

AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

Therapy for Children With Invasive Pneumococcal Infections

ABSTRACT. This statement provides guidelines for therapy of children with serious infections possibly caused by *Streptococcus pneumoniae*. Resistance of invasive pneumococcal strains to penicillin, cefotaxime, and ceftriaxone has increased over the past few years. Reports of failures of cefotaxime or ceftriaxone in the treatment of children with meningitis caused by resistant *S pneumoniae* necessitates a revision of Academy recommendations. For nonmeningeal infections, modifications of the initial therapy need to be considered only for patients who are critically ill and those who have a severe underlying or potentially immunocompromising condition or patients from whom a highly resistant strain is isolated. Because vancomycin is the only antibiotic to which all *S pneumoniae* strains are susceptible, its use should be restricted to minimize the emergence of vancomycin-resistant organisms. Patients with probable aseptic (viral) meningitis should not be treated with vancomycin. These recommendations are subject to change as new information becomes available.

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; MIC, minimum inhibitory concentration; CSF, cerebrospinal fluid; IV, intravenously; MBC, minimal bactericidal concentration; NCCLS, National Committee for Clinical Laboratory Standards.

ANTIMICROBIAL RESISTANCE IN *STREPTOCOCCUS PNEUMONIAE*

Epidemiology of Antimicrobial Resistance

The Centers for Disease Control and Prevention (CDC) suggest that the same nomenclature used to define resistance for other bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, be used for *S pneumoniae*. All organisms with a minimum inhibitory concentration (MIC) equal to or greater than that defined for the intermediate category of resistance will be classified as *nonsusceptible* (Table 1). *Resistant* organisms will have an MIC equal to or greater than that defined for the resistant category. These latter organisms were formerly known as *highly resistant*. Strains in the resistant category for the penicillins, cephalosporins, and other β -lactam antibiotics are of particular concern, because they are generally also resistant to most other antibiotics, including the cephalosporins, trimethoprim-sulfamethoxazole, erythromycin, chloramphenicol, and tetracycline.¹ In children older than 2 months, *Streptococcus pneumoniae* is the most common cause of invasive bacte-

rial infections. The prevalence of infections caused by penicillin-*nonsusceptible S pneumoniae* for all ages has increased in the United States during the last 5 years (Figure).²⁻⁶ In recent years, in children, the proportion of penicillin-*nonsusceptible* invasive isolates has varied from 0% to 41%. Of these *nonsusceptible* isolates, 5% to 21% were resistant (Table 1). The incidence of cefotaxime- and ceftriaxone-*nonsusceptible* isolates has increased to 20% in some areas (Table 2).⁷⁻²⁵

Mechanism of Antimicrobial Resistance

Penicillins, cephalosporins, and other β -lactam antibiotics kill *S pneumoniae* by binding irreversibly to high molecular weight enzymes located in the bacterial cell wall. These enzymes, also known as penicillin-binding proteins, are responsible for synthesizing peptidoglycan for new cell wall formation. Chromosomal gene changes can alter the structure of these enzymes, thereby decreasing the binding affinity for penicillin and the cephalosporins and resulting in resistance.²⁶ Resistance of *S pneumoniae* to penicillin and cephalosporins is not mediated by β -lactamase enzymes. Consequently, treatment of pneumococcal infections resistant to these antibiotics with β -lactamase-resistant drugs, such as extended spectrum cephalosporins or combinations of broad spectrum penicillins plus clavulanate or sulbactam, offers no advantage.

The highest levels of resistance reported have been MICs of 8 to 16 $\mu\text{g}/\text{mL}$ for penicillin²⁷ and 16 to 32 $\mu\text{g}/\text{mL}$ for cefotaxime and ceftriaxone.²⁸⁻³⁰ Although uncommon, resistance also has been described for clindamycin, rifampin, and imipenem.

METHODOLOGY

In developing this statement, the Committee reviewed all available information relative to several areas: (1) prevalence of β -lactam-resistant pneumococcal disease in children in the United States; (2) optimal laboratory diagnosis of drug-resistant pneumococci; (3) in vitro antimicrobial susceptibilities of *nonsusceptible* pneumococci, particularly those using time-kill methods; (4) pharmacokinetic and efficacy studies of antimicrobials for the treatment of meningitis in animal models; (5) pharmacokinetic studies of antimicrobials alone and in combination in children with meningitis; (6) case reports; (7) retrospective and prospective studies of *nonsusceptible* pneumococcal infections in children examining both bacteriologic and clinical outcome variables; and, (8) the effect of dexamethasone on cerebrospinal fluid

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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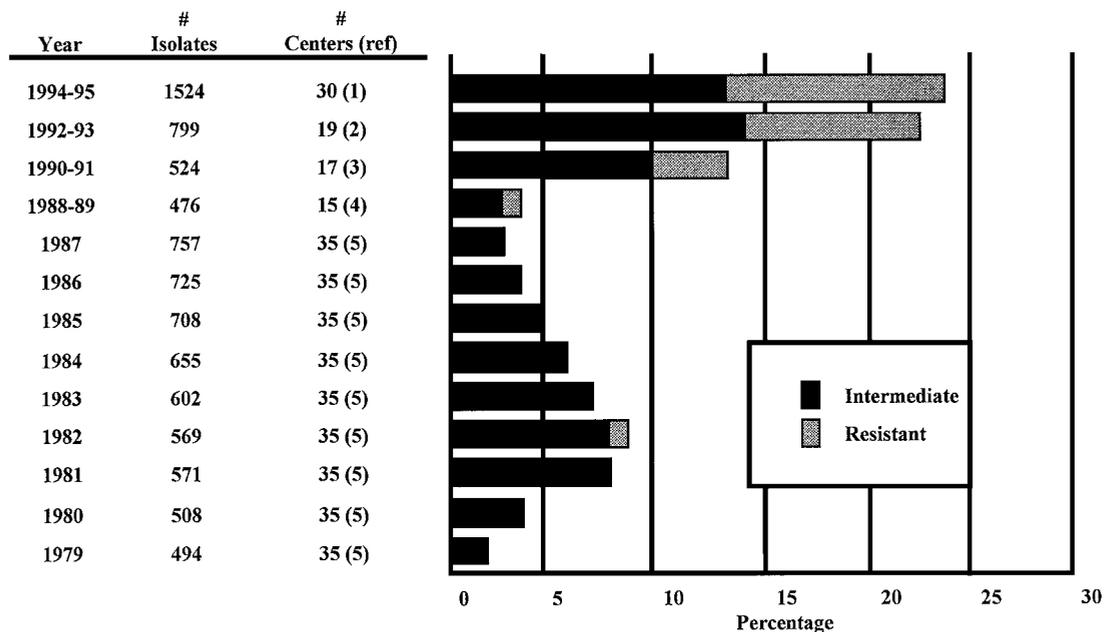


Figure. Prevalence of penicillin-resistant *Streptococcus pneumoniae* in the United States, 1979–1995. (Adapted from Doern GV. *Mediguide to Infectious Diseases*. 1995;15:1-4).

(CSF) antimicrobial concentrations in animal models and in children.

A med-line search initially identified 250 articles for review. Additional articles published during the time of statement development as well as lectures and abstracts presented at regional and national

TABLE 1. Interpretive Criteria for Antimicrobial Susceptibilities Using Minimal Inhibitory Concentration Breakpoints, $\mu\text{g}/\text{mL}^*$

Antimicrobial	Susceptible	Nonsusceptible	
		Intermediate	Resistant
Penicillin	≤ 0.06	0.1–1	≥ 2
Ceftriaxone*	≤ 0.5	1	≥ 2
Vancomycin	≤ 1	—§	—
Rifampin	≤ 1	2	≥ 4
Chloramphenicol	≤ 4	—	≥ 8
Clindamycin†	≤ 0.25	0.5	≥ 1
Erythromycin†	≤ 0.25	0.5	≥ 1
Meropenem‡	≤ 0.12	≥ 0.25	—
Imipenem	≤ 0.12	0.25–0.5	≥ 1
TMP/SMX	$\leq 0.5/5$	$1/19$ – $2/38$	$\geq 4/76$

NCCLS Interpretive Criteria³¹: values based on broth microdilution testing. If the E test commercial strip method is used, MIC values between the conventional \log_2 concentrations should be rounded to the next higher MIC value, eg, an E test MIC of 0.38 should be rounded to 0.5 $\mu\text{g}/\text{mL}$; an E test MIC of 1.5 should be rounded to 2 $\mu\text{g}/\text{mL}$.

* Standards for ceftriaxone, cefotaxime, and cefuroxime are the same; strains in the *intermediate* category may require maximum doses of these drugs to treat nonmeningeal infections.

† *S pneumoniae* isolates *nonsusceptible* to erythromycin will also be *nonsusceptible* to clarithromycin and azithromycin.

‡ Susceptibility interpretive criteria have not yet been established by the NCCLS. Values listed are those used for clinical studies that resulted in FDA approval of meropenem for pediatric bacterial meningitis; most penicillin *nonsusceptible S pneumoniae* will have a meropenem MIC $\leq 0.5 \mu\text{g}/\text{mL}$.

§ The absence of *resistant* strains precludes defining any results categories other than “susceptible.” Strains yielding results suggestive of a “*nonsusceptible*” category should be submitted to a reference laboratory for additional testing.²⁸

meetings during this time were included in the Committee’s deliberations. Additional articles were identified from personal files of Committee members, CDC reports, and bibliographies of articles. After evaluating all the articles for relevance and validity, 160 were selected for complete review.

The recommendations were drawn from an analysis of this literature and were augmented by expert consensus opinion. In areas for which the literature did not provide strong scientific evidence to support specific recommendations, the Committee used nominal group process to achieve consensus.

Expert consultants, including all of the Committee liaison representatives, reviewed the recommendations on several occasions. They were also reviewed by the AAP Committee on Practice and Ambulatory Medicine and The CDC Drug Resistant *Streptococcus pneumoniae* Therapeutic Working Group.

Antimicrobial Susceptibility Testing

Pneumococci, which are *nonsusceptible* to penicillin, cefotaxime, ceftriaxone, and other antimicrobial agents, are divided into the categories of *intermediate* and *resistant* based on the predicted ability of these drugs to treat pneumococcal infections effectively (Table 1).³¹ β -Lactam antibiotic concentrations in CSF adequate to treat *nonsusceptible* organisms may not be achieved consistently.³² Serum concentrations of antibiotics after parenteral administration are much higher. Therefore, for nonmeningeal infections, organisms usually may be treated successfully with those β -lactam antibiotics to which they are *nonsusceptible*.³³ For some *resistant* organisms, however, a change of antimicrobial may be necessary depending on the clinical course.

All pneumococcal isolates from normally sterile body sites should be tested for penicillin, cefotaxime, and ceftriaxone susceptibility using the guidelines of

TABLE 2. Penicillin and Cefotaxime or Ceftriaxone Susceptibilities of Invasive Isolates From Children: United States, 1978–1995*

Location	Ref No.	Time	Penicillin Nonsusceptible			Cefotaxime or Ceftriaxone Nonsusceptible		
			I, %	R, %	NS Total, %	I, %	R, %	NS Total, %
Collaborative Study†	7	1993–1994	9.6	3.9	13.5	3.4	0.5	3.9
		1994–1995	8.4	8.9	17.3	4.9	1.1	6
		9/95–12/95	14.6	12.6	27.2	5.8	3.9	9.7
Atlanta	8	1994	14	13	27	7	6	13
Dallas		1981–1983	8	0	8.1	0	0	0
Dallas	9	1991–1992	8.6	3	11.6	—	—	8
		1993	14.5	4	18.5	—	—	12.9
		1994	—	—	22	—	—	7
Dallas County	12	1995‡	20	21	41	8	12	20
		1992	—	—	12	—	—	6
Falls Church, VA	13	1993	—	—	27	—	—	12
		1993–1995	17	6	23	—	—	—
Houston	14, 15	1989	7.8	0	7.8	—	—	NA
		1990	3	0	3	—	—	NA
		1991	12.3	0	12.3	—	—	NA
Huntington, WV	16	1983–94	22.7	0	22.7	—	—	—
		Jacksonville	17	1989	8	3	11	—
Little Rock	18	1993	14	7	21	—	—	NA
		1991	—	—	12	—	—	NA
Memphis	19	1993	12	3	16	—	—	NA
		1994	9	6	15	3	8	11
Mobile	20	1993	17	7	24	2	9	11
		1995§	25	14	39	9	8	17
		1992–1994	—	—	15	0	0	0
Oklahoma	21	1978	16	0	16	—	—	NA
		1984	15.9	0	12.2	—	—	NA
		1989–1990	7.6	1.4	9	—	—	NA
Southern California	22	1993–1995	12.8	2.1	14.5	6.8	0	6.8
St Louis	23	1984–1990	0.8	—	0.8	—	—	NA
		1991	14	—	14	—	—	NA
		1992	15	—	15	—	—	NA
		1993	12	4	16	—	—	NA
Walter Reed Army Medical Center	24	1992–93	22	0	22	—	—	—
		1994	17	17	34	—	—	—
Washington, DC	25	1992–1993	8.3	4.6	12.9	—	—	5.1

* NS, nonsusceptible; I, intermediate; R, resistant (former category of high-level resistance); NA, data not available.

† Includes nine children's hospitals in Houston, TX; Little Rock, AK; Columbus, OH; Pittsburgh, PA; Chicago, IL; Los Angeles, CA; San Diego, CA; Denver, CO; and Winston Salem, NC.

‡ Unpublished data from George H. McCracken Jr, MD (data available on request).

§ Unpublished data from Fred F. Barrett, MD (data available on request).

|| Data include some isolates from adults.

the National Committee for Clinical Laboratory Standards (NCCLS).³¹

Manual agar or broth dilution techniques provide the most accurate quantitative results and should be used whenever possible.³⁴ Many hospital laboratories are not equipped to perform these techniques and will depend on the E test (Epsilonometric test, AB Biodisk North America Inc., Culver City, CA). The E test is a plastic strip containing an antimicrobial concentration gradient. It is simple to use and reasonably reliable for determining MIC values.^{25,34} However, the separation between susceptible, intermediate, and resistant categories may not always be distinct, and interpretation may vary with the observer.^{34,35} If the patient is not responding as well as anticipated, the possibility that the E test could have been misread by one MIC value should be considered. Other test methods approved by the Food and Drug Administration for the quantitative susceptibility testing of pneumococci include Microtech, Pasco, or Sensititre. Other automated test methods are not reliable and should not be used.³⁶

Most laboratories using NCCLS guidelines for sus-

ceptibility testing will need 48 to 72 hours to provide results for pneumococcal antibiotic susceptibilities.³¹ To abbreviate this process, when the CSF smear shows characteristic gram-positive diplococci, some laboratories place the penicillin and cefotaxime (or ceftriaxone) E test strips directly on the agar plates at the time of CSF inoculation. This procedure is not standardized, and the results should be confirmed using the standard NCCLS protocols.

When quantitative testing methods are not available, the qualitative screening test using a 1- μ g oxacillin disk reliably identifies all penicillin-susceptible pneumococci that have a disk zone diameter of 20 mm or greater. For organisms with an oxacillin disk zone size less than 20 mm, indicating potential nonsusceptibility to penicillin, additional quantitative susceptibility testing must be performed. Up to 40% of these organisms will be susceptible to penicillin (although resistant to oxacillin), and the size of the zone around the disk does not accurately distinguish between organisms with an MIC defined as *intermediate* or *resistant* (Table 1).^{14,37}

If the organism is penicillin-nonsusceptible by any

form of testing, additional quantitative susceptibility testing should be performed for cefotaxime or ceftriaxone. The MIC results for either drug adequately parallel each other; thus, only one needs to be tested. Strains *resistant* to penicillin are more likely to be *resistant* to cefotaxime and ceftriaxone. Furthermore, clones of pneumococci have been isolated that are much more resistant to cefotaxime and ceftriaxone than to penicillin.^{23,29,30} Susceptibility testing also should be determined for other clinically relevant drugs for meningitis treatment, which should include vancomycin, meropenem, and rifampin. For nonmeningeal invasive infections, susceptibility testing should be performed for erythromycin, trimethoprim-sulfamethoxazole, clindamycin, cefuroxime and potentially imipenem, meropenem and chloramphenicol (Table 1). Strains resistant to erythromycin are also resistant to the related antibiotics clarithromycin and azithromycin.

Isolation of *S pneumoniae* with a vancomycin MIC greater than 1 µg/mL should be reported immediately to the state health department. Because no isolates of *S pneumoniae* with an MIC this high have been identified, the state health department will arrange for confirmation testing. Identification of such isolates is critical for both local and national surveillance programs and for providing feedback to area physicians. For the same reasons, organisms *resistant* to penicillin and cefotaxime, or ceftriaxone should also be reported to the state health department.

MENINGITIS

Distinguishing Aseptic (Viral) From Bacterial Meningitis

Many more cases of aseptic meningitis occur than pneumococcal meningitis. In 1993, 12 848 cases of aseptic meningitis were reported to the CDC.³⁸ Because most physicians do not report such cases, it is probable that a more accurate annual incidence figure would be at least threefold higher, or approximately 30 000 cases per year. The estimated incidence of pneumococcal meningitis for all age groups is 1 to 2 cases per 100 000 population.³⁹ For the population of the United States, this represents approximately 3000 to 5000 cases per year. Thus, there will be 6 to 10 cases of aseptic meningitis for every case of pneumococcal meningitis, particularly during the summer and fall.

To prevent the development of vancomycin-resistant *S pneumoniae*, it is imperative that use of vancomycin be minimized. Children with suspected or proved aseptic meningitis should not receive vancomycin. For children pretreated with antibiotics or those for whom the clinical and CSF findings are equivocal, the decision of whether to begin antibiotic therapy is more difficult.⁴⁰ Several indices may be helpful in reaching a decision. For younger children with pneumococcal meningitis, 90% to 100% of the time, the Gram-stained smear of the CSF is positive.⁴¹ In older children and adults, only 50% to 68% of Gram-stained smears of CSF are positive.^{42,43} The latex agglutination test using CSF is more rapid and more sensitive than Gram-staining,⁴⁴ but a negative

test does not rule out a diagnosis of pneumococcal meningitis. Preceding antibiotic therapy is unlikely to change CSF parameters sufficiently to interfere with the ability to distinguish viral from suspected bacterial meningitis.⁴⁵⁻⁴⁷ For the young infant, the distinction between aseptic and bacterial meningitis may be particularly difficult.⁴⁸ A total protein concentration of 100 mg/dL or greater is rare in infants with aseptic meningitis and may be helpful in separating bacterial from viral meningitis.

In some circumstances, distinguishing between viral and early bacterial meningitis in children older than 1 month continues to be difficult. In most settings, a bacterial cause will be responsible in less than half of these children. The likelihood of children having bacterial meningitis caused by *S pneumoniae* resistant to cefotaxime and ceftriaxone is less than 20% in most areas. If previously administered oral or intramuscular antibiotics suppress the presence of the organism on a Gram-stained smear, resistance of the causative organism to the high doses of cefotaxime or ceftriaxone administered for meningitis will be unlikely.

Initial Therapy for Children With Bacterial Meningitis

Optimal management of bacterial meningitis requires treatment with antimicrobial agents at dosages that achieve concentrations providing bactericidal activity in CSF diluted 1:8.⁴⁹

Antimicrobials of Potential Use for the Treatment of Pneumococcal Meningitis

Penicillin

The recommended dosage of penicillin G for pneumococcal meningitis is 250 000 to 400 000 U/kg/d (150 to 240 mg), given intravenously (IV) in four to six divided doses (Table 3). A dose of 250 000 U/kg/d (150 mg) given in six divided doses results in mean CSF concentrations of 0.8 µg/mL sustained throughout the 4 hours between infusions.⁵⁰ For penicillin-susceptible pneumococci (MIC ≤ 0.06 µg/mL), this concentration of penicillin approaches the desired bactericidal concentration in the CSF. However, for penicillin-*nonsusceptible* pneumococci (MIC ≥ 0.1 µg/mL), penicillin concentrations in the CSF will be inadequate to kill the organism.

Cefotaxime and Ceftriaxone

In patients with meningitis caused by penicillin-*nonsusceptible* pneumococci, the treatment drug of choice is cefotaxime or ceftriaxone, providing the organism is susceptible. All other cephalosporins have higher MICs for penicillin-*nonsusceptible* organisms and should not be administered for meningitis. In a recent study, concentrations of ceftriaxone in the CSF were 0.9 to 30 µg/mL 2.8 hours after administration of recommended IV doses.³² These concentrations are high enough for successful therapy of meningitis caused by susceptible organisms.

Therapeutic failures occur when cefotaxime or ceftriaxone is used for strains *resistant* to these antibiotics (MIC ≥ 2 µg/mL).^{9,28,29,51-53} When the MIC is 1.0 µg/mL for cefotaxime or ceftriaxone, indicating

TABLE 3. Doses of Intravenous Antimicrobials for Invasive Pneumococcal Infections*†

Antimicrobial	Meningitis Dose, kg/d	Infections Outside the CSF		
		Dose Interval	Dose, kg/d	Dose Interval
Penicillin G	250 000–400 000 U¶	Every 4–6 h	Same	Same
Cefotaxime	225–300 mg*	Every 6–8 h	150–225 mg	Same
Ceftriaxone	100 mg	Every 12–24 h	80–100 mg	Same
Vancomycin	60 mg	Every 6 h	40–60 mg	Same
Rifampin‡	20 mg	Every 12 h	Not indicated	—
Chloramphenicol§	75–100 mg	Every 6 h	Same	Same
Clindamycin§	Not indicated	—	25–40 mg	Every 6–8 h
Imipenemcilastatin	Not indicated	—	60 mg	Every 6 h
Meropenem	120 mg	Every 8 h	60 mg	Same

* Dose supercedes Peter G, ed. 1994 *Red Book: Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 1994.

† Doses are for children 1 month of age or older.

‡ Indications for use are not yet fully defined.

§ Consider only for patients with life-threatening allergic response after administration of β -lactam antibiotics.

|| FDA approved only for bacterial meningitis in children 3 months of age or older and for intra-abdominal infections.

¶ Because 1 U = 0.6 μ g, this range is equal to 150 to 240 mg/kg/d.

an *intermediate* level of resistance, some patients have been treated successfully with cefotaxime or ceftriaxone alone.⁵⁴ The response is unpredictable, however, possibly because of individual variations in the CSF concentrations of cefotaxime or ceftriaxone or in the E test interpretations.

Administration of 100 mg/kg of ceftriaxone once a day is effective for the treatment of meningitis caused by penicillin-susceptible *S. pneumoniae*.^{32,55,56} For penicillin-nonsusceptible but ceftriaxone-susceptible organisms, administration twice a day may be preferred. If a once-a-day regimen is chosen, the full dose must be given at the same time every day.

The recommended dosage of cefotaxime for meningitis is 200 to 225 mg/kg/d IV in three to four divided doses. Some experts recommend initiating therapy with dosages as high as 300 mg/kg/d given in four divided doses until susceptibility results are available.^{57,58} The higher serum and CSF concentrations achieved by high-dose therapy may be beneficial for patients with organisms in the *intermediate* category. For *resistant* strains, however, these concentrations may not be high enough for therapy to be successful.

Vancomycin

A limited number of alternatives are available for the treatment of meningitis caused by pneumococci that are *nonsusceptible* to penicillin and cefotaxime and ceftriaxone. In children, vancomycin enters the CSF in the presence of inflamed meninges to provide concentrations of 2.0 to 5.9 μ g/mL within 2.8 hours of an IV dose.³² Although all strains of pneumococci currently tested have been susceptible *in vitro* to vancomycin, failures of vancomycin to treat meningitis or to prevent its development or progression have been reported when dosages less than 60 mg/kg/d were administered.^{59,60} These reports are supported by studies in a rabbit model that suggest bactericidal levels of vancomycin in the CSF may be difficult to maintain.⁶¹ For these reasons, vancomycin should not be used alone for therapy of meningitis.

Combination Vancomycin–Cefotaxime (or Ceftriaxone) Therapy

For pneumococci that are *nonsusceptible* to cefotaxime and ceftriaxone, combination therapy of vancomycin plus cefotaxime or ceftriaxone produces a synergistic effect *in vitro*,⁶² in the animal model,⁶¹ and in the CSF of children with meningitis.³² Thus, for initial empirical therapy, this combination should be highly effective and may prevent the emergence of resistance to either drug alone.⁶³

Rifampin and Combination Therapy Using Rifampin With Vancomycin or Cefotaxime (or Ceftriaxone)

Rifampin is active against most, but not all, penicillin-nonsusceptible pneumococci.²⁶ Rifampin should never be used alone, because strains *resistant* to rifampin have been isolated, and in some settings, resistance can develop rapidly during therapy.⁶⁴ Whereas β -lactam antibiotics are rapidly bactericidal, rifampin is only slowly bactericidal against *S. pneumoniae* *in vitro*.⁶² In one rabbit model of meningitis, the combination of vancomycin and rifampin was slowly bactericidal, and 13 of 15 animals had sterile CSF cultures after 24 hours.⁶¹ For the combination of ceftriaxone and rifampin in the same model, a bactericidal effect was achieved in 24 hours, even against a strain *resistant* to ceftriaxone (MIC of 4 μ g/mL).⁶⁵ In this model, the addition of rifampin to ceftriaxone was as effective as the addition of vancomycin to ceftriaxone in treating cefotaxime- and ceftriaxone-nonsusceptible pneumococcal meningitis.

There is a discrepancy between the poor *in vitro* bactericidal activity of rifampin when combined with cefotaxime, ceftriaxone, or vancomycin and the apparent efficacy of these combinations in the rabbit pneumococcal meningitis model.⁶⁶ More information is needed to clarify the therapeutic efficacy of rifampin-containing antibiotic combinations for drug-nonsusceptible pneumococcal meningitis. Until such information is available, rifampin should be added only if the organism is demonstrated to be susceptible, and there is a delay in the expected clinical or bacteriologic response.

Chloramphenicol

Chloramphenicol, when administered at 50 to 100 mg/kg/d IV in four divided doses, achieves effective concentrations in the CSF for penicillin-susceptible pneumococci. For children with penicillin-*nonsusceptible*, chloramphenicol-susceptible pneumococcal strains, however, treatment with chloramphenicol has often not been successful.⁶⁷ These failures may occur, because strains having chloramphenicol MICs indicating susceptibility may have minimal bactericidal concentrations (MBCs) of 8 µg/mL or greater, indicating resistance to killing. Adequate bactericidal activity cannot be achieved in the CSF when the MBC values are this high. Thus, chloramphenicol should not be used to treat penicillin-*nonsusceptible* pneumococci unless the causative strain is known to have a chloramphenicol MBC value of 4 µg/mL or less.⁶⁷ Most laboratories need at least 3 to 4 days to obtain this information, because the organism must be sent to a reference laboratory. Inadequate data are available to support the use of chloramphenicol in combination with other antimicrobial agents for management of penicillin-*nonsusceptible* pneumococcal meningitis.

Imipenem and Meropenem

Imipenem is a carbapenem antibiotic with a broad spectrum of activity against a variety of organisms, including penicillin-*nonsusceptible* pneumococci. Although most strains of *S pneumoniae* are susceptible to imipenem, resistant strains have been isolated.^{19,25} The potential epileptogenic properties of imipenem in patients with disease of the central nervous system, including meningitis, preclude routine use of this antibiotic.⁶⁸

Meropenem is a carbapenem antimicrobial similar to imipenem and recently approved by the Food and Drug Administration for treatment of bacterial meningitis in children 3 months of age or older. The epileptogenic potential is much less than that of imipenem, and in most cases, meropenem will be active against isolates *nonsusceptible* to penicillin. Although clinical experience is limited, for meropenem-susceptible isolates, meropenem alone or in combination may provide a satisfactory alternative for patients who do not tolerate vancomycin.⁶⁹

Use of Dexamethasone for Patients With Pneumococcal Meningitis

Current recommendations suggest that dexamethasone be *considered* for children with pneumococcal meningitis.⁷⁰ The effectiveness of dexamethasone for preventing sequelae of pneumococcal meningitis is unproved, and expert opinion is divided on its use.⁷¹⁻⁷³ No large, single prospective controlled study of the use of dexamethasone to prevent hearing loss or other sequelae in children with pneumococcal meningitis has been performed.

Cell wall components from organisms that have been rapidly lysed by antibiotics are believed to induce the release of cytokines into the subarachnoid space. These cytokines seem to play a seminal role in the initial events of meningeal inflammation.⁷¹ To prevent or modify cytokine release in pneumococcal

meningitis, dexamethasone, if used should be given *shortly before or at the time of antibiotic administration*.^{71,72}

In the rabbit model of meningitis, dexamethasone interferes with the penetration of ceftriaxone and vancomycin into the CSF when either is administered alone.^{43,65} When the antibiotics were given together with dexamethasone in one model, the combination was effective against a pneumococcal strain with a ceftriaxone MIC of 1 µg/mL.⁶⁵ For a *resistant* strain, however, dexamethasone reduced the bactericidal efficacy of the combination. Dexamethasone did not affect the penetration of rifampin, and the combination of ceftriaxone plus rifampin effectively eradicated this same *resistant* strain.⁶⁵

The penetration of ceftriaxone and vancomycin into the CSF in children³² is better than that demonstrated in the rabbit model.⁶⁵ In children with bacterial meningitis *receiving dexamethasone*, the CSF ceftriaxone concentrations have been reported to be 0.9 to 30 µg/mL³² and 0.7 to 9.2 µg/mL.⁷⁴ These concentrations are similar to those reported previously in the absence of dexamethasone.⁷⁵ The vancomycin levels in the CSF were 2.0 to 5.9 µg/mL and represent 20% of serum levels,³² much better than the 3% penetration reported for the animal model.⁶⁵ Rifampin levels in the CSF were 0.3 to 1.9 µg/mL.³² The CSF of children who received dexamethasone and the antibiotic combinations of ceftriaxone plus vancomycin or ceftriaxone plus rifampin, when incubated in vitro with pneumococcal strains *resistant* to ceftriaxone, had significantly enhanced bactericidal activity when compared with the CSF from a child who received dexamethasone and ceftriaxone alone, indicating a significantly enhanced effect from either combination.³²

Dexamethasone therapy can decrease fever, giving a false impression of clinical improvement, even though CSF sterilization has not been achieved.^{9,25,51} If dexamethasone is administered, careful and frequent observation of the patient is indicated.^{28,51,59}

Assessment of Efficacy of Therapy After 24 to 48 Hours

Penicillin-*nonsusceptible* organisms do not cause disease of greater severity than disease caused by penicillin-susceptible strains.³³ To assess the efficacy of therapy, the clinical course should be followed closely. A positive blood culture 24 to 36 hours after initiating therapy can indicate a hidden focus of infection, a resistant organism, or continued bacterial replication in the CSF. Another lumbar puncture should be considered within 24 to 48 hours to document eradication of the pathogen, particularly if (1) the organism is demonstrated to be potentially *nonsusceptible* to penicillin by quantitative (MIC) or oxacillin disk testing, the cefotaxime or ceftriaxone susceptibility results are not yet available, and the clinical condition has not improved or has worsened; or (2) the child has received dexamethasone, which might interfere with the interpretation of the clinical response. Some experts believe that a second lumbar puncture is not necessary if therapy was initiated with vancomycin plus cefotaxime (or ceftriaxone),

and the clinical response has been good, particularly if dexamethasone was not used.

Continuation of Antimicrobial Therapy

To curtail continued emergence of antimicrobial resistance, it is imperative that antibiotic therapy be reviewed as soon as the quantitative susceptibility test results are available (Table 4). If the organism is susceptible to penicillin, cefotaxime, or ceftriaxone, *vancomycin should be discontinued* and penicillin, cefotaxime, or ceftriaxone continued for the usual course of therapy.⁴⁰ If resistance to penicillin and cefotaxime and ceftriaxone is documented, vancomycin plus cefotaxime or ceftriaxone should be continued for the full course of therapy. If the patient's clinical condition has not improved or has worsened while receiving this combination of antibiotics or if a follow-up CSF examination indicates failure to reduce the number of organisms substantially or to eradicate the organism, some experts would add rifampin to the vancomycin and cefotaxime or ceftriaxone combination.¹¹ Other experts would discontinue vancomycin and continue therapy with ceftriaxone plus rifampin, providing the organism is susceptible to rifampin.¹⁰

NONMENINGEAL INVASIVE INFECTIONS

Immunocompetent Host

Although more than 100 nonmeningeal invasive infections (excluding otitis media) caused by penicillin-*nonsusceptible* pneumococci have been reported since 1977,^{7,15,33,76-78} reports of treatment failures using standard therapy have been exceedingly rare. This is most likely a result of the high concentrations of antibiotics achieved in serum. This is particularly true for cefotaxime and ceftriaxone, in which serum concentrations after recommended doses often exceed by 100-fold the MIC for *S pneumoniae* strains with an MIC of 0.1 to 1 $\mu\text{g}/\text{mL}$ for these antibiotics.³²

Only one prospective study comparing the outcomes of nonmeningeal invasive infections caused by both susceptible and *nonsusceptible* pneumococci has been performed in children. In this study, the outcome of nonmeningeal infections caused by penicillin-*nonsusceptible* organisms correlated with the severity of the illness on admission and the presence of underlying disease and not on the susceptibility of the organism to penicillin.³³ This finding may result from the fact that most of the reported infections were caused by organisms with an MIC of 0.1 to 1 $\mu\text{g}/\text{mL}$. Of interest, four patients with pneumonia attributable to organisms with MICs in this range

received only oral amoxicillin (peak serum levels of 6 to 14 $\mu\text{g}/\text{mL}$), and the disease in all patients responded rapidly.³³ Some infections caused by *resistant* pneumococci with an MIC of 4 $\mu\text{g}/\text{mL}$ or greater have responded to ampicillin (100 mg/kg/d, IV).³³ Carefully controlled prospective studies evaluating outcome variables for patients with nonmeningeal infections caused by pneumococci *nonsusceptible* to the β -lactam antibiotics are needed.

For *immunocompetent* patients with possible invasive pneumococcal infections who do not have meningitis and are not critically ill on admission, standard antibiotic therapy that may include cefuroxime should continue to be used. Therapy does not need to be altered if the organism is reported to have a penicillin MIC of 0.1 to 1 $\mu\text{g}/\text{mL}$ and the patient is responding well. If the organism is *resistant* to penicillin (MIC ≥ 2.0 $\mu\text{g}/\text{mL}$), changes in antimicrobial therapy should be based on the clinical response and not on the MIC value. Additional *initial* antibiotic coverage for potential penicillin-*nonsusceptible* strains could be considered for patients who are critically ill, including those with myopericarditis, severe multilobar pneumonia with hypoxia, or hypotension.

Immunocompromised Host

Immunocompromised children may be at increased risk for severe infections caused by drug-*nonsusceptible* pneumococci, because they often receive frequent courses of antimicrobials for therapy or prophylaxis, allowing for the selection of resistant strains. Immunocompromising conditions that place children at risk for severe pneumococcal disease include sickle cell disease, other hemoglobinopathies, congenital or acquired immunoglobulin deficiencies, agammaglobulinemia, nephrotic syndrome, human immunodeficiency virus infection, immunosuppressive medications, or congenital or acquired asplenia.

For children who are immunocompromised as a result of asplenia or other altered immune function, it is not yet known whether serum levels of penicillin, cefotaxime, or ceftriaxone are adequate to treat nonmeningeal pneumococcal infections caused by *nonsusceptible* strains. For critically ill children who are immunocompromised, some experts would initiate empiric therapy with vancomycin and cefotaxime or ceftriaxone until susceptibility results are available.⁷⁹ Subsequent therapy should be based on test results for antibiotic susceptibility and the patient's clinical course.

TABLE 4. Antimicrobial Therapy for Bacterial Meningitis Caused by *S pneumoniae* Once Susceptibility Test Results Are Available

Susceptibility Test Results*	Antibiotic Management
Susceptible to penicillin	Discontinue vancomycin and begin penicillin or continue cefotaxime or ceftriaxone alone†
Nonsusceptible to penicillin (intermediate or resistant category) and susceptible to cefotaxime and ceftriaxone	Discontinue vancomycin and continue cefotaxime‡ or ceftriaxone
Nonsusceptible to penicillin (intermediate or resistant category) and nonsusceptible to cefotaxime and ceftriaxone (intermediate or resistant category)	Continue vancomycin plus cefotaxime or‡ ceftriaxone Rifampin may be added or substituted for vancomycin in selected situations; see recommendation #7

* E test or broth dilution studies.

† Some physicians may choose this alternative for convenience and cost savings.

‡ Some physicians may want to increase the cefotaxime dose to 300 mg/kg/d

Neonatal Infection

Invasive pneumococcal infections are rare but well described in neonates.⁸⁰ Two neonates with penicillin-*nonsusceptible* pneumococcal infections have been reported.^{33,81} The initial empirical antibiotic regimen for neonatal sepsis and meningitis should be adequate for all pneumococcal infections with the exception of meningitis caused by a cefotaxime- or ceftriaxone- and penicillin-*nonsusceptible* strain. For patients in this age group with CSF smears that show gram-positive diplococci and bacterial antigen tests supporting a diagnosis of pneumococcal meningitis, consideration should be given to the initial empirical addition of vancomycin to the therapeutic regimen.

INFECTION CONTROL MEASURES

Nosocomial acquisition of pneumococcal infections by children and their caregivers is rare in the United States. Antimicrobial-*nonsusceptible* pneumococcal infections are transmitted by the same routes as susceptible organisms. The CDC recommends Standard Precautions for all patients with invasive pneumococcal infections.⁸² Standard Precautions synthesize the major features of the former categories of Universal Precautions and Body Substance Isolation. They apply to blood, all body fluids except sweat, nonintact skin, and mucous membranes and "are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals."⁸² Airborne, Droplet and Contact Precautions are not recommended for invasive pneumococcal infections. For the details of the use of Standard Precautions, the CDC guidelines⁸² or an Infection Control Practitioner should be consulted. Nasopharyngeal cultures of family members or intimate contacts are not indicated.

RECOMMENDATIONS

Susceptibility Testing

1. Children with moderate to severe bacterial infections should have cultures obtained from appropriate, potentially infected, normally sterile body fluids to determine the cause of the infection and allow for susceptibility testing of the organism.
2. Quantitative (ie, MIC) susceptibility testing for penicillin and cefotaxime or ceftriaxone should be performed on all pneumococci isolated from normally sterile body fluids whenever possible. If the patient has meningitis and the organism is *nonsusceptible* to penicillin, cefotaxime, and ceftriaxone, disk or MIC susceptibility testing for vancomycin, meropenem, and rifampin should be performed. If the patient has a nonmeningeal infection and the organism is *resistant* to penicillin, cefotaxime, and ceftriaxone, disk, or MIC susceptibility testing for vancomycin, rifampin, clindamycin, trimethoprim-sulfamethoxazole, erythromycin, imipenem, meropenem, and chloramphenicol should be considered.

If quantitative susceptibility testing is not available in the laboratory, screening for penicillin resistance using the 1- μ g oxacillin disk and NCCLS guidelines

should be performed for all pneumococcal isolates from normally sterile body sites. Organisms with an oxacillin disk zone size less than 20 mm should be referred for quantitative susceptibility testing.

3. Isolation of *S pneumoniae* with a vancomycin MIC greater than 1 μ g/mL should be reported immediately to the state health department.

Management of Children With Bacterial Meningitis Possibly Caused by *S pneumoniae*

4. Vancomycin plus cefotaxime or ceftriaxone should be administered initially to all children older than 1 month with definite or probable bacterial meningitis. (Some experts believe that vancomycin need not be used if there is compelling evidence that the cause is an organism other than *S pneumoniae*, such as Gram-negative diplococci on a smear of CSF during an outbreak of meningococcal disease.)

Because pneumococcal meningitis may occur in infants younger than 1 month, consideration should be given to the addition of vancomycin to the usual antibiotic combination for neonatal sepsis especially if: (1) the CSF smear shows characteristic Gram-positive diplococci or (2) bacterial antigen testing supports a diagnosis of pneumococcal meningitis.

For children with immediate hypersensitivity to the β -lactam antibiotics, the combination of vancomycin plus rifampin should be considered.

5. A lumbar puncture should be considered after 24 to 48 hours to evaluate therapy if (1) the organism is penicillin-*nonsusceptible* by quantitative (MIC) or oxacillin disk testing, the results from cefotaxime and ceftriaxone quantitative susceptibility testing are not yet available, and the child's condition has not improved or has worsened or (2) the child has received dexamethasone, which might interfere with the ability to interpret the clinical response.
6. Once the results of susceptibility testing are available, modifications of therapy should be made as indicated in Table 4. If the organism is susceptible to penicillin or cefotaxime or ceftriaxone, *vancomycin should be discontinued*, and penicillin or cefotaxime or ceftriaxone should be continued. Vancomycin plus cefotaxime or ceftriaxone should be continued only if the organism is *nonsusceptible* to penicillin *and* to cefotaxime or ceftriaxone.
7. Addition of rifampin or substitution of rifampin for vancomycin after 24 to 48 hours of therapy could be considered if the organism is susceptible to rifampin and if (1) after 24 to 48 hours, despite therapy with vancomycin plus cefotaxime or ceftriaxone, the clinical condition has worsened; (2) the follow-up Gram-stained smear or culture of CSF indicates failure to eradicate or to substantially reduce the number of organisms; or (3) the organism has an unusually high cefotaxime or ceftriaxone MIC of 4 μ g/mL or greater. Consultation with an infectious disease specialist should also be considered.

Management of Children With Probable Aseptic Meningitis

8. During the summer and fall, children will be hospitalized for severe headache, vomiting, fever, a stiff neck, and CSF pleocytosis caused by enteroviruses. Although antibiotics are not always indicated, some practitioners will choose to treat these children with ceftriaxone or cefotaxime until the CSF and blood cultures are negative even when all laboratory results suggest aseptic meningitis. Vancomycin should not be used under these circumstances unless the child appears toxic and/or is hypotensive.

Management of Nonmeningeal Invasive Pneumococcal Infections Requiring Hospitalization

9. For nonmeningeal invasive infections in the previously well child who is not critically ill, antimicrobials currently in use to treat *S pneumoniae* and other potential pathogens should be initiated at usually recommended doses.
10. For a select group of children with invasive infections potentially attributable to *S pneumoniae* who are critically ill, additional initial antibiotic coverage for possible penicillin- and cefotaxime- or ceftriaxone-nonsusceptible strains could be considered. Such patients might include those with myopericarditis or severe multilobar pneumonia with hypoxia or hypotension. If vancomycin is administered, it should be discontinued as soon as antibiotic susceptibilities demonstrate effective alternative agents.
11. If the organism has an MIC of 2 $\mu\text{g}/\text{mL}$ or greater to penicillin, cefotaxime, and ceftriaxone, therapy should be adjusted based on the clinical response, susceptibilities to other antimicrobials, and results of follow-up cultures of blood and other body fluids. The local, county, and state health departments should be notified of these organisms and the help of an infectious disease specialist considered.
12. For the child with severe β -lactam allergy, initial management for a potential pneumococcal infection could include vancomycin or clindamycin, in addition to antimicrobial coverage for other potential pathogens as indicated. Continuation of therapy should be guided by the results of susceptibility testing. Vancomycin should not be continued if the organism is susceptible to other appropriate, non- β -lactam antibiotics. Consultation with an infectious disease specialist should be considered.

Management of Nonmeningeal Invasive Pneumococcal Infections in the Immunocompromised Host

13. No modifications need to be made to the current management of possible pneumococcal infections in immunocompromised children, providing they are not critically ill. For critically ill patients, consideration should be given to initiating therapy with vancomycin and cefotaxime or ceftriaxone. *Vancomycin should be discontinued as soon as susceptibility results indicate effective alternative antimicrobials.*

Use of Vancomycin

14. At the time vancomycin therapy is initiated in children, urinalysis should be performed, and serum creatinine and blood urea nitrogen concentrations should be determined. Renal function should then be followed closely and appropriate dosage modifications made if renal function is compromised.
15. Physicians should consider determining trough serum concentrations for children who have renal impairment, are critically ill, are receiving concurrent ototoxic or nephrotoxic drugs, or are younger than 3 months. Trough concentrations of vancomycin, which can be obtained before the third dose, should be 10 to 15 $\mu\text{g}/\text{mL}$ or less.
16. A peak serum vancomycin concentration can be obtained 30 to 60 minutes after completion of a 30-minute infusion for the patient whose condition does not improve or for the patient with an organism resistant to penicillin, cefotaxime, and ceftriaxone. Therapeutic peak serum vancomycin concentrations for meningitis fall within the range of 35 to 40 $\mu\text{g}/\text{mL}$.

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