Therapeutic Strategy of Infections Caused by Antibiotic -Resistant Pneumococci

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SUMMARY

Pneumococci are the commonest bacterial pathogens in acute otitis media, acute sinusitis, community-acquired pneumonia, and acute exacerbations of chronic bronchitis. Treatment of these diseases is usually on an outpatient basis and is empiric, and is designed to cover other common causes of these diseases such as *Haemophilus influenzae* and *Moraxella catarrhalis* as the etiologic agents is not usually identified. Treatment of these diseases has recently been complicated by the development of antimicrobial resistance of these pathogens, particularly beta-lactam, macrolide and cotrimoxazole resistance in *S. pneumoniae*, and beta-lactam resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* due to beta-lactamase production.

Pneumococi are also the commonest bacterial cause of meningitis in children and adults worldwide, and treatment is problematic due to limited penetration of many agents into cerebrospinal fluid.

Strains of pneumococci resistant to antimicrobial agents have now been reported from all continents and have become the predominant pathogens in some areas, with many strains being multiply resistant. Because of the importance of pneumococci in the etiology of meningitis, minimal inhibitory concentrations (MICs) of penicillin G of ¡ Â0.06 § ¶ml are regarded as susceptible, while MICs of 0.1 to 1 § ¶ml are intermediate and MICs of ¡ Ã2 § ¶ml are resistant.

Treatment of resistant pneumococcal infections is therefore based on the site of infection, degree of penicillin G resistance and presence of resistance to other agents of the infecting strain, severity of disease, presence of underlying conditions, and dose and route of administration of antimicrobial agents. Current treatment recommendations are empiric or based on retrospective case studies, and adequate prospective studies need to be performe to provide more definitive data.

INTRODUCTION

Development of resistance of pneumococci to penicillin in vitro as well as in vivo in a mouse model was reported soon after the introduction of penicillin in 1943. However, it was only in 1967 that pneumococci with decreased susceptibility to penicillin were first reported from human clinical isolates, and strains with higher levels of resistance as well as resistance to many other agents have been recognized since 1977 [8]. Resistant pneumococci have now been reported from all continents and are the predominant pathogens in some areas. The therapy of resistant pneumococcal infections is covered in this presentation.

Until the clinical emergence of pencillin-resistant strains, susceptibility testing of pneumococci was regarded as superfluous. Since the description of highly resistant as well as multiply-resistant strains in the 1970s susceptibility testing is now essential, and all clinically-significant isolates should be screened at least for penicillin susceptibility [8].

Subsequently strains with high-level resistance to third generation cephalosporins were described associated with clinical failure in meningitis in four patients in 1991, with MICs of these cephalosporins being **higher** than MICs of penicillin, unlike previously encountered strains where third-generation cephalosporin MICs were one to two doubling dilutions **lower** than those of penicillin [2,11].

Pneumococci have penicillin MICs at all concentrations from 0.008 to > 16 § ¶ml, and do not have clearly defined populations at any specific MICs. Therefore, the definition of susceptibility and resistance to penicillin is somewhat arbitrary due to lack of defined bimodal populations and inadequate clinical data, and clinical application must be based on the site of infection and the pharmacokinetics of the agent administered. Strains with minimal inhibitory concentrations (MICs) of penicillin G of ¡ Â0.06 § ¶ml are regarded as susceptible, while strains with MICs of 0.12 to 1 § ¶ml are intermediate and ¡ Ã2§ ¶ml are resistant[9]. These breakpoints are primarily based on fully-susceptible strains having MICs of 0.008 to 0.03 § ¶ml, and appear to have good clinical correlation in meningitis and in infections treated with oral ¥ âlactams.

ETIOLOGY OF RESPIRATORY TRACT INFECTIOINS

Pneumococci are the commonest bacterial pathogens in respiratory tract infections such as acute otitis media, acute sinusitis, community-acquired pneumonia, and acute exacerbations of chronic bronchitis. Treatment of these diseases is usually on an outpatient basis and is empiric, and is designed to cover other common causes of these diseases such as *Haemophilus influenzae* and *Moraxella catarrhalis* as the etiologic agent is not usually identified. Treatment of these diseases has recently been complicated by the development of antimicrobial resistance of these pathogens, particularly beta-lactam, macrolide and contrimoxazole resistance in *S. pneumoniae*, and beta-lactam, macrolide and cotrimoxazole resistance in S.pneumoniae, and beta-lactam resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* due to beta-lactamase production. While current treatment usually covers beta-lactamase-producing pathogens, they have generally not been modified to take resistant pneumococci into account.

CHOICE OF AGENTS REQUIRING TESTING

Choice of agents depends of the nature and severity of the pneumococcal infection, clinical practices of physicians, requirement for oral versus parenteral agents, use of empiric regimens, cost and availability of antimicrobials, and knowledge of susceptibility of related agents [8]. While treatment of strains susceptible to agents in clinical use is well-established, little clinical data is available for resistant strains.

Agents suggested for initial testing include penicillin G, chloramphenicol, erythromycin, tetracycline and cotrimoxazole. If penicillin resistance if found additional testing is required to determine susceptibility to cephalosporins such as cefotxime and ceftriaxone (see above); imipenem and vancomycin may also be tested if clinically indicated. Oral beta-lactams, with the exception of amoxicillin and cefuroxime axetil, should not be tested until further clinical data become available for resistant pneumococcal infections and clinically-relevant breakpoints developed.

TREATMENT

Treatment of resistant pneumococcal infections is complicated by factors such as delays in recognizing the presence and degree of resistance in strains, variability of drug levels at different sites, particularly in cerebrospinal fluid (CSF), natural history of diseases at different sites and in different age groups, stage of infection at which initial or appropriate therapy is initiated, and presence of underlying conditions such as malnutrition, immunodeficiency or malignancy. Little prospective clinical data is currently available to guide clinical use, and most recommendations are still tentative and largely empiric [1,3].

MENINGITIS

Meningitis and overwhelming bacteremia are the most serious forms of disease, and are the least responsive to therapy due to poor CSF drug penetration in meningitis or massive organism load in bacteremia. Experimental assessment of treatment of resistant pneumococcal meningitis has ben evaluated in animal models [8]. Cefotaxime has been shown to penetrate into CSF less well (3.5% of serum level) than newer cephalosporins such as cefpimazole (16.5%), cefepime (BMY 28142) (20.2%) and cefpirome (HR 810)(21.8%). Survival only occurred when SCF drug levels exceeded MBCs of the infecting strains by between 10-and 30-fold.

Experimental CSF cephalosporin penetration
Percentage of serum level

Cefotaxime	3.5%
Cefpimazole	16.5%
Cefepime (BMY 28142)	20.2%
Cefpirome (HR 810)	21.8%

Survival only occurred when CSF drug levels exceeded MBCs of the infecting strain by between 10-and 30-fold

Clinically, patients with meningitis due to penicillin resistant strains (MICs ¡ Ã2§ ¶ /ml) have shown clinical failure with penicillin G therapy, although some patients with intermediately resistant strains have responded to high dose penicillin therapy

(500,000U/kg per day). Cefotaxime at 250 to 350 mg/kg per day in adults has shown fairly good clinical utility in patients with meningitis caused by strains with penicillin MICs as high as 4 § ¶ml (7 cures, 1 relapse and 1 death). Vancomycin (30 to 45 mg/kg per day in adults) has shown disappointing results in some cases, related in some, but not all, instances to variability of CSF levels of the drug, and in one case report daily intrathecal doses of 25mg were successfully administered. Chloramphenicol (100mg/kg per day) has shown clinical failure in cases caused by penicillin resistant but chloramphenicol susceptible strains [4]. These failures have been postulated to be due to the poor bactericidal activity of chloramphenicol against penicillin resistant strains, which may be associated with the loss of autolysin seen in penicillin resistant strains. A consensus report in 1997 on therapy of penumococcal meningitis in infants and children recommends cefotaxime or ceftriaxone **plus** vancomycin for empiric therapy and for strains intermediate or resistant to penicillin but susceptible to the cephalosporins [1]. Optimal therapy for strains resistant to cefotaxime or ceftriaxone is unknown, and current recommendations are to use the above therapy as the combination is synergistic, with repeat lumbar puncture to monitor for bacteriological failure; addition of rifampin is also suggested, although both vancomycin and rifampin are very slowly bactericidal[1]. Use of imipenem is discouraged as this agent has been reported to cause seizures in some patients. Meropenem has been reported to be effective in treatment of meningitis in children caused by resistant strains without central nervous system side-effect[1,4]. Assessment of results of therapy of meningitis in adults caused by resistant strains is complicated by the relative rarity of this disease in adults and the high mortality rate that occurs even when caused by susceptible strains.

BACTEREMIA

In penicillin resistant pneumococcal bacteremia, the outcome in both adults and children may be related to underlying pedictors of mortality rather than beta-lactam resistance of strains [1,10]. Penicillin, ampicillin, cefuroxime, cefotaxime and ceftriaxone in adequate dosage are therefore all regarded as adequate based on current levels of resistance [1,10]. Recommended adult IV doses are 150,000 -200,000 U penicillin G per kg per day (2 million U every 4 hours) ; 2 g ampicillin every 6 hours; 1-2 g ceftriaxone every 24 hours; and 1-2 g cefotaxime every 6 hours.

Severe pneumococcal pneumonia, Barcelona, Spain, 1984-1993 506 patients, 392 with bacteremia		
Susceptibility	Therapy	
	Penicillin or ampicillin	Cefotaxime or Ceftiaxone
Penicillin susceptible (MICs ¡ Â0.06 § ¶ml)	19% (N = 126)	25% (N= 127)
Penicillin resistant (MICs 0.12 - 4 § ¶ml)	25% (N = 24)	22% (N=59)
Cephalosporin susceptible (MICs ¡ Â0.5 § ¶ml)	24% (N = 168)	20% (N =145)
Cephalosporin resistant (MICs 1-4 § ¶ml)	22% (N = 18)	20% (N=5)
Differences not statistically significantly different when adjusted for severity of underlying diseases. From Pallares et al., NEJM 1995, 333:474-480		

RESPIRATORY TRACT INFECTIONS

Community-acquired sinusitis, pneumonia, and acute exacerbations of chronic bronchitis are usually treated empirically on an outpatient basis, and little information is available on the effect of pneumococcal resistance on choice of agents and morbidity.

ACTIVITY OF ORAL BETA-LACTAMS AGAINST PNEUMOCOCCI

Agent	MIC_{90} (§ ¶ml)			Peak serum level (§ ¶ml)
	Penicillin susceptible[a]	Penicillin intermediate[b]	Penicillin resistant[c]	
Amoxicillin	0.015 - 0.03	0.12 - 1	2	3.5 - 7
Cefpodoxime	0.06 - 0.25	1 - 4	4	1.4 - 3.8
Cefuroxime axetil	0.03 - 0.125	1 - 4	4 - 8	2 - 7
Cefaclor	0.5 - 2	8 - 16	16 -¡ Ã32	7 - 13
Cefixime	0.25 - 1	8 - 32	¡ Ã32	3 - 4.6
Cefprozil	0.25 - 1	8	¡ Ã32	6 - 10
Loracarbef	1.5 -2	64	¡ Ã128	13 - 19

[a]MICs ¡ Â0.06 § ¶ml [b]MICs 0.1 - 1 § ¶ml [c]MICs ¡ Ã2§ ¶ml

Selected agents approved in the USA for treatment of respiratory tract infections

Penicillins Amoxicillin amoxicillin-clavulanate	**Cephalosporins** Cefaclor Cefixime Cefpodoxime Cefprozil Ceftibuten cefuroxime zxetil loracarbef
Macrolides Azithromycin clarithromycin erythromycin	**Quinolones** ciprofloxacin levofloxacin ofloxacin sparfloxacin
Teracyclines Doxycycline	

OTITIS MEDIA

Otitis media caused by resistant pneumococci is probably a greatly underestimated problem due to the infrequency of obtaining diagnostic material from the middle ear. As meningitis is a significant complication of otitis media in patients under 12 months of age, treatment of otitis media is important in prevention of complications as well as treating the primary infection. Optimal therapy both of acute otitis media and for the prevention of recurrent otitis media by antimicrobial prophylaxis or placement of tympanotomy tubes remains controversial. Cefuroxime axetil and amoxicillin-clavulanate have been studied in penicillin-susceptible and resistant otitis media, and specific breakpoints are now available for these agents [5,7,9[. Use of higher doses of amoxicillin (80 - 100 mg/kg/day) produces higher serum levels and longer times above MICs, and clinical studies are needed to evaluate this approach [1,7].

OUTCOME OF PNEUMOCOCCAL OTITIS MEDIA
BASED ON CEFUROXIME SUSCEPTIBILITY
Cefuroxime axetil at 30 mg/kg/day bid for 8 days

Cefuroxime MICs	Clinical success
Susceptible MICs ¡ Â0.5 § ¶ml	43/46 (93.5%)
Intermediate MICs 1 § ¶ml	0/1 (0%)
Resistant MICs ¡ Ã2§ ¶ml	29/37* (78.3%)

** Penicillin MICs all ¡ Ã1§ ¶ml, with 30 at 2 § ¶ml*

From Gehanno et al., Antimicrob Agents Chemother 39:271-272,1995

OUTCOME OF AMOXICILLIN-CLAVULANATE THERAPY
OF PNEUMOCOCCAL OTITIS MEDIA
Amoxicillin-clavulanate 40/10 mg/kg/day tid for 10 dyas

Penicillin MIC (§ ¶ml)	No. of patients	Outcome et end of therapy		
		Success*	Failure	Undetermined
¡ Â0.06 (S)	197	93%	4%	3%
0.12 0 1 (I)	65	92%	0%	8%
¡ Ã2 (R)	25	92%	8%	0%

** Clinical cure or improvement*

From Hoberman et al., Pediatric Infectious Disease Journal 15:955-962, 1996

CONCLUSIONS

Although considerable progress has been made in antimicrobial therapy in the last 50 years, pneumococci have acquired resistance to many classes of antimicrobials. This is of particular concern in meningitis due to poor drug penetration into CSF, and also in oral therapy of respiratory tract infections. The current susceptibility of pneumococi to oral agent show the magnitude of the problem [6.8].

MICs of selected oral agents against 973 pneumococci isolated in USA and Western Europe in 1994		
Agent	Modal MIC (§ ¶ml)	MIC_{90} (§ ¶ml)
Pennicillin	0.03	2
Ampicillin	0.03	4
Amoxicillin	0.03	2
Amoxicillin-clavulanate	0.03	2
Cefuroxime	0.03	8
Cefaclor	1	> 64
Cefixime	0.25	8
Azithromycin	0.06	¡ Ã32
Clarithromycin	0.03	¡ Ã32
Erythromycin	0.03	¡ Ã32
From Groneberg et al., Diagn Microbiol Infect Dis 25:169 - 181, 1996		

While the presence and extent of pneumococcal resistance has been recognized worldwide, limited progress has been made in prevention and treatment of resistant pneumococcal infections, eradication of nasopharyngeal carriage, prevention of community and nosocomial spread, and vaccine development. Problems of specific clinical concern are the treatment of meningitis due to penicillin resistant strains, and of otitis media caused by multiply-resistant strains often resistant to all currently available classes of oral agents. Clinical microbiology laboratories must screen all clinically significant isolates for resistance, and prospective studies need to be carried out in areas where resistant strains are prevalent to define therapy of infections due to strains of varying levels of penicillin resistance as well as resistance to other agents.

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