Laryngoscope Investigative Otolaryngology

The Role of Antibiotics in Pediatric Chronic Rhinosinusitis

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Objectives: Presenting the role of antibiotics in pediatric chronic rhinosinusitis based on its pathophysiology and microbiology.

Data source: Review of the literature searching PubMed for microbiology and treatment of pediatric chronic rhinosinusitis.

Results: Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal sinuses that persists for 12 weeks or longer, despite medical management. The microbiology of rhinosinusitis evolves through several stages. The early phase (acute) is generally caused by a virus that may be followed by an aerobic bacterial infection in 2% to 10% of patients. Aerobic (*Staphylococcus aureus*) and anaerobic (Prevotella and Fusobacteria) members of the oral flora emerge as predominant sinus cavity isolates. Antimicrobials are one component of comprehensive medical and surgical management for this disorder. Because most of these infections are polymicrobial and many include beta-lactamase producing aerobic and anaerobic organisms, amoxicillin-clavulanate is the first-line regimen for most patients. Clindamycin is adequate for penicillin-allergic children and is also generally appropriate for methicillin resistant *Staphylococcus aureus* treatment is administered for at least three weeks and may be extended for up to 10 weeks in refractory cases. A culture preferably from the sinus cavity should be obtained from individuals who have not shown improvement or deteriorated despite therapy.

Conclusions: Antimicrobial therapy of pediatric chronic rhinosinusitis should be adequate against the potential aerobic and anaerobic pathogens.

Key Words: Chronic sinusitis, anaerobes, *Stapylococcus aureus,* antimicrobials, children.

Level of Evidence: 7.

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as a complex inflammatory condition of the paranasal sinuses and linings of the nasal passages that lasts 12 weeks or longer, despite medical management.[1] It is estimated that 5% to 13% of viral upper respiratory tract infections in children may progress to acute rhinosinusitis,[2,3] and a proportion of these progressing to a Pediatric CRS (PCRS). PCRS can also occur and/or be aggravated by allergic rhinitis and adenoid disease.[4,5]

The factors that may enhance the development of CRS include anatomical blockage, exposure to allergens and irritants, defects in mucociliary function, immunodeficiency, and bacterial, viral, and fungal infection. The frequent end result of these is local inflammation and swelling of the sinonasal mucosa leading to impairment of normal sinus drainage and secondary bacterial infections.[6] However, the natural history data is not always available to be assured that that is the case in a particular patient.

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CRS represents a multifactorial inflammatory process, rather than a persistent bacterial infection. The medical management of CRS is presently focused upon controlling the inflammation that predisposes children to obstruction, thus reducing the incidence of infections. Most children require initial antibiotics to clear acute bacterial sinus infection and intermittently afterwards to treat acute exacerbations of CRS.[7]

This review describes the role of antibiotics in the management of PCRS.

MICROBIOLOGY

The exact etiology of the inflammatory process associated with CRS is uncertain. However, the presence of bacteria in the sinus cavity has been well established.[8,9] It is plausible that in CRS, mucociliary clearance and host defenses are impaired to the point that the cavity becomes colonized with greater number of nasal bacterial flora. Most clinicians believe that micro-organisms play a major role in the etiology and pathogenesis of most cases of CRS, and administer antimicrobial therapy. In contrast to the consensus regarding the bacteriology of acute rhinosinusitis, there is no agreement about the bacteriology of CRS. The issues that confound the reliability of many of microbiological studies include: variability in methods used to sample the sinus cavity; failure to sterilize the area through which the trocar or endoscope is passed; differences in sinuses or areas that are sampled; lack of evaluation of the inflammatory response or quantitation of bacteria; effects of previous or currently use antimicrobials; variable patient selection (i.e., age, gender, duration and extent of disease, surgical or

non-surgical subjects); presence of nasal polyps and time of culture; and transport and culture methods.

The CRS evolves formation of a biofilm that could play a major role in the pathogenesis and persistence of the infection.[10] This structure is formed by adherent microorganisms and is surrounded by an extracellular polymeric material. The biofilm is made of numerous and variable organisms and provides them many advantages, such as passive resistance, synergistic metabolic cooperation, influence of metabolic and other by-products, shielding of beta-lactam sensitive bacteria by beta-lactamase producing ones, quorum sensing systems, an enlarged gene pool with more efficient DNA, and many other synergies giving them a competitive advantage. The higher the diversity of microorganisms, the greater the survivability of the biofilm.[11]

The microbiology of rhinosinusitis involves several stages. The early phase (acute rhinosinusitis or ARS) is usually caused by a viral infection (rhinovirus, adenovirus, influenza, or parainfluenza) which generally persists up to 10 days.[7] In some individuals, a secondary bacterial infection emerges. The commonest bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. If the bacterial ARS does not dissipate, members of the anaerobic oropharyngeal flora and *Staphylococcus aureus* emerge as a pathogens.[2,8,12–25]

A unique infection in children is the simultaneous occurrence of chronic otitis media with effusion and maxillary CRS.[18] Microbiologic concordance between the ear and sinus was found in 22 (69%) of 32 culture-positive patients The most frequently recovered isolates were *H. influenzae, S. pneumoniae, Prevotella* spp, and *Peptostreptococcus* spp.

Anaerobic bacteria have been found in over two-thirds of both children[12,17,18] and adults with CRS in studies that employed adequate methods for specimen collection, transportation, and cultivation.[8,13–16] Repeated endoscopic cultures obtained from five individuals with ARS who did not respond to antibiotic therapy illustrated the emergence of antimicrobial resistant anaerobic bacteria. These included pigmented *Prevotella* spp*, Porphyromonas* spp*, Fusobacterium nucleatum, and Peptostreptococcus* spp.[20]

The factors promoting the emergence of anaerobic organisms include the selective pressure of antimicrobials enabling resistant organisms to survive, inflammation and edema that reduces blood supply to the sinuses, leading to low oxygen tension,[21] aerobic bacteria consumption of oxygen decreasing the pH inside the sinuses,[22] and expression of virulence factors by anaerobes, such as a capsule.[16]

Aerobic gram-negative bacilli such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* spp, *Proteus mirabilis,* and *Escherichia coli*, have been recovered in CRS, mostly in those with underlying medical conditions such as cystic fibrosis (in the case of Pseudomonas) or diabetes, and in the immunocompromised (neutropenia, critical illness, diabetes mellitus, or HIV).[23–25]

Aerobic gram-negative bacilli have been isolated more frequently in those who have been repeatedly treated with antibiotics or have undergone sinus surgery.[24,27] *S. aureus*, including methicillin resistant staphylococcus aureus (MRSA), can colonizes the nasal mucosa and is found more often in those with CRS.[28] The rate of recovery of MRSA increased in the past decade and accounted for over two-thirds of *S. aureus* isolates.[29,30] Polymicrobial infection is common and may be synergistic in nature.[26] *Stapylococcus epidermidis* is a colonizer of the nasal cavity, and its pathogenicity is questionable.[24]

Fungi can cause allergic fungal rhinosinusitis, fungal colonization, or invasive sinusitis. invasive fungal sinusitis generally occurs in immunocompromised hosts and can be rapidly progressive or indolent.

Odontogenic sinusitis is a well-recognized entity and accounts for approximately 10–12% of cases of maxillary sinusitis[31] and may be either acute or chronic. This condition is rarer in children as compared with adults. The microbiology of odontogenic sinusitis is polymicrobial and reflect the aerobic and anaerobic oral flora.[31] The association between periapical abscesses and rhinosinusitis was established in a study of pus aspirated from five upper jaw periapical abscesses and their corresponding maxillary sinuses.[32]

BETA LACTAMASE PRODUCING BACTERIA

The recovery rate of aerobic and anaerobic beta lactamase producing bacteria (BLPB) in the oropharynx has increased in recent years, and these organisms were isolated in over half of the patients with head and neck infections including sinusitis.[33] The BLPB isolated in PCRS were *S.aureus, H. influenzae, and M. cattarrhalis,* pigmented *Prevotella, Porphyromonas,* and *Fusobacterium* species. BLPB can be involved directly in the infection, protecting not only themselves from the activity of penicillins but also penicillin-susceptible organisms. This can occur when beta-lactamase is secreted into the infected tissue or abscess and inactivates the penicillins' beta-lactam ring before it can kill the susceptible bacteria.[34,35]

Recent receipt of antibiotics, and day care attendance increases the risk of acquiring antimicrobial resistant organisms.[36] The high incidence of recovery of BLPB in upper respiratory tract infections may be due to the selection of these organisms following antibiotic therapy with a beta-lactam antibiotic.[36,37]

The actual activity of the enzyme beta-lactamase and the phenomenon of "shielding" were demonstrated in chronically inflamed sinuses fluids where BLPB were found in 10 of 13 CRS aspirates.[34] The predominate isolated BLPB were *Prevotella* and *Fusobacterium* spp. The recovery of BLPB is not surprising, since all of the patients received antimicrobial therapy that might have selected for the emergence or selection of these organisms.

ANTIMICROBIAL THERAPY

Medical therapy's goal is to enhance sinus drainage, reduce chronic inflammation, and eradicate pathogens. This often requires a combination of topical or oral glucocorticoids, antimicrobials, and nasal irrigation. When these measures fail, the patient should be referred to an otolaryngologist for consideration of sinus surgery.

There is limited data and grade 1 evidence that antibiotics alone are beneficial in the treatment of PCRS. Current approach is to employ antimicrobials combined with topical or systemic glucocorticoids, and sometimes other agents.[38]

Studies examining the effects of comprehensive medical therapy are lacking, although most experts believe that antimicrobials are an important component of therapy for this disease.

A nine-member panel of otolaryngologists reach consensus that 20 consecutive days of antibiotic therapy may produce a superior clinical response in PCRS patients compared to 10 days of antibiotic therapy.[39] The panel also reached a consensus that culture-directed antibiotic therapy may improve outcomes for PCRS patients who have not responded to empiric antibiotic therapy. The panel did not reach consensus that the current evidence supports the use of topical antibiotic therapy or antral irrigation in managing children with PCRS.

Randomized trials in adults that compared different antimicrobials found them to have similar cure rates.[40,41] However, observational studies suggested that agents effective against anaerobic and BLPB provided greater efficacy.[16,42] Brook and Yocum[42] retrospectively investigated the microbiology and management of 40 children who suffered from CRS. The 15 patients who received clindamycin had the most rapid response to therapy and a change of therapy and surgical intervention was required in one case. Of the 16 patients who received amoxicillin or ampicillin, 16 responded to therapy, six needed a change of therapy, including four who also had surgical intervention. Of the six who were treated with erythromycin, three needed antibiotic change, two with surgical intervention. Of the three that received cefaclor, two were cured, and one had an antibiotic change. A randomized trial of 206 adults with CRS, showed a significantly higher relapse in those receiving cefuroxime compared with those treated with amoxicillin-clavulanate (7% versus 0%).[40]

Antibiotic selection depends upon factors that include drug allergies, cost, and the incidence of and/or risk of the presence of BLPB and MRSA.

The initial selection of the antimicrobial therapy is generally empiric especially for community-acquired infections unless a patient had failed to respond to previous therapy. The agents selected should be effective against the most likely bacterial pathogens, including both aerobic (*S. pneumoniae, H. influenzae,* and *M. catarrhalis*) and anaerobic bacteria (*Fusobacterium nucleatum*, pigmented *Prevotella*, *Porphyromonas*, and *Peptostreptococcus* spp). Coverage for MRSA may be indicated.

A culture preferably from directly from the sinus cavity or endoscopically should be obtained in those who have not shown improvement or deteriorated despite therapy.[43]

Antimicrobial resistance has been increasing for the past two decades. These include the production of beta-lactamase and cephalosporinase.[44]

Amoxicillin-clavulanate is the first-line oral agent for most patients. Clindamycin can be administered to those with penicillin-allergy or where MRSA is suspected. Alternatives oral agents that cover MRSA include trimethoprim-sulfamethoxazole (TMP-SMX) and linezolid, which should be added to one of the above regimens that covers anaerobes.

These three regimens are effective against most aerobic and anaerobic microorganisms:

• Amoxicillin-clavulanate (in children: 45 mg/kg per day divided every 12 hours; in adults: 500 mg three times daily OR 875 mg twice daily OR two 1,000 mg extended-release tablets twice daily). "High-dose" (2 g orally twice daily or 90 mg/kg/day orally twice daily) amoxicillin-clavulanate is recommended for children from geographic regions with high endemic rates ($\geq$10%) of invasive penicillin-nonsusceptible (PNS) S. pneumoniae, those with severe infection (e.g., evidence of systemic toxicity with fever of 39°C [102°F] or higher, and threat of suppurative complications), attendance at day-care, age <2, recent hospitalization, antibiotic use within the past month, or who are immunocompromised.[45]

- Clindamycin (in children: 20–40 mg/kg per day orally divided every 6–8 hours; in adults: 300 mg four times daily or 450 mg three times daily)
- Moxifloxacin (400 mg once daily) generally in adults only

Regimens reserved for refractory cases include metronidazole that is effective against anaerobes plus an agent active against aerobic and facultative bacteria:

- Metronidazole (30–50 mg/kg/day in divided doses three times daily; maximum daily dose: 2,250 mg/day) PLUS one of the following: cefuroxime axetil, cefdinir, cefpodoxime proxetil, levofloxacin (generally in adults only), azithromycin, clarithromycin, or trimethoprim-sulfamethoxazole (TMP-SMX).

Immunocompromised patients and those with cystic fibrosis or diabetes should be treated with antimicrobials that provide coverage against *Pseudomonas* spp. Appropriate cultures should be obtained to guide the ultimate antimicrobial choice.

Children with concurrent odontogenic infections should be also treated by a dentist. Antimicrobials are only an adjuvant to resolving the dental origin of the infection.

Antimicrobial treatment is generally given for at least three weeks and may be extended to 10 in refractory cases. Those who might benefit from the longer therapies are patients who failed prior ones, have severe symptoms, experience a longer illness, or had extensive surgery.

Parenteral therapy is administered to children who are seriously ill, undergoing surgery, or in whom compliance is questionable. Parenteral antimicrobials effective against both anaerobes and aerobes include ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, moxifloxacin, the carbapenems (i.e., imipenem, meropenem, doripenem), and the second-generation cephalosporins, cefoxitin.

Parenteral antimicrobials active against MRSA include vancomycin, linezolid, and daptomycin, and

Ceftaroline. For *P. aeruginosa* active antibiotics include a fluoroquinolone (in adults) (e.g., ciporofloxacin or levofloxacin); a third- or fourth-generation cephalosporin with antipseudomonal activity (ceftazidime or cefepime); an aminoglycoside; or the carbapenems (imipenem or meropenem).

Metronidazole may also be given parenterally to cover anaerobes in combination with an agent with aerobic activity.

In contrast to acute sinusitis, which generally is treated with an antimicrobial, many clinicians believe that functional endoscopic sinus surgery (FESS) and not antibiotics is the mainstay of therapy in CRS. The use of only antimicrobial without FESS of accumulated pus may not result in clearance of the infection. The chronically inflamed sinus membranes with diminished vascularity may not contain adequate antibiotic concentration even when the serums level is therapeutic. Furthermore, the reduction in the pH and oxygen tension inside the inflamed sinus may interfere with the activity of antimicrobials resulting in bacterial survival despite a high antibiotic concentration

DRUG-ELUTING NASAL IMPLANTS

Although the primary treatment of CRS is antibiotics and corticosteroids, some patients with medically refractory CRS require FESS.[46] Nasal implants, stents, and packing can be utilized as adjuncts to endoscopic sinus surgery mainly to control hemorrhage, and prevent adhesions formation.[47]

The middle meatus can be implanted with a spacer, implant or a sponge that can remain in place and biodegrade releasing drug load (corticosteroid or antibiotic) over an extended period of time without causing any tissue damage.[48]

In spite of many advantages of drug-eluting nasal implants for CRS, many challenges still remain including the development of toxic shock syndrome, implant blockage and granulation build-up.[49] More research is required to provide sufficient data to show the clinical efficacy and outcomes of drug-eluting stents, packings or implants.

CONCLUSION

S. aureus, and anaerobic Gram-negative bacteria predominate in PCRS. The persistence of the infection can promote the growth of anaerobic bacteria. The initial selection of the antimicrobial therapy is generally empiric and is based on the expected microbiology of the sinus infection. However, in patients who fails to show significant improvement or exhibit deterioration despite therapy, it is important to select antimicrobials based upon appropriate sinus culture.

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