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Multiresistant Bacterial Infections in Pediatric Otolaryngology

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Introduction

The last decade has seen a significant increase in the prevalence of multiresistant bacterial infections affecting the head and neck. Various studies have shown that the proportion of head and neck abscesses caused by community aquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) have increased from 0-9% at the start of the millennium to 33-64% in its latter half [1-3]. A recent study has even shown the proportion of CA-MRSA to be as high as 76%. [4] Following introduction of the pneumococcal 7-valent vaccine (PCV7) in 2000, nasopharygneal carrier and transmission rates of vaccine strains decreased [5], but higher number of infections from non-vaccine and multi-drug resistant strains were reported in several studies with *Streptococcus pneumoniae* 19 A being the most commonly seen in the head and neck region[6,7] In this chapter will discuss the etiology, presentation and treatment of the most common multiresistant bacterial infections seen in pediatric otolaryngology.

Methicillin Resistant *Staphylococcus aureus* (MRSA)

The most common manifestation of CA-MRSA is skin and soft tissue infections such as cellulitis, furuncle, carbuncle, or abscess [8]. In the head and neck, children can present with superficial facial or neck abscesses of the skin, lymphadenitis, or deep lymph node abscesses of the jugular chain, posterior triangle nodes, or submandibular region. Also possible are medial abscesses of the retropharyngeal, parapharyngeal, and peritonsillar regions [2,3].

Presenting signs and symptoms include a mass or swelling, fever, pain, decreased neck mobility, sore throat, decreased oral intake, irritability, leukocytosis, and a preceding upper respiratory tract infection. There do not appear to be differences between methicillin sensitive *Staphylococcus aureus* (MSSA) and methicillin resistant *Staphylococcus aureus* (MRSA) with respect to age, location, and presenting symptoms [3]. Compared with non-staphylococcal infections, however, MRSA and MSSA tend to affect younger individuals in general and have a much higher propensity to afflict specifically those less than 1 year of age [8].

S. aureus is much more likely to cause lateral (anterior and posterior triangle nodes) as well as submandibular or submental abscesses, whereas the medial abscesses mentioned above are much more commonly caused by non-staphylococcal organisms. The most common non-*S. aureus* organisms to cause abscesses of the head and neck are group A *Streptococcus*, namely, *Streptococcus milleri,* and *Streptococcus epidermidis.* Up to 10% of neck infections will grow mixed flora and approximately 25% may yield no growth when cultured [8]. These factors should be taken into consideration when treatment options are considered.

Although most CA-MRSA infections are of the skin and soft tissue, this organism can cause severe, life-threatening sepsis and necrotizing pneumonia. In two small series focusing specifically on children, presenting signs and symptoms of systemic CA-MRSA infection included fever, localized joint pain, myalgia, diffuse rash, and leukocytosis or leucopenia [9,10].

Antibiotic Choice

Treatment of CA-MRSA cellulitis and superficially purulent skin infections is primarily by antibiotic therapy. CA-MRSA tends to be, but is not uniformly sensitive to clindamycin, rifampin, trimethoprim-sulfamethoxazole, and sometimes tetracyclines. Rates of resistance to these agents tend to be less than 10% but this does vary by geographic area **[10,11]**. CA-MRSA is by definition resistant to the penicillins, is clinically resistant to cephalosporins, and tends to have high rates of resistance to quinolones and macrolides. Typically, fewer than 10% of CA-MRSA isolates demonstrate erythromycin-induced clindamycin resistance, or so called type B macrolide-lincosamide-streptogramin (MLS_B) resistance, but again variability depending on geographic region exists [12,13]. It has been suggested that empiric therapy with clindamycin in areas with high rates of MLS_B resistance should be avoided. Of course it may be used for definitive therapy should the individual culture results indicate full susceptibility to the drug. Choices for intravenous antibiotics include vancomycin and gentamicin, both of which have excellent efficacy against CA-MRSA. Antibiograms are typically available from area hospitals or academic centers and can be valuable guides in determining the community physician's choice in empiric antibiotic therapy.

One pressing question concerning antibiotic therapy is whether or not consistent empiric use of an agent to which CA-MRSA is susceptible will lead to the development of resistance to that agent. This does not appear to be the case. In at least one academic center, the consistent empiric use of clindamycin as a first line therapy for CA-MRSA did not alter the proportion of clindamycin resistance over 2 years (98% vs. 97%) [14].

Two fundamental means of b-lactam resistance exist. The first means is the production of b-lactamase, an extracellular enzyme that binds to and enzymatically cleaves the b-lactam ring, rendering the antibiotic inactive. The second means of b-lactam resistance is the alteration of the peptidoglycan crosslinking enzymes **[15]**. This type of b-lactam resistance is effective against methicillin and other b-lactamase-resistant penicillins because it alters the final target of the antibiotic. In *S. aureus*, the emergence of the *gene mec* resulted in the alteration of the peptidoglycan crosslinking enzymes and was responsible for the appearance of MRSA within just a couple of years of the introduction of methicillin into clinical practice in the early 1960s.

The USA300 strain of *S. aureus* is the most common CA-MRSA strain in the United States. USA300 grows more rapidly, causes more severe infections, and spreads more widely geographically than other MRSA and MSSA strains [15-17].

Treatment

Treatment of CA-MRSA cellulitis and superficially purulent skin infections is primarily by antibiotic therapy. CA-MRSA tends to be, but is not uniformly sensitive to clindamycin, rifampin, trimethoprim-sulfamethoxazole, and sometimes the tetracyclines. Rates of resistance to these agents tend to be less than 10% but this does vary by geographic area [16,18]. CA-MRSA is by definition resistant to the penicillins, is clinically resistant to cephalosporins, and tends to have high rates of resistance to quinolones and macrolides. Typically, fewer than 10% of CA-MRSA isolates demonstrate erythromycin-induced clindamycin resistance, or so called type B macrolide-lincosamide-streptogramin (MLS_B) resistance, but again variability depending on geographic region exists [13,14]. Antibiograms are typically available from area hospitals or academic centers and can be valuable guides in determining the community physician's choice in empiric antibiotic therapy.

With the above caveats in mind, the following treatment algorithm for CA-MRSA infections of the head and neck is proposed. Given the significant symptomatic overlap between staphylococcal and non-staphylococcal infection lymphadenitis, initial empiric therapy should be directed at both types of infection.

Clindamycin is an appropriate choice of therapy for this purpose. In addition, trimethoprim-sulfamethoxazole provides excellent coverage and may be useful in areas where clindamycin-resistant MRSA is prevalent. Children with neck lymphadenopathy and high fever with evidence of a phlegmon on imaging should be admitted for intravenous therapy. A failure to improve within 48 hours warrants surgical treatment. Otolaryngologic consultation for airway evaluation and surgical intervention can be made earlier at the discretion of the admitting team. Contrast-enhanced CT may help differentiate abscess from lymphadenitis or phlegmon, and is important for surgical planning in order to ensure that multiple loculations or occult abscesses are surgically drained. However, given the small but apparently real risk of malignancy associated with high resolution CT of the head and neck [19], the decision for CT may be reserved for those patients which may present with a possible deep space abscess and when the physical findings of erythema, pain and fluctuance are not obvious. Ultrasound is a good alternative for patients that present with superficial or lateral neck lymphadenitis. Abscesses larger than 5 centimeters are likely to require both I&D and a longer course of antibiotic therapy. The treatment of systemic MRSA illness, pneumonia, or sepsis requires intravenous antibiotic therapy and intensive care unit support, a full discussion of which is beyond the scope of this chapter.

***Streptococcus pneumoniae* 19A**

Streptococcus pneumoniae is commonly found in the upper respiratory tract of healthy individuals, and can cause acute otitis media (AOM) (isolated in 40% of cases[5]), rhinosinusitis, bacteremia (responsible for up to 85% of pediatric occult cases of bacteremia), meningitis (most common cause of bacterial meningitis in children, particularly after cochlear implants or traumatic cerebrospinal fluid leak), pneumonia (most common bacterial cause of pediatric pneumonia, especially under 5 years of age) and systemic invasive infections[21]. Pneumococci are gram-

positive, encapsulated, lancet-shaped diplococci and are transmitted by respiratory droplet contact. Risk of invasive pneumococcal infections is seen in children less than 2 years and particularly patients with humoral immune deficiencies, decreased splenic function, immunosuppression, chronic renal failure, chronic pulmonary disease diabetes mellitus, cochlear implants, traumatic cerebrospinal fluid leaks and malignancies[5]. Over ninety serotypes of S. pneumonia have been identified, with serotypes 4, 6B, 9V, 14, 18C, 19A/F and 23F causing more aggressive, invasive disease, and frequently antibiotic resistant [5,21,22].

Multi-drug resistant *Streptococcus pneumoniae* was first reported in the 1960s with increasing incidence of penicillin resistance after 1990, and rapid emergence of multi-drug resistant serotypes over the past decade. *S. pneumoniae* 19A (Sp19A) is one of the more common multi-drug resistant serotypes found in pediatric patients, and was first reported in the United States in 1986 [7]. Following introduction of the pneumococcal 7-valent vaccine (PCV7) in 2000, nasopharygneal carrier and transmission rates of vaccine strains decreased[4], but higher number of infections from non-vaccine and multi-drug resistant strains were reported in several studies[7,23].

Although the exact mechanism is unknown, higher numbers of non-vaccine strain infections could be facilitated by the reduction in vaccine strains, known as replacement phenomenon[23-25]. *Streptococcus pneumoniae* is the most common cause of acute otitis media and mastoiditis in children, and in some studies, Sp19A has been the predominant pneumococcal serotype associated with coalescent mastoiditis[25]. Coinciding with increasing incidence of Sp19A, this serotype is also accumulating more drug resistance to available antibiotics, particularly penicillin[7]. Resistance to erythromycin and tetracyclines has also been reported [6]. In one study, a broadly-resistant strain of Sp19A was isolated, with clinical resistance to low- and high-dose amoxicillin (AMX), amoxicillin-clavulanate (AMX-CLAV) and ceftriaxone (CEFTIRIAX), but remaining susceptibility to levofloxacin with resolution of infection[6]. But we should remember that quinolones (levofloxacin) are not recommended for pediatric patients. Current antibiotic recommendations for otitis media and sinusitis include AMX (low- or high-dose) as the initial drug of choice, with failures requiring AMX-CLAV or a cephalosporin (cefuroxime, cefdinir, cefpodoxime or CEFTRIAX) or myringotomy with culture-directed therapy.

Pseudomonas aeruginosa

Cystic fibrosis patients often become chronically infected with multiresistant *Pseudomonas aeruginosa*. Infections often initially begin as an acute infection with *Staphylococcus aureus* which eventually develop into a chronic infection. Chronic infections cause acute periodic exacerbations marked by increased sputum production and sharp decline in pulmonary function. These chronic infections are commonly caused by *P. aeruginosa* and cause extensive pulmonary damage. The goal of treatment is therefore to limit deterioration of the lungs. Combination intravenous antibiotics are usually given for 2 weeks to treat acute exacerbations with an aminoglycoside in addition to an antibiotic that acts on the bacterial wall (such as ceftaxidime or meropenem) being the commonest combination [26].

The prevalence of multiresistant infections is on the rise particularly in CF patients. This is secondary to repeated and prolonged use of antibiotics for exacerbations of symptoms or as part of a planned regular treatment leading to selective pressures. *Pseudomonas aeruginosa* obtains its resistances through various mechanisms, including production of antibiotic-modifying enzymes, target modification, and altered permeability of efflux [27]. Therefore, the use of two antipseudomonal antibiotics is recommended to discourage resistance formation among *P. aeruginosa* and has additionally been found to have synergistic effects.

The interesting finding regarding combination therapy is that patients have been shown to respond to antibiotic treatments even though their isolates of *P. aeruginosa* are resistant [28]. This process is not completely understood although there are several theories behind this finding. Resistant *P. aeruginosa* isolates may be less fit and less pathogenic than susceptible organisms. Another thought is that some bugs found in the normal flora of the upper respiratory tract have been shown to increase the pathogenicity of *P. aeruginosa* by modulating gene expression through *quorum sensing* [29]. The pathogenicity of the *P. aeruginosa* may therefore be diminished if the antibiotics were to effectively eliminate other species. Reversion to susceptibility is another possibility for patient's response to antibiotic treatment after being diagnosed with multiresistant *P. aeruginosa*. This suggests that patients are infected with multiple strains of *P. aeruginosa* and previous susceptibility profiles should be considered when selecting an antimicrobial regimen [30].

Another therapeutic option available to physicians is the use of inhaled antibiotic therapy. Possible uses of aerosol antibiotics include prophylaxis, eradication of early infection, suppression of chronic infection, and treatment of acute pulmonary exacerbations. This has the intended benefit of delivering relative high doses of antibiotic therapy directly to the site of the infection while minimizing systemic exposure. This is greatly advantageous when compared to IV aminoglycoside usage. Intravenous medications have very poor penetration into the endobronchial space and therefore require high dosages to be efficacious. However, inhaled therapy tends to be time consuming (up to 20 minutes per treatment) and requires specialized equipment. Newer modalities of aerosoled equipment has helped to reduce the time needed for deliver (down to 2-3 minutes) as well as negating the need for repeated equipment cleaning [31].

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