Appropriate Antibiotic Use in Treating Respiratory Tract Infections

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Presentation Summary

The emergence of drug-resistant pathogens, especially *Streptococcus pneumoniae* and *Haemophilus influenzae*, has complicated empiric treatment of both upper and lower respiratory tract infections. Clinicians are now forced to reevaluate their choices of first-line antibiotics. Although some bacterial respiratory infections may resolve spontaneously, the use of antibiotics has demonstrated a faster resolution of symptoms and prevention of sequelae and recurrences, thereby improving the patient's quality of life and ability to function. Therefore, it is recommended that all diagnosed bacterial respiratory infections be treated with an antibiotic. Factors that clinicians need to consider in prescribing an antibiotic are the predominant causative pathogens, rates of pathogen resistance, patient history, the bacteriologic and clinical efficacy, safety profile, dosing regimen, and cost effectiveness of available antibiotic choices.

Many upper and lower respiratory tract diseases, both infectious and noninfectious, present with similar signs and symptoms. However, most respiratory tract infections (RTIs) are viral in origin and do not respond to antibiotic therapy. The first step in appropriate antibiotic prescribing is to distinguish between infectious and noninfectious respiratory conditions and then to ascertain whether the etiology of the infection is viral or bacterial.

Diagnosing Bacterial RTIs

The term *otitis media* covers a range of conditions that includes acute otitis media (AOM), otitis media with effusion, external otitis, and chronic suppurative otitis. Many symptoms of AOM (eg, cough, fever, irritability, congestion) are also associated with viral upper respiratory tract infections (URIs). Diagnosis of AOM requires documented middle ear effusion, signs of inflammation during an otoscopic examination, and recent onset of signs and symptoms of local or systemic illness (eg, otalgia, fever, lethargy).[1] Earache is the most prominent symptom and is often the factor that distinguishes AOM from a viral URI.[1]

The symptoms associated with sinusitis (eg, sneezing, rhinorrhea, nasal congestion, postnasal drip, cough, ear fullness) can be attributed to a number of associated diseases of the upper respiratory tract (eg, bacterial sinusitis, viral URI, allergic rhinitis).[2] Bacterial sinusitis is often misdiagnosed. A diagnosis of acute bacterial sinusitis can be made in a patient who has had a viral URI that persists beyond 10 days, or worsens after 5 to 7 days, and is accompanied by some or all of the following symptoms: nasal drainage, nasal congestion, facial pressure/pain (especially when unilateral and focused in the region of a particular sinus), postnasal drainage, hyposmia/anosmia, fever, cough, fatigue, dental pain, and ear pressure/fullness.[3]

The symptoms of acute exacerbation of chronic bronchitis (AECB) are easily confused with other respiratory diseases such as influenza, pneumonia, asthma, and, in particular, acute bronchitis. Whereas viral infections are responsible for as much as 95% of acute bronchitis cases[4] approximately half of AECB cases are bacterial in origin.[5] The cardinal symptoms of AECB are increased dyspnea, increased sputum volume, and increased sputum purulence.[5] Increased frequency and severity of cough, malaise, and appetite loss may also be present.[6]

Decision to Treat RTIs with an Antibiotic

Although many cases of bacterial AOM, acute sinusitis, and AECB will resolve without antibiotic treatment, a number of important factors should be considered when deciding whether to treat these infections with antibiotics.

Acute Otitis Media. Approximately 30% of children with AOM do not have a bacterial pathogen in middle ear fluid,[7] and a bacterial infection in some patients will clear without an antibiotic. However, because it is not possible to predict in which cases AOM will resolve spontaneously, it is recommended that all diagnosed cases of AOM be treated with an antibiotic. A number of outcome data support this recommendation[8]:

- Most infections caused by *Streptococcus pneumoniae* and half of those caused by *Haemophilus influenzae* do not resolve microbiologically without an antibiotic.
- Symptoms resolve more rapidly and effectively with antibiotic therapy than without it. Patients get well faster and families can return to normal activities more quickly.
- Antibiotic treatment results in decreased middle ear effusion (which is associated with hearing loss) and fewer suppurative complications (eg, acute mastoiditis), corrective surgeries, and recurrences of AOM.

Sinusitis. Although the predicted spontaneous resolution rate for sinusitis is approximately 50% in children and adults, treatment guidelines recommend administration of antibiotics for all acute, uncomplicated cases.[3] The rationale behind the recommendation suggests that antibiotics reduce or eliminate bacteria in the maxillary sinuses; improve uncomfortable and painful symptoms; and help prevent recurrences, sequelae, and chronicity.

Acute Exacerbations of Chronic Bronchitis. The role of bacteria in causing AECB is uncertain because pathogens may be present when the bronchitis is stable. In addition to precipitating exacerbations, bacteria may also serve as secondary infecting agents during or after viral infection and contribute to progressive airway destruction by inducing inflammatory immune responses and the production of inflammatory products. Therefore, antibiotics are recommended in patients with diagnosed AECB[5] who satisfy the criteria defined by Anthonisen et al.[9] Short-term benefits of antibiotic therapy include reduced duration of symptoms, increased possibility of a clinical cure, and decreased possibility of clinical deterioration. Associated benefits include reduced risk of hospitalization, less time lost from work, and prevention of progression from airway infection to pneumonia.[5] Potential long-term benefits include prevention of progressive deterioration of the airways, prolongation of time between exacerbations, and prevention of secondary bacterial colonization following a primary viral infection.[5]

Factors in Empiric Selection of an Antibiotic

To prevent further development of antibiotic resistance, clinicians must prescribe antibiotics that effectively eradicate causative pathogens in patients with AOM, acute sinusitis, or AECB. One of the biggest challenges clinicians face in selecting appropriate antibiotics is that pathogens cannot be evaluated during an office visit. Cost and time constraints often prevent routine culturing of organisms before initiating treatment, thus most RTIs are treated empirically. Fortunately, better information is now available to help with antibiotic selection, including resistance and surveillance data, pharmacokinetic/pharmacodynamic (PK/PD) breakpoints for a more accurate analysis of susceptibility and clinical efficacy, and sound clinical data on therapeutic outcomes.

A number of factors need to be considered before selecting an antibiotic for each patient, including suspected causative pathogen(s), local resistance patterns, bacteriologic and clinical efficacy of antibiotics, patient history, antibiotic safety profile, dosing regimen, and cost effectiveness. Although causative pathogens cannot be determined without culturing, likely pathogens may be suggested by the site of infection (**Table**) and age of patients. For example, *S pneumoniae* is generally the predominant pathogen causing AOM, but *Moraxella catarrhalis* is often the first pathogen isolated in initial infections in children under 6 months of age.[10] *S pneumoniae* is also the predominant pathogen in acute sinusitis, but *H influenzae* is the predominant pathogen causing AECB.[11] The local prevalence of resistant strains of suspected causative pathogens should also be determined, if reliable information is available. In areas where resistance is high, second-line antimicrobial agents with broader coverage may offer an advantage over first-line drugs.

Table. Principal Bacterial Causes of Community RTIs

	Prevalence (%)		
	Streptococcus pneumoniae	***Haemophilus influenzae***	***Moraxella catarrhalis***
Acute sinusitis (adults)	31	21	2
Acute otitis media	29	26	12
Acute exacerbations of chronic bronchitis	15 to 30	40 to 60	15 to 30

RTIs= respiratory tract infections.
Source: References 7, 11, 16.

In this era of increasing resistance, the most important factors in antibiotic selection are bacteriologic and clinical efficacy against suspected causative pathogens, both susceptible and resistant. Because clinical efficacy depends on both the minimum inhibitory concentration (MIC) of the drug in vitro and the drug concentration at the site of infection in vivo, a new approach has been developed to measure susceptibility breakpoints that correlate the PK and PD properties of antibiotics. Bacteriologic and clinical efficacy should be evaluated based on these PK/PD breakpoints. Antibiotics that are not effective against suspected susceptible and resistant pathogens should be eliminated from consideration. Two recent surveillance surveys using PK/PD breakpoints[12,13] provide an overview of antimicrobial activity against common respiratory pathogens.

When clinicians submit respiratory tract cultures, particularly from the ears and sinuses, the susceptibility patterns reported by various clinical laboratories can be incomplete or misleading. The largest problem concerns inappropriate breakpoints: The definitions of susceptible, intermediate, and resistant often do not correlate with predicted or observed clinical activity. The most recent recommended breakpoints from the National Committee for Clinical Laboratory Standards (NCCLS) for *S pneumoniae* have been appropriately adjusted so they are reasonably consistent with PK/PD derived breakpoints and achievable extracellular tissue levels. However, the *H influenzae* breakpoints have not been adjusted, therefore cephalosporins and macrolides are interpreted as being clinically active because of inappropriately high breakpoints. The NCCLS has this issue on their agenda this year, and one can expect the *S pneumoniae* and *H influenzae* breakpoints to be the same when all changes have been made.

Because the activity of most agents is fairly consistent against various strains of *H influenzae*, the clinician can be reasonably well served by understanding which agents have excellent (quinolones, third-generation cephalosporins, high-dose amoxicillin-clavulanate) and good (cefuroxime axetil and cefdinir) *H influenzae* activity. The other choices can be expected to have fair to poor bacteriologic activity against *H influenzae*. Unfortunately a number of the commonly prescribed antimicrobials have activity against *H influenzae* that is not demonstrably better than placebo. However, patients with nontypeable strains of *H influenzae* given placebo may get well, especially if otherwise healthy patients and older children are treated.

Clinical laboratories should report the actual amoxicillin MIC value for ear, nose, and sinus isolates of *S pneumoniae* when the isolates fail the oxacillin disk screening test. Because amoxicillin, particularly at higher doses, is reasonably active against strains with MICs of 2 and 4 μg/mL[14] (values that would lead to a classification of "penicillin resistant"), clinicians could more appropriately decide on therapies and evaluate response trends. Further, such reporting would help track the continued rise of pneumococcal amoxicillin MICs.

The safety profiles of various common antibiotics differ considerably, thus they can be important determinants of patient compliance. Patients also tend to comply better with more convenient dosing regimens (ie, fewer doses per day and shorter therapy regimens). Several agents (ie, cefixime, cefprozil, azithromycin, levofloxacin, gatifloxacin, and moxifloxacin) can be taken once daily; azithromycin is taken for only 5 days. Palatability of antibiotic formulations can also affect compliance and should be considered. For example, both cefixime and clarithromycin have a bitter taste. Antibiotics are often associated with gastrointestinal disturbances, which also may affect compliance.

Another important factor in selecting an antibiotic is overall cost effectiveness of antibiotic therapy. Cost effectiveness takes into account the cost of initial treatment, the cost of treatment failures and subsequent course(s) of antibiotics, complications, treating adverse events, poor quality of life, lost productivity, and absences from work. Prescribing solely on the basis of initial drug acquisition cost is not cost effective. It merely shifts the costs backward to recurrences and hospitalizations, which are more expensive and can be avoided.

Finally, patient history must be considered when selecting an antibiotic. Information about recent antibiotic use and treatment failure with a particular agent or class of drugs should be elicited because prior antibiotic use is a major risk factor in the development of infection as a result of antibiotic-resistant strains. Patient history will also reveal known hypersensitivity to particular antibiotics, the patient's age, and day care attendance, which is a significant risk factor for infection with a resistant pathogen.[15]

Conclusion

In today's multidrug-resistant environment, the best strategy to ensure clinical cure in patients with RTIs is to select antibiotics that have demonstrated superior efficacy against susceptible and resistant strains of suspected causative pathogens. Information on local resistance patterns, data from clinical studies on therapeutic outcomes, and surveillance surveys based on PK/PD breakpoints can assist clinicians in deciding on appropriate agents. Other factors that may enhance compliance and help prevent treatment failures include a convenient dosing regimen, few adverse effects, and palatability. The prevention of treatment failures should be one of the most important factors to consider when comparing the cost effectiveness of antibiotic therapies.

··· REFERENCES ···

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