chloramphenicol	Ciprofloxacin
Staphylococcus aureus (MSSA)								
Staphylococcus aureus (MRSA)								
Pseudomonas aeruginosa								
Burkholderia cepacia complex								
Haemophilus influenzae								
Stenotrophomonas maltophilia								
Achromobacter xylosoxidans								
NTM								
Streptococcus								
Veillonella								
Others								
Inclusion/Exclusion criteria								

Data extracted by								
Upper respiratory specimen								
	Nasal specimen							
	Nasopharyngeal specimen							
	Oropharyngeal specimen							
	Other							
Lower respiratory specimen								
	Sputum							
	Induced sputum							
	BAL							
	Lung aspirate							
	Other							
Antibiotic therapy								
	Already on antibiotic(s)							
	Not on antibiotic(s)							
	Unclear							
Method of identifying species								
	Culture							
	PCR							
	Other							
Biofilm detection								
Antimicrobial resistance (Yes/No)								
Remarks								
Comparison group (non-CF bronchiectasis)	No.							
	Age							
	• Adults > 18 years							
	• Children < 18 years							
	• Mixed (not possible to separate)							
	Sex							
	AST method							
	• AST definition							
	• Ability to detect mutants							
	• Advantages							
	• Disadvantages							
	Antibiotic susceptibility (S/I/R; MIC)							
Microorganism	Piperacillin-tazobactam	Amoxycillin	Clarithromycin	Ciprofloxacin	Ceftazidime	Cefuroxime	Cefotaxime	Flucloxacillin
Haemophilus influenzae								
Pseudomonas aeruginosa								
Moraxella catarrhalis								

Data extracted by
NTM
Staphylococcus aureus
Streptococcus
Veillonella
Prevotella
Others
Inclusion/Exclusion criteria
Upper respiratory specimen
Nasal specimen
Nasopharyngeal specimen
Oropharyngeal specimen
Other
Lower respiratory specimen
Sputum
Induced sputum
BAL
Lung aspirate
Other
Antibiotic therapy
Already on antibiotic(s)
Not on antibiotic(s)
Unclear
Method of identifying species
Culture
PCR
Other
Biofilm detection
Antimicrobial resistance (Yes/No)
Remarks

Assessment of risk of bias in included studies

The authors will independently assess the risk of bias for each included trial using the Newcastle Ottawa Scale (NOS) (19). NOS is used to assess the quality of non-randomised studies including case-control and cohort studies to be used in a systematic review. The NOS contains eight items, categorized into three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. For each item a series of response options is provided. A star system is used to allow a semi-quantitative assessment of study quality. A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability. High-quality studies will be defined as a score 6 or more of 9 total points (20).

Statistical analysis

We will present the data with descriptive statistics and provide pooled estimates of outcome parameters, wherever it is feasible to perform meta-analysis using a random effects model. Pooled estimates will be presented with a 95% confidence interval.

Dealing with missing data

We will contact the corresponding authors of studies where data is/are missing and try to obtain the missing data. If this fails, we will try and impute data where possible. If that is not feasible, we will state as such.

Assessment of heterogeneity

Heterogeneity in studies will be explored by visual inspection of forest plot as well as using the Higgins and Thompson I^2 method (21). The I^2 heterogeneity will be categorized as follows: 0–50% low, 50–75% moderate, and > 75% considerable heterogeneity.

Assessment of reporting biases

Wherever possible, we will obtain the original trial protocols for comparison with the published papers to ensure that all outcomes are reported. If it is not possible to obtain the trial protocols, we will scrutinize the 'Methods' section of the published paper(s) to ensure full reporting of all measured variables. If negative data are not fully reported, we will contact the primary investigators for these data. If these are sufficient, we will explore these for reporting bias using a funnel plot. We will also assess publication bias by looking for evidence of conference presentations not followed by subsequent journal publications.

Subgroup analysis and investigation of heterogeneity

We will analyze results separately by the following characteristics:

1. Age group of patients: Children (< 18 years) versus adults (≥ 18 years)
2. Already on antibiotics versus not on antibiotics
3. Clinical state viz acute pulmonary exacerbation versus surveillance culture.
4. Type of respiratory specimen (upper versus lower respiratory specimen)
5. Method used for identification of bacterial species (culture versus non-culture methods)

Selectivity analysis

We will explore the impact of study quality by examining the difference(s) in pooled estimates of the outcomes by comparing the overall result with the pooled estimates when only high quality studies are combined.

Summary of findings table

We will present two summary of findings tables; one comparing respiratory pathogen colonization in those with CF vs. non-CF bronchiectasis (Table 1), and the other comparing antimicrobial susceptibility patterns of individual bacterial species in CF versus non-CF bronchiectasis (Table 2).

Discussion

To date, there are no locally applicable evidence-based guidelines for antimicrobial treatment of non-CF bronchiectasis patients. In general, treatment in non-CF bronchiectasis is based on extrapolation of clinical trials done in subjects with CF bronchiectasis (22, 23). Hence comparing the antibiotic susceptibility pattern in CF bronchiectasis with non-CF bronchiectasis would aid in improved management of both the conditions. Furthermore, the understanding of the microbiota in both CF and non-CF population would aid in more personalized treatment approaches. Understanding the antimicrobial susceptibility patterns against specific organisms, can facilitate appropriate rather than empiric therapy, and hopefully reduce the burden of antimicrobial resistance created by rampant usage of antibiotics.

Abbreviations

CF	Cystic fibrosis
AST	Antimicrobial susceptibility
NOS	Newcastle Ottawa Scale
MeSH	Medical Subject Headings

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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No specific funding has been allocated for the study.

Authors' contributions

JLM and SV will independently extract and analyze the data. All authors will critically analyze the draft for important intellectual content before the final publication.

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