Sinus bacteriology in patients with cystic fibrosis or primary ciliary dyskinesia: A systematic review

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ABSTRACT

Background: *A correlation exists between the microbial flora of the upper and lower airways in patients with cystic fibrosis (CF) or with primary ciliary dyskinesia (PCD). The sinuses can function as a bacterial reservoir where gram-negative bacteria adapt to the airways and repeatedly are aspirated to and colonize the lungs according to the theory of the united (unified) airways. Whereas the pattern of bacterial flora in the lower airways has been extensively studied, the upper airways have drawn limited attention.*

Objective: *Our aim was to review the literature that reported bacterial flora in the sinuses and nasal cavities of patients with CF or PCD.*

Methods: *A number of medical literature data bases were systematically searched between January 1960 and July 2016. We applied the following inclusion criteria: a minimum of one case of PCD (or Kartagener syndrome) or CF, and microbiology analyses from the nose or paranasal sinuses.*

Results: *We included 46 studies (1823 patients) from 16 countries. Staphylococcus aureus was found in 30% of the noses and sinuses of patients with CF. Other common bacteria found included Pseudomonas aeruginosa, coagulase negative staphylococci, and Haemophilus influenzae. In PCD, H. influenzae was the most common bacteria (28%), followed by Streptococcus pneumoniae and P. aeruginosa. If studies that included nonsurgical swab and blowing samples were excluded, then P. aeruginosa was the most common bacterium in patients with CF (34%) and in patients with PCD (50%), followed by S. aureus* and *H. influenza.*

Conclusion: *S. aureus, P. aeruginosa, coagulase negative staphylococci, and H. influenzae dominated in the upper airways of patients with CF. In patients with PCD, H. influenzae, S. pneumoniae,* and *P. aeruginosa dominated. When studies that included swab and blowing samples were excluded, P. aeruginosa was the most common bacterium in both groups. Direct comparisons among the studies were restricted due to very heterogeneous methods, and a better standardization of procedures and outcomes is needed.*

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Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the CF transmembrane conductance regulator gene.[1] The CF transmembrane conductance regulator gene is responsible for chloride transport over the cell membrane.[2] The defect causes tenacious and viscous mucus, which further impairs the movement of cilia.[3,4] In Europe, the incidence of CF is ~1 in 2300,[5] and it is the most common genetic lethal disease among whites.[6] Primary ciliary dyskinesia (PCD) is similarly an autosomal recessive genetic disorder caused by mutations in genes responsible for the function and structure of cilia.[7] PCD affects ~1 in 15,000 individuals,[8] and ~50% of patients with PCD have Kartagener syndrome, characterized by the triad of chronic rhinosinusitis (CRS), bronchiectasis, and situs inversus.[9] The incidence may be higher because patients with mild phenotypes may remain undiagnosed and the diagnostic procedures require advanced and expensive equipment. Both diseases impair the sinonasal and pulmonary mucociliary clearance, which promotes recurrent colonization and infection with microorganisms in the upper and lower airways.[10,11]

The airways, according to the united (unified) airways concept, can be seen as a single unit. A strong correlation exists between the upper and lower airway bacteriology in patients with CF and PCD. Bacteria isolated from the lungs and sinuses in the same patient often have the same genotype,[12–14] which supports the theory that the sinuses function as a bacterial reservoir where bacteria can adapt to the airways and become aspirated to the lungs and *vice versa*.[12] In the early stages of lung colonization, the migration of pathogens may mainly occur in a downward direction, with the sinuses as a primary focus.[12] Several studies found concordance between upper and lower airway bacteriology in both patients with CF[13–17] and those with PCD.[11] Although the pattern of bacterial flora in the lower airways has been extensively studied, the upper airways have drawn limited attention. The primary aim of this study was to review existing studies that cover the bacterial flora in sinuses and the nasal cavity in patients with CF and patients with PCD, and to discuss factors that may influence the result.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18]

Systematic Literature Search and Eligibility Criteria

In February 2016, one author (M.E.M.) systematically searched the PubMed, Embase (Elsevier B.V. Registered Office, Amsterdam, the Netherlands), and Cochrane Library (London, UK) data bases for articles written in the English language by using the following search strategy, including Medical Subject Heading terms and keywords: "nose" or "paranasal sinus" or "paranasal sinuses" or "sinus" and "microbiology" or "bacteria" or "mucociliary transport" and "cystic fibrosis" or "cf" or "primary ciliary dyskinesia" or "pcd" or "ciliary

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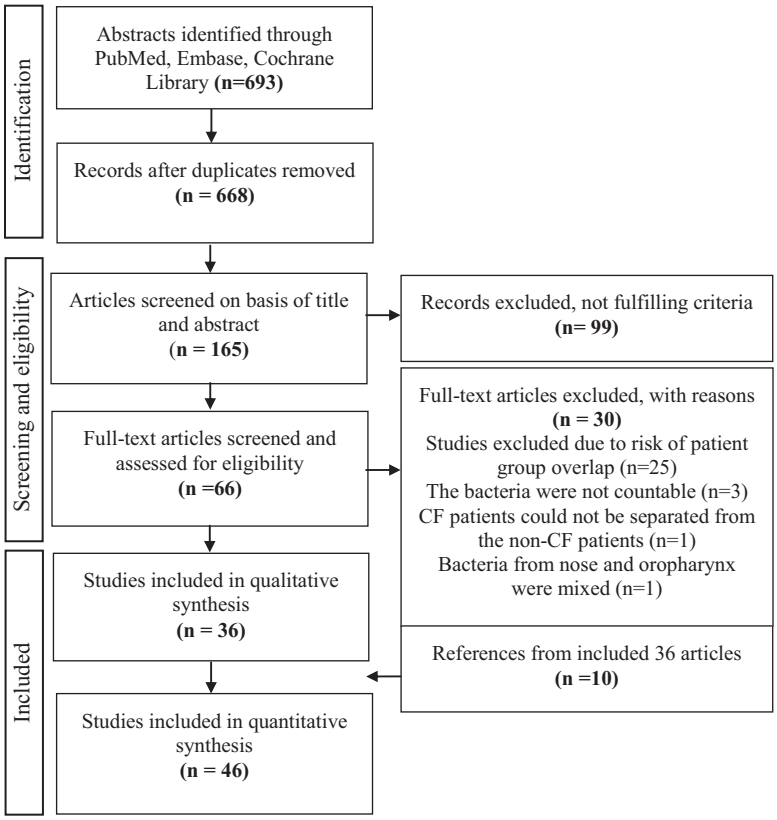

Figure 1. *Flowchart. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram: Study selection process (from Ref. 18).*

motility disorder" or "immotile cilia syndrome" or "kartagener syndrome" or "kartagener's syndrome." One author (M.E.M.) independently reviewed abstracts, accessed the full-text copies of relevant articles, and reviewed the reference lists.

The inclusion criteria were as follows: one or more cases of PCD (or Kartagener syndrome) or CF and bacterial flora analysis from the nose or the paranasal sinuses. The criteria were restricted to January 1960 to July 2016, and animal experiments were excluded. Articles or parts of the results were excluded if the number of bacterial species were not counted (*e.g.,* listed as follows: *e.g., Pseudomonas aeruginosa, Staphylococcus aureus*) or nonspecific (*e.g.,* other bacteria, other). Furthermore, to avoid patient group overlap, only one article was chosen among the articles with the same authors, patients from the same institution, or within a possible overlap period. The article chosen was consequently the one with the greatest number of patients included based on the sinonasal procedures. Four studies presented their results in relation to the number of procedures instead of per patient. The proportions were given in percentages, which were recalculated to provide a more general estimate according to the number of patients (*e.g., S. aureus* accounted for 47% of the samples ×46 patients/100 = 22 patients). The general estimates were accepted. The data were calculated and presented as before and after exclusion of studies that used blowing samples and swabs as methods that were not described as a part of a surgical procedure and, therefore, most likely represented the contaminating flora of the anterior nares. Some studies did not describe the methods applied for collecting samples.

Data Analysis

One author (M.E.M.) extracted the relevant data from the articles and entered them into a spreadsheet that included the institution and country, age, year of publication, number of patients, type of bacteria, anatomic location(s) (*e.g.,* maxillary sinus), sampling method (*e.g.,* endoscopy), use of antibiotics (yes or no and, if yes, antibiotic specified), and culture or molecular methods (*e.g.,* agar or polymerase chain reaction [PCR]). Included studies were divided into two groups based on patients with PCD and patients with CF.

RESULTS

Overall, we included 46 studies with a total of 1823 patients (Fig. 1). The PCD group accounted for 3 studies,[11,19,20] with a total of 105 patients, and the CF group accounted for 43 studies[5,6,10,13,14,16,17,21–56] and 1718 patients. The origins of the studies are noted in the Online Supplemental Material.[5,6,10,11,13,14,16,17,19–56] The most common bacteria isolated in the upper airways in CF were *S. aureus* (including methicillin resistant *S. aureus,* methicillin sensitive *S. aureus,* and glycopeptide intermediate *S. aureus*), which were identified in 513 patients (30%). The second most common bacterium was *P. aeruginosa*, which was isolated in 437 patients (25%). The third and fourth most common bacteria were coagulase negative staphylococci (CoNS) (5%) and *Haemophilus influenza* (4%). Overall, 55% of the patients with CF were either colonized in the nose or the sinuses with *P. aeruginosa, S. aureus*, or both (Table 1).

In subanalyses based of the number of patients in the studies that investigated the occurrence of *S. aureus* (1449 patients), 35% of the patients were infected with *S. aureus*. In comparison, in studies that investigated the occurrence of *P. aeruginosa* (1383 patients), 32% were infected with *P. aeruginosa.* Based on these data, *S. aureus* was still more common in relation to the specific number of patients in studies in which it had been identified or specifically investigated. The most common upper airway pathogen in patients with PCD was *H. influenzae*, which was isolated in 29 patients (28%), followed by *S. pneumoniae* in 17%. *P. aeruginosa* and *S. aureus* were found in 14% and 3% of the patients, respectively. In total, 17% of the patients with PCD were colonized with one or both of these bacteria (Table 2). Sampling methods included sinus surgery with the use of endoscopy (54%), lavage and/or washouts (15%), and swabs (30%), which were some-

Table 1 **The most common bacteria isolated from the nose and sinuses in patients with cystic fibrosis, including swab and blowing sample studies***

Bacteria	Patients, no.#	Prevalence, %
Staphylococcus aureus	513	30
Pseudomonas aeruginosa	437	25
Coagulase negative *Staphylococcus*	88	5
Haemophilus influenzae	74	4
Streptococcus pneumoniae	29	2
Corynebacteria species	21	1
Burkholderia cepacia complex	20	1
Stenotrophomonas maltophilia	19	1
Moraxella catarrhalis	16	1
Escherichia coli	15	1
Achromobacter xylosoxidans	10	1

**High numbers of α-hemolytic streptococci, other streptococci species, and Neisseria were isolated but not included because they were not identified by species and are a part of the contaminating normal flora.*
#Of 1718 patients, the number of times the bacteria were isolated; data are cumulative, i.e., one patient could have had more than one species of bacteria isolated from the nose or sinuses.

Table 2 **The most common bacteria isolated from the nose and sinuses in patients with primary ciliary dyskinesia, including swab sample studies**

Bacteria	Patients, no.*	Prevalence, %
Haemophilus influenzae	29	28
Streptococcus pneumoniae	18	17
Pseudomonas aeruginosa	15	14
Moraxella catarrhalis	6	6
Staphylococcus aureus	3	3
Other	3	3

**Of a total of 105 patients, the number of times that the bacteria were isolated; data are cumulative, i.e., one patient could have had more than one species of bacteria isolated from the nose or sinuses.*

Table 3 **Other procedures (that could be used to collect samples)**

Other Procedures (26%)
Antrostomy
Caldwell-Luc
Revision surgery
Frontal sinus obliteration
Transseptal sphenoidectomy
Ethmoidectomy

times done in combination with endoscopy or other procedures (26%) (Table 3). Sinus surgery with or without endoscopy was used to collect aspirate samples (22%), biopsy specimens and/or smears (11%), pus and/or secretions (7%), or crusts (4%). Nose blowing samples accounted for 2%. Data were cumulative, which meant that several methods could be used in one study.

The most common sampling sites were the maxillary sinus (30%), middle meatus (24%), paranasal sinus unspecified (including the sinus ostia) (20%), nose specified (anterior nares, posterior nares, nostrils, inferior turbinate, and meatus) (20%), nose unspecified (17%), ethmoid sinuses (20%), frontal sinuses (9%), sphenoid sinuses (11%), and external nares (2%). Data presented were cumulative, which meant that samples could be obtained from more than one anatomic location per study. Forty-one percent of the studies[13,17,20–22,24,26,27,29,30,38–42,45,50,52,53] provided information about the use of antibiotics before or during the sampling procedure. In four studies,[14,16,25,33] it was unclear whether the patients received antibiotics before or during sampling. Fifty percent of the studies[10,11,13,14,17,22–24,26–33,36,38,39,42,45,47,49] provided information about culture methods. Most studies[10,11,14,17,22–24,27–32,38,39,42,45,47,49] used conventional culture methods (41%). In four studies,[22,35,37,40] the method applied was unclear (referred to other articles, "microbiologic examination," or "bacteriologic examination"). However, molecular methods (*e.g.*, PCR) were applied in 26%.[13,14,17,24,26–30,33,36,42]

Table 4 **The most common bacteria isolated from the nose and sinuses in patients with cystic fibrosis, without swab and blowing sample studies***

Bacteria	Patients, no.#	Prevalence, %
Pseudomonas aeruginosa	383	34
Staphylococcus aureus	320	28
Haemophilus influenzae	56	5
Coagulase negative *Staphylococcus*	40	3.5
Burkholderia cepacia complex	20	2
Stenotrophomonas maltophilia	17	1.5
Streptococcus pneumoniae	17	1.5
Escherichia coli	14	1.2
Achromobacter xylosoxidans	10	1
Moraxella catarrhalis	9	1
Streptococcus viridans	8	1

**High numbers of α-hemolytic streptococci, other streptococci species, and Neisseria were isolated but not included because they were not species identified and are a part of the contaminating normal flora.*
#Of 1131 patients, the number of times the bacteria were isolated; data are cumulative, i.e., one patient could have had more than one species of bacteria isolated from the nose or sinuses.

Table 5 **The most common bacteria isolated from the nose and sinuses in patients with primary ciliary dyskinesia, without swab sample studies**

Bacteria	Patients, no.*	Prevalence, %
Pseudomonas aeruginosa	4	50
Haemophilus influenzae	1	12.5
Staphylococcus aureus	1	12.5

**Of a total of 8 patients, the number of times the bacteria were isolated; data are cumulative, i.e., one patient could have had more than one species of bacteria isolated from the nose or sinuses.*

When excluding studies that used only swabs and blowing samples, nine studies[13,19,20,24,27–31] were excluded, which left a total of 37 studies[5,6,10,11,14,16,17,21–23,25,26,32–56] with 1139 patients. In CF, seven articles[13,24,27–31] were excluded, which left 1131 patients with CF, and two PCD articles[19,20] were excluded, which left eight patients with PCD in the study. In patients with CF, the most common bacteria were then *P. aeruginosa* found in 383 patients (34%), *S. aureus* (28%), and *H. influenzae* (5%). CoNS was found in 3.5% of the patients (Table 4). Among the seven excluded CF studies,[13,24,27–31] three studies[24,27,29] investigated only the presence of *S. aureus* and one study investigated exclusively for *P. aeruginosa*,[30] and the last three were mixed.[13,28,31] In the patients with PCD, the most commonly found bacteria were *P. aeruginosa* (found in four patients [50%]), *S. aureus* (12.5%), and *H. influenza* (12.5%) (Table 5).

DISCUSSION

To our knowledge, we presented the first systematic review that addressed sinus and nose bacteriology in patients with PCD and in patients with CF. As expected, we found that *S. aureus*, *P. aeruginosa*,

CoNS, and *H. influenzae* were the predominant bacteria that colonized the upper airways in patients with CF. In patients with PCD, *H. influenzae, S. pneumoniae*, and *P. aeruginosa* were the predominant bacteria. We found that the order of the bacteria changed when studies that included nonsurgically obtained swab samples as well as blowing samples were removed. The most common bacterium was then *P. aeruginosa,* followed by *S. aureus,* and *H. influenza* in both groups.

In a review by Brook,[57] he indicated that, in healthy individuals, the normal flora in the nose consists of *S. aureus, Staphylococcus epidermidis*, α-streptococci and γ-streptococci, *Propionibacterium acnes*, and aerobic *Diphtheroids*. However, the listed bacteria exist as normal flora in the anterior nares due to contamination. Furthermore, CoNS is regarded as a contaminant and a part of the normal flora in the vestibulum nasi and the skin. Of healthy people, ~30% carry *S. aureus* in vestibulum nasi.[58] The resistance of *S. aureus* to antibiotics is reported to increase with exposure to a hospital environment.[59] Methicillin resistant *S. aureus* is especially isolated in individuals with health care–associated exposure.[60–62] Controversy remains as to whether there is a nonpathologic bacterial flora in the healthy sinus. Nevertheless, α-hemolytic streptococci and β-hemolytic streptococci, *S. aureus*, *H. parainfluenzae,* and anaerobes have been isolated from nondiseased sinuses.[63] A study by Cleland *et al.*[64] found *Acinetobacter johnsonii* to be abundant in the healthy sinus and, furthermore, to increase in patients with CRS after surgery, which indicates a potential association between this bacterium and health.[64]

In acute bacterial rhinosinusitis in patients not suffering from CF or PCD, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenza*, and *Moraxella catarrhalis* are the most common bacteria.[57] In CRS, *S. aureus* and anaerobic bacteria predominate,[57] but CoNS are also is present in high numbers.[65] Furthermore, *P. aeruginosa* is often isolated from patients with nosocomial CRS, immune deficiencies, and CF.[22,57] *P. aeruginosa*, *S. aureus*, and *H. influenzae* are frequently isolated from the sinuses of patients with CF, and CoNS,[6,13,21,32] as this survey also demonstrated in patients with CF. In patients with PCD, *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and *S. aureus* are the most common bacteria isolated from the lungs.[66] *P. aeruginosa* frequently colonizes the lower respiratory tract in patients with PCD, and the prevalence increases with age.[66] Few reports on sinus bacteriology in patients with PCD have been published; however, a Danish study[67] (not included due to patient group overlap with the study by Mygind and Pedersen[19]) found that *H. influenzae* was the most common bacteria in the nose and sinuses, followed by *S. pneumoniae*, *P. aeruginosa*, and *S. aureus*, which is in agreement with the results before the exclusion of the swab sample studies, which possibly indicates that *P. aeruginosa* becomes more abundant when the sample method involves surgery in this patient group.

In CF, patients are also infected in an age-dependent sequence. Several studies reported *S. aureus* and *H. influenzae* to be the most common bacteria in the upper airways in pediatric patients.[32,68] With increasing age, *P. aeruginosa* was found more frequently, which is also characteristic for a more advanced stage of the disease.[17,68] This is also the pattern seen in the lungs.[23,69,70] There are no data on age variation in the sinus bacteriology in patients with PCD, but, in the lungs, it is reported that the majority of patients are colonized with *H. influenzae* and *M. catarrhalis* during childhood, whereas *P. aeruginosa* is seen later in life, with the incidence increasing with age.[66] The bacteriology in the lungs of patients with PCD seemed to have similarities with non-CF bronchiectasis bacteriology.[66]

Goerke *et al.*[24] reported that the prevalence of *S. aureus* among patients with CF is significantly higher in those who had not received antibiotics and higher than in healthy controls, which indicates that presample antibiotics can influence growth of *S. aureus* in the nose. Moreover, a study by Gitomer *et al.*[71] showed that *S. aureus* transformed into small colony variants after exposure to gentamycin *in vitro,* which indicated that this resistant type of *S. aureus* increases with longtime exposure to antibiotics, which is the case in patients with CF and PCD. However, only 41% of the studies that comprise the present review provided information about the use of antibiotics, which is an obvious limitation. In addition, it was impossible in most cases to separate patients who received antibiotics from those who did not.

Use of culture and/or molecular methods can influence the variety, abundance, and type of bacteria found. A study by Rudkjøbing *et al.*[72] indicated that a combination of molecular methods and culture-dependent routine diagnosis is an optimal way to find the greatest variety in detecting aerobes, anaerobes, and facultative anaerobes in the sinuses in patients with CF. However, the experience of patients with CF in our center indicates that classic culture methods sufficiently detects the clinically important bacteria.[73] Moreover, PCR detects a broad variety of bacteria but may blur which bacteria are relevant to treat.

The sampling method may also influence the result. Sinus aspiration is the criterion standard for obtaining secretions from the sinuses, but it is invasive.[25] Nasal lavages are suggested as a noninvasive alternative[13] and were used in 15% of the studies[10,13,20,33,35,37,54] in this review. However, cultures from nasal lavage may presumably not represent all the sinuses and the sample may be contaminated from the nasopharynx.[74] In addition, the procedure may require some experience, and inadequate flushing may only rinse the vestibulum[13] Furthermore, in a recent study by Kim *et al.*,[26] *S. aureus* was shown to grow in intramucosal colonies in the sinuses in patients with CF. Intramucosal colonies may not be detected without invasive methods. Nasal swabs and blowing samples are both regarded as less sensitive and might not be an optimal method.[13]

Several articles were rather nonspecific with regard to information about the sampling site, *e.g.,* writing "paranasal sinus," which made it impossible to further localize the specific sampling site. We included studies from 1960 to 2016, which may have led to differences in the methods applied to sampling because the sinonasal endoscopic technique was introduced in the 1980s.[75] Furthermore, patients admitted for endoscopic sinus surgery are a select group who probably have the most severe CRS, which we considered a serious limitation. Nevertheless, CRS is almost universal and underdiagnosed in CF.

Our study had other limitations. There was a lack of information and no standardization in the way that the findings in each article were measured, which made it difficult to provide a complete overview. Standardization and information on patients' age, use of antibiotics, culture methods, sample methods *etc.,* are issues that are important when making an overview on CRS bacteriology.[57] Factors such as genotype and lung infection status are important to include as well. In addition, it would have been valuable to analyze adult and pediatric data separately, but this was not possible because this further information was not provided in the majority of the articles. Neither was a division of patients based on lung infection status possible because too few of the studies had divided as such. Furthermore, many studies were not comparable because of the heterogeneity of the information and the variety of bacteria investigated. For example, a study that exclusively searches for *P. aeruginosa or S. aureus* will bias the overall result.

Moreover, there were a number of articles by the same authors or from the same centers, with a risk of inclusion of the same results from the same patients in the present review. In such cases, the article with the largest number of patients was included. Only the authors at the Copenhagen University Hospital were contacted regarding two articles with a wide range of years (*i.e.,* 32 years) between the two publications. There was no overlap in patients between the two articles, which resulted in an inclusion of both articles. Generally, more exclusion criteria could have been applied to our search in an attempt to avoid or limit the number of bias and reduce the heterogenicity. Nevertheless, the heterogenicity in the articles affected the outcome of this paper. In our opinion, it would be impossible to avoid the heterogenicity completely, and, to apply more exclusion criteria, furthermore, would decrease a small study population. Bacterial cultures were not the main outcome in most of

the articles included in our review; therefore, information about this may be present in full-text articles without being visible in the abstracts, which led to assessments of many less obvious full-text articles. Two conference abstracts were included because the bacterial isolates were relevant to include in the study. To the best of our knowledge, full-text articles from the same author or center have not been published afterward.

CONCLUSION

To our knowledge, we presented the first systematic review of upper airway pathogens in patients with CF or PCD. *S. aureus*, *P. aeruginosa*, CoNS, and *H. influenzae* seemed to be the most abundant bacteria in the nose and sinuses of patients with CF. *H. influenzae*, *S. pneumoniae*, and *P. aeruginosa* were the bacteria most frequently found in patients with PCD. *P. aeruginosa* seemed to be the most abundant in both patients with PCD and patients with CF after articles that included swab and blowing samples[13,19,20,24,27–31] were removed. Only three studies[11,19,20] in patients with PCD were included in the first analysis, and only one[11] after swab sample studies were included. More studies that investigate the bacterial status in these patients are needed. Due to the heterogeneity with regard to methods and materials used in the included studies with the risk of bias made a firm conclusion difficult. A number of factors, such as the age of the patients, sampling methods, use of antibiotics, and culture methods, and, furthermore, lung infection status and use of a control study may have influenced the results.

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