Upper airway · 2: Bronchiectasis, cystic fibrosis and sinusitis

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ABSTRACT

The nose and paranasal sinuses are contiguous with the lower respiratory tract. Patients with bronchiectasis and cystic fibrosis commonly have sinonasal disease, which is thought to have the same aetiology and pathophysiology as the chronic lung disease. Despite this, the conditions are rarely considered together and there is very little literature on the treatment of sinonasal disease in bronchiectasis. In addition to being a common cause of comorbidity, there is evidence suggesting that sinonasal disease may directly influence the bronchial condition. This article reviews sinonasal disease in bronchiectasis and cystic fibrosis and addresses the possible interactions between the health and disease of the upper and lower airways.

The upper respiratory tract comprising the nose and paranasal sinuses has the same mucosal lining as the lower airways, and both compartments are involved together in health and disease. The relevance of this ‘single airway’ concept has been demonstrated with asthma, allergic rhinitis and nasal polypsis, but it may be similarly useful in chronic infective respiratory conditions. Investigation of the upper airway may be useful as a marker of disease in the less accessible lower airway. In addition, treatment of one compartment may have benefits throughout the whole respiratory tract. Improvements in sinus health have been reflected in improved lower airway disease in asthma. This has not been studied in bronchiectasis or cystic fibrosis, but the implications are similar in that viral and bacterial infections can pass from one to the other.

Mucociliary clearance is an important first-line defence of both the upper and lower respiratory tracts. The nose, sinuses, trachea and bronchi are lined by ciliated and mucus-producing cells which form the mucociliary escalator and trap inhaled matter and propel it to the nasopharynx, where it can be expectorated or swallowed. Mucus transport depends on both the integrity and function of the ciliated epithelium and the properties of the mucus. The cilia beat at a rate of between 12 and 16 strokes per second in a consistent direction and in a coordinated fashion. The periciliary fluid layer is of the required depth equalling the vertical height of a cilium, and the mucus must be of suitable rheology for transport.

Impaired sinonasal clearance leads to stasis of secretions, which are only removed from the nasal cavity by blowing or postnasal drip. This makes the host prone to bacterial infection which results in neutrophilic inflammation leading to chronic rhinosinusitis. Bacterial products and neutrophilic inflammation damage the epithelium and stimulate excess mucus production, and mucosal swelling blocks the sinus ostia, further impairing mucus clearance. Bacterial infection and damage caused by the host inflammatory response interact, perpetuating the disease process, and in chronic rhinosinusitis the disease can become independent of continued bacterial infection. Similarly, impaired clearance from the lower airways leads to chronic respiratory infection and inflammation that has been termed a ‘vicious circle’, leading to the progression of bronchiectasis. It is therefore not surprising that bronchiectasis and sinusitis often coexist.

Other important host defences in the upper respiratory tract include immunoglobulins, defensins and antibacterial components of the mucus such as lysozyme. The defences can be impaired by primary or secondary abnormalities (table 1). The upper respiratory tract is often exposed first to an infectious agent and to higher concentrations of inhaled matter and, for this reason, the initial symptoms may come from this site and may be more severe.

SINONASAL DISEASE

The nasal cavity conditions the air we breathe, and it also acts as a first line of defence by impacting unwanted particles on the mucosa and excluding them from the lower respiratory tract. The paranasal sinuses (frontal, maxillary, ethmoid and sphenoid) are air-filled spaces within the skull. They reduce the weight of the skull and humidify and heat inhaled air. These cavities connect with the nose via small orifices called ostia, which may become blocked by swelling of inflamed mucosa.

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. Diagnostic criteria include the presence of two or more symptoms which should include one of nasal obstruction/congestion or anterior/posterior rhinorrhoea. Other symptoms include anosmia and facial pain or pressure. The patient’s symptom score can describe severity of disease on a visual analogue scale. Patients should also have evidence of rhinosinusitis on examination with polyps, mucopurulent discharge or oedema around the middle meatus on nasendoscopy or mucosal changes evident on the CT scan.

Acute rhinosinusitis consists of symptoms lasting <12 weeks, and can be subdivided into acute viral rhinosinusitis with a duration of <10 days and acute non-viral rhinosinusitis with symptoms lasting between 10 days and 12 weeks. Chronic rhinosinusitis is defined by persistent symptoms lasting >12 weeks. It can be subdivided...
by the presence or absence of nasal polyps. Nasal polyposis is a chronic inflammatory disease of the nose and sinus mucosa. The polyps occur when the oedematous lining of the nasal mucosa becomes dependent, causing some obstruction of the nasal cavity. They can be found throughout the upper respiratory tract but are most commonly located around the ostiomeatal complex. Nasal polyposis is frequently associated with asthma, cystic fibrosis (CF), primary ciliary dyskinesia (PCD) and aspirin sensitivity. Polyps are classified as: 0, no polyps; 1, mild (not reaching the upper edge of the inferior turbinate); 2, moderate (between the upper and lower edges of the inferior turbinate); and 3, severe (reaching the lower edge of the inferior turbinate). The aetiology of chronic rhinosinusitis may be infective or non-infective. The pathogenic role played by bacteria in chronic rhinosinusitis is unknown. On the one hand they may be an important stimulus of neutrophilic inflammation, whereas they can also be seen as passengers taking advantage of the inflammatory milieu created by poor drainage from obstructed ostia. The role of anaerobic bacteria in these circumstances is also uncertain. It is also unknown whether the different sinonasal pathologies are independent diseases or part of a spectrum with nasal polyps, the result of chronic rhinosinusitis which arises from an episode of acute rhinosinusitis. Complications of chronic sinusitis include mucocoele formation which are cysts lined by respiratory epithelium. They occur in the sinus cavities and can cause erosion of the surrounding bony structures. Less commonly, orbital and intracranial spread of infection, osteomyelitis and cavernous sinus thrombosis may occur.

Between 2.7% and 6.6% of the population are thought to have chronic rhinosinusitis. There is an increased incidence in patients with chronic inflammatory lower respiratory disease and associations have been demonstrated with asthma and chronic obstructive pulmonary disease (COPD), in addition to bronchiectasis. Chronic rhinosinusitis can impact heavily on quality of life with significant impairments noted on both general and specific health status instruments. One study showed that patients with chronic rhinosinusitis had more general body pain and worse social functioning than those with COPD or heart failure. Despite this, there is no clear correlation between the severity of sinonasal disease and quality of life.

BRONCHIECTASIS

Bronchiectasis is defined as the abnormal dilation of the bronchi due to the loss of elastic and muscular components of the wall thought to be due to destruction by enzymes such as collagenase and elastase from neutrophils. Clinically, it is characterised by excess mucus production and recurrent lower respiratory tract infections. It is the end result of several different aetiologies (table 2). The most common causes of bronchiectasis are idiopathic and postinfective damage. Chronic rhinosinusitis occurs in 45–84% of patients with idiopathic bronchiectasis and is less common in patients with postinfective bronchiectasis where an acute infection has damaged the bronchial tree. It is almost universal, and often more severe, when the sinusitis and bronchiectasis share a common aetiology due to the host defence abnormalities listed in table 1. These conditions include ciliary defects in PCD and mucous abnormalities in CF.

Primary ciliary dyskinesia (PCD)

Each ciliated epithelial cell contains 50–200 motile cilia responsible for the removal of mucus and attached foreign material. The cilia are 5–7 μm in length and consist of nine peripheral microtubule pairs with dynein arms and radial spokes and two central microtubules. The cilia have a forward extended stroke which contacts the viscous outer mucous layer, followed by a reverse stroke where it returns back to the starting point within the watery periciliary layer. PCD is an autosomal recessive condition whereby ciliary motility is absent or severely impaired leading to sinusitis, otitis media, glue ear, chronic bronchitis, bronchiectasis and male infertility. The association of situs inversus characterises Kartagener’s syndrome. There are many different ultrastructural ciliary defects, with abnormalities in the dynein arms most frequent. Patients have congested noses from birth and often have difficulty breast feeding due to the inability to nose breathe. This history should alert the paediatrician to the need for cilia investigation. A common physical sign is pooling of mucus in the floor of the nasal cavity.

Young’s syndrome

Young’s syndrome is characterised by bronchiectasis, chronic rhinosinusitis and male infertility. Ciliary function is found to be normal and clearance is impaired because the mucus is

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**Table 1** Host defence abnormalities leading to chronic bacterial infection of the upper and lower airways

<table>
<thead>
<tr>
<th>Host defence</th>
<th>Primary</th>
<th>Secondary</th>
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<tr>
<td>Cilia</td>
<td>Kartagener’s syndrome</td>
<td>Viral infection</td>
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<td></td>
<td>Primary ciliary dyskinesia</td>
<td>Cigarette smoke</td>
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<tr>
<td>Mucus</td>
<td>Young’s syndrome</td>
<td>Viral infection</td>
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<td></td>
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<td>Cigarette smoke</td>
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<td></td>
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<td>Allergy</td>
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<td>Periciliary fluid</td>
<td>Cystic fibrosis</td>
<td>Air conditioning</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>Common variable immunodeficiency</td>
<td>Dehydration</td>
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<tr>
<td>Unknown</td>
<td>Idiopathic bronchiectasis</td>
<td>Panbronchiolitis</td>
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<td></td>
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<td>Yellow nail syndrome</td>
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<td></td>
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<td>Ulcerative colitis</td>
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</table>

**Table 2** Common causes of bronchiectasis and chronic rhinosinusitis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Examples</th>
<th>Prevalence of chronic rhinosinusitis</th>
<th>References</th>
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<tbody>
<tr>
<td>Idiopathic</td>
<td></td>
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<tr>
<td>Abnormal mucociliary clearance</td>
<td>PCD</td>
<td></td>
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<tr>
<td></td>
<td>CF</td>
<td></td>
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<tr>
<td>Immunocompromise</td>
<td>HIV</td>
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<td>Postinfective</td>
<td>Tuberculosis</td>
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<tr>
<td></td>
<td>Non-tuberculous</td>
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<tr>
<td></td>
<td>mycobacteria (eg, MAC)</td>
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<td></td>
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<tr>
<td></td>
<td>Whooing cough</td>
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<td></td>
<td>Measles</td>
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<tr>
<td></td>
<td>Measles</td>
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<td></td>
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<tr>
<td>Excessive immune response</td>
<td>ABPA</td>
<td>40–90%</td>
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<tr>
<td></td>
<td>GvHD</td>
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<tr>
<td>Mechanical obstruction</td>
<td>Inflammatory bowel disease</td>
<td>Infrequent</td>
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<td></td>
<td>Tumour</td>
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<td>Foreign body</td>
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<td></td>
<td>Lymphadenopathy</td>
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ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; GvHD, graft versus host disease; HIV, human immunodeficiency virus; MAC, mycobacterium avium complex; PCD, primary ciliary dyskinesia.
viscous. There is an association with mercury poisoning in childhood from teething powders and treatment of worm infections. Diagnosis is made on exclusion of CF and PCD, or the characteristic finding of obstruction by waxy material at the caput during scrotal exploration for infertility.

Cystic fibrosis (CF)

CF is a single gene autosomal recessive condition characterised by a defect in the CF transmembrane conductance regulator gene product that leads to abnormalities of ion flux at the epithelial surface. The increased sodium absorption leads to periciliary liquid depletion and abnormal mucus movement. Clinically, patients progress to chronic respiratory failure caused by bacterial infections and have pancreatic insufficiency.

CLINICAL ASSESSMENT OF SINONASAL DISEASE IN BRONCHIECTASIS

Assessment of mucociliary clearance

Nasal mucociliary clearance can be tested by a saccharin method whereby a small saccharin particle is placed on the medial side of the inferior turbinate and the time taken to experience the taste recorded, with abnormal values typically >20 min. More objective measures include the use of colloid particles labelled with technetium-99 and a gamma camera for detection.

The structure and function of the cilia is assessed following a nasal brush biopsy, whereby a cytology brush (or equivalent) is used to scrape epithelial cells from the inferior turbinate. Ciliary beat pattern can then be assessed under a light microscope, and the frequency measured by the interruption of a light beam with a photometer. Electron microscopy is used to assess ciliary ultrastructure and to determine orientation.

The above tests are relatively simple and minimally invasive and, in addition to giving information regarding the mucociliary escalator in the nose, can be extrapolated to the lower respiratory tract. Studies have shown a correlation between the saccharin test results and the pulmonary clearance of an inhaled radiolabelled isotope, and nasal and tracheal beat frequencies have also been shown to be correlated.

Expired nitric oxide levels may be useful in the assessment of a patient with bronchiectasis. They can be used as a screening tool for PCD. In PCD the nitric oxide levels are low, particularly in the nose, possibly due to the reduced activity of nitric oxide synthase. This contrasts with non-PCD bronchiectasis where the bronchial levels are higher than in healthy controls. It is important to note that reduced nitric oxide levels are also found in CF and both acute and chronic rhinosinusitis, but not to the same degree.

Assessment of upper airway

Assessment of the upper airway begins with a review of the symptoms experienced by the patient and an assessment of their severity. The amount and type of discharge, and any facial pain or smell disturbance should be recorded. The degree of nasal obstruction is usually also a subjective measurement, although nasal peak flow can provide an objective measure and other techniques such as rhinomanometry and acoustic rhinometry may be available in some centres.

Anterior rhinoscopy is required for all patients with chronic nasal disease but may miss small polyps. Endoscopy significantly increases the detection of nasal polyps. Radiography of the sinuses can be misleading and, if needed, CT is the imaging modality of choice. Nevertheless, approximately one-third of the population have abnormal CT scans so it should not be used as a primary investigation in rhinosinusitis but in cases of failure of treatment, preoperatively and for complications of sinonasal disease. Mucosal changes at the ostiomeatal complex or in the sinuses are most commonly seen on CT scans. The Lund-Mackay scoring system scores from 0 to 2 depending on the absence, partial or complete opacification of each sinus.

SINONASAL DISEASE IN NON-CF BRONCHIECTASIS

In a Japanese study, 5% of patients with chronic rhinosinusitis were found to have bronchiectasis whereas 45% of patients with idiopathic bronchiectasis had chronic rhinosinusitis. In a UK study, 84% of patients with idiopathic bronchiectasis and 50% of those with postinfective bronchiectasis had chronic rhinosinusitis. The major symptoms include anterior and posterior rhinorrhea, anosmia and nasal obstruction. Nasal polyps occur in up to 40%. Staphylococcus aureus, coagulase negative staphylococcus and anaerobic and Gram-negative bacteria are the most frequent upper airway microbes in bronchiectasis. Sinonasal disease is universal in PCD and Young’s syndrome. Characteristic radiological findings include poorly developed frontal sinuses in PCD.

SINONASAL DISEASE IN CF

Almost every patient with CF has nasal and paranasal sinus disease. Furthermore, heterozygote CF carriers appear to have an increased incidence of sinonasal disease. The main symptoms include nasal obstruction, rhinorrhea, headache and anosmia. Despite this, fewer than 10% of patients with CF typically report significant symptoms. This is probably because they have come to accept the symptoms as “normal”.

Abnormalities in endoscopic examinations are almost always found and consist of turbinate congestion in 58% and nasal polyposis in one-third of patients. Histologically, the polyps in CF are different from those in asthma with a lack of dense eosinophilic infiltrate and the preponderance of acid mucin in the glands of CF polyps. Characteristic CF changes in include bulging of the lateral nasal wall, demineralisation of the uncinate process and hypoplasia of the paranasal sinuses. Repeat CT scans are not, however, useful in following response to treatments. Sinus cultures in patients with CF are mostly positive with S aureus and Haemophilus influenzae prevalent in the younger age group and Pseudomonas aeruginosa important in older patients. Other positive cultures include anaerobes and other microbes commonly seen in lower respiratory tract infections. In addition, fungi were isolated from the sinuses in up to one-third of patients with CF undergoing endoscopic sinus surgery. The importance of fungi in chronic rhinosinusitis is unknown, however an IgE-mediated inflammatory response may occur. Allergic fungal sinusitis was diagnosed in 6.7% of the patients with CF, which is the same incidence as in chronic rhinosinusitis in the general population.
particularly poor in patients with concurrent CF or bronchiectasis. Initial therapy should be medical with the aim to relieve symptoms, improve quality of life and avoid disease complications. Chronic rhinosinusitis often responds incompletely to treatment, which is usually continued long term.4

Medical

Common medical treatments include saline irrigation, antibiotics, topical or systemic steroids, decongestants, antihistamines (which may help with superadded allergic symptoms) and N-acetylcysteine.

Improved drainage

Saline irrigation may help to clear secretions and nasal crustings. This can be with a simple saline nasal spray (eg, Sterimar) or more vigorous douching (eg, Sinu-rinse). Applications can be repeated several times per day to improve symptoms and before other topical treatments, such as steroids, to improve exposure to the drug by the clearance of secretions. Douching is a safe and inexpensive treatment and has been shown to improve symptoms of chronic rhinosinusitis.4 The saline may also be hypertonic, which can lead to an osmotic mucosal decongestant effect and may assist mucus clearance. Topical decongestants can be used to relieve symptoms of blockage and facial congestion. They should only be used for short periods to avoid rhinitis medicamentosa.45 They can be used before application of topical corticosteroids when the nose is very blocked to improve mucosal exposure.

Steroids

The use of topical nasal steroids in chronic rhinosinusitis has been associated with improvements in both symptoms and objective measures in most randomised controlled studies.46 47 There is no evidence for the use of systemic corticosteroids in these patients. In patients who also have nasal polyps, topical steroids have also been shown to reduce polyp size and symptoms.48 Treatment with a 2-week course of systemic corticosteroids in this group has improved symptoms and polyp size compared with placebo.49 Topical nasal steroids were evaluated in a small RCT of patients with CF and nasal polyps with a reduction in polyp size, judged endoscopically, and an improvement of symptoms. There was no long-term follow-up in this study.49 Adopting an “upside down” head position for 3 min can increase exposure to the topical steroid. This has been shown to improve objective measures of benefit.50

Antibiotics

Topical ointments (eg, Bactroban (mupirocin) and Naseptin (chlorhexidine hydrochloride + neomycin sulphate)) can be helpful when there is vestibulitis and crusting, however there are no studies supporting their clinical effectiveness. There are also limited data supporting the use of systemic antibiotics in chronic rhinosinusitis. Short-term antibiotics (2 weeks) can be used for acute exacerbations. There has been an increased use of systemic macrolide antibiotics for their anti-inflammatory properties for a variety of chronic inflammatory conditions including bronchiectasis, CF, asthma and COPD.52 In particular, there has been a substantial improvement in the prognosis of patients with diffuse panbronchiolitis with the use of macrolides.53 In chronic rhinosinusitis, roxithromycin was trialled for 5 months in an RCT and demonstrated improvements in a variety of indices including symptom scores and endoscopy appearances.54 Long-term clarithromycin has also been shown to reduce lavage fluid markers of inflammation.55 Macrolides are thought to reduce inflammatory cytokines (eg, interleukin 8, tumour necrosis factor α), inflammatory cell recruitment and free radical production.56 57 They also have been shown to improve ciliary motility58 and reduce biofilm production.61 The macrolides have not yet been specifically studied in patients with CF or bronchiectasis with chronic rhinosinusitis.

Other agents

The topical mucolytic, dornase alfa, has been assessed in two RCTs in the postoperative management of sinonasal disease in patients with CF. Both studies found some improvement in endoscopic appearance and symptoms.52 60 N-acetylcysteine is also commonly used in chronic rhinosinusitis, but there is no strong evidence of benefit. There are no RCTs for the use of antieukotrienes in chronic rhinosinusitis, although they have shown some benefit in a subgroup of patients with nasal polyps and asthma.64 Antihistamines may be useful in patients with superadded allergic symptoms.65 The development of nasal nebulisers (Pari, USA) may lead to future therapies—such as hypertonic saline, DNase and antibiotics—being delivered by this route if carefully controlled studies show benefit.

Surgery

The majority of sinus surgery is now performed endoscopically with the aim of improving drainage. This includes sinus washout, increasing the size of the ostia and sinus scalps to remove hypertrophied mucosa. The improvement in endoscopic surgery has removed the need for more invasive operations such as the removal of diseased maxillary tissue in the Caldwell-Luc operation.

Endoscopic sinus surgery is generally reserved for patients who do not respond to medical treatment. Endoscopic sinus surgery is well tolerated in patients with CF,66 however the lack of symptomatic complaints and the disparity between CT findings and clinical disease in this population makes patient selection difficult. Sinus surgery has been shown to reduce symptoms in patients with CF,67 68 but there is a lack of evidence suggesting a long-term improvement, particularly with respect to further hospitalisation or lung function parameters.69 70 Some authors have suggested persistent nasal obstruction, particularly when demonstrated anatomically, severe symptoms and a correlation between pulmonary exacerbations and sinus symptoms as possible markers of suitable patients.70

Table 3 Consideration of sinonasal disease in bronchiectasis

<table>
<thead>
<tr>
<th>Importance of upper airway</th>
<th>Value of upper airway assessment</th>
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<tr>
<td>Morbidity attached to upper airways disease</td>
<td>Reduction in inflammation may improve quality of life</td>
</tr>
<tr>
<td>Similar mucosal surfaces and inflammatory response</td>
<td>Potential marker of lower airway disease</td>
</tr>
<tr>
<td>Paranasal sinuses and nose may act as reservoir for respiratory pathogens</td>
<td>Potential site for future research to assess drug responses</td>
</tr>
<tr>
<td>Treatment may reduce lower respiratory inflammation</td>
<td>Treatment may reduce lower respiratory inflammation</td>
</tr>
<tr>
<td>Pseudomonas eradication regimens may require sinonasal elimination</td>
<td>Treatment of sinonasal disease may reduce frequency of lower respiratory infection</td>
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<tr>
<td>Treatment for lung transplant patients may reduce recolonisation of transplanted lung</td>
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INTERACTION BETWEEN UPPER AND LOWER AIRWAYS

Sinonasal disease is associated with significant morbidity in patients with chronic respiratory disease. However, there is increasing evidence that it should not be considered in isolation and that it can also significantly impact on lower respiratory health (table 3). Most research has been performed in asthma. In these patients there is evidence that inflammation in nasal polyposis is similar to that in the lower respiratory tract with eosinophilic inflammation and IgE production, suggesting that the two conditions are different manifestations of the same disease.71 There are also data suggesting that the severity of sinonasal disease correlates with the severity of asthma.72 Similarly, a study in children with CF showed a correlation between the severity of sinus and pulmonary disease.73 Treatment of the sinonasal condition in asthma can also improve the lower respiratory tract disease. In patients with nasal polyps, treatment with functional endoscopic sinus surgery led to an improvement of asthma symptoms and peak expiratory flow rates in addition to the upper airway parameters.49

In bronchiectasis it is also likely that chronic rhinosinusitis will impact on the chronic lower respiratory infections. Chronic sinus inflammation can remodel the upper airways to become a reservoir for opportunistic infections that can descend into the lower respiratory tract. Supporting this hypothesis are studies which showed the same bacterial clones inhabiting both the upper and lower respiratory tracts. A recent study used molecular typing of S aureus and P aeruginosa in both nasal lavage and excreted sputum samples to show a high concordance of identical strains.75 This confirmed previous studies which had showed similar results from more invasive sampling methods.76 77 One of these studies described a temporal relationship, with younger CF patients developing only sinus infections while older patients had evidence of both upper and lower respiratory tract colonisation suggesting a likely migration of organisms from the upper respiratory tract.78 Infection of the bronchial tree may be easier to eradicate with systemic and topical antibiotics, whereas poor access to and drainage from the bronchial tree may be easier to eradicate with systemic and nasal polyps.20 — a summary. Prim Care Respir J 2008;17:79–89.


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