

Intramuscular Antibiotics in the Treatment of Pediatric Upper Respiratory Tract Infections

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Abstract

More than 30% of pediatric visits in the United States are due to an upper respiratory tract infection, otitis media, sinusitis, or pharyngitis, which account for 50% to 60% of all outpatient antibiotic prescriptions. The majority of pediatric patients with probable bacterial etiology can be treated with oral antibiotics without difficulty. However, there are certain circumstances that preclude the use of oral therapy in a child, specifically decreased gastrointestinal absorption due to persistent vomiting or diarrhea, refusal to take oral medications, uncertain compliance with therapy, or lack of an oral agent with appropriate antimicrobial activity. In these situations, parenteral therapy is required. Intravenous antibiotics are often administered, and in outpatient management, the intramuscular antibiotics are an attractive and effective choice. The appropriate use of these agents for the treatment of pediatric upper respiratory tract infections and current therapeutic recommendations are discussed.

(*Am J Manag Care* 1999;5(suppl):S915-S922)

An infection of the upper respiratory tract is one of the most common reasons for a child to visit the physician. More than 30% of pediatric visits in the United States are the result of an upper respiratory tract infection, otitis media, sinusitis, or pharyngitis,¹ which account for 50% to 60% of all outpatient antibiotic prescriptions.^{2,3} While a viral infection predominantly requires supportive therapy, a diagnosis of otitis media, sinusitis, or pharyngitis of probable bacterial etiology usually warrants treatment with an antimicrobial agent. The majority of pediatric patients can be treated with oral antibiotics without difficulty. However, there are certain circumstances that preclude the use of oral therapy in a child. In these situations, parenteral therapy is required. Intravenous (IV) antibiotics are often administered, and in outpatient management, the intramuscular (IM) antibiotics are an attractive and effective choice.

Many antimicrobial agents that are given intravenously can also be delivered IM. However, certain antibiotics are particularly well suited to IM administration because of their slow release, prolonged serum concentration, or long elimination half-life, resulting in a longer dosing interval. The IM antibiotic agents most commonly used in the outpatient setting are ceftriaxone and benzathine penicillin G, either alone or combined with procaine penicillin G. This arti-

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cle reviews the appropriate use of these agents for the treatment of pediatric upper respiratory tract infections and discusses the current therapeutic recommendations.

Mechanism and Efficacy of Ceftriaxone

Ceftriaxone is a semisynthetic third-generation cephalosporin that can be administered intravenously or intramuscularly. It has a broad spectrum of activity against Gram-positive aerobes, most Gram-negative aerobes, and some anaerobes. With a prolonged plasma concentration, ceftriaxone can be dosed at a 24-hour interval and has been approved by the Food and Drug Administration (FDA) for the treatment of acute bacterial otitis media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.⁴

Recently, the use of ceftriaxone for the treatment of otitis media has undergone significant study and discussion. In 1993, Green and Rothrock⁵ conducted the only randomized, double-blind, controlled trial comparing a single dose of IM ceftriaxone (50 mg/kg) with 10 days of oral amoxicillin for the treatment of acute otitis media, and demonstrated an efficacy of 91% for both. Further randomized, single-blind trials were conducted to compare IM ceftriaxone with oral trimethoprim/sulfamethoxazole,⁶ regular-dose amoxicillin/clavulanate,⁷ and high-dose amoxicillin/clavulanate.⁸ All 3 trials showed similar cure rates between the 2 antibiotics studied (93% to 95%, 95%, and 79% to 83%, respectively), with no difference in the improvement of symptoms or middle ear effusions. A study by Varsano and associates,⁷ demonstrated a small but significantly lower rate of recurrence with ceftriaxone compared with regular-dose amoxicillin/clavulanate. However, in the Cohen and associates study,⁸ high-dose amoxicillin/clavulanate was found to be associated with a lower rate of

nasopharyngeal carriage of organisms posttherapy.

Parent Preference. Because there has been no clear clinical advantage to the use of ceftriaxone over oral therapy in treating acute otitis media, other factors must be considered when choosing antibiotic therapy. Parents were surveyed in several studies and showed a consistent preference for IM therapy; even those parents whose children had a case of acute otitis media that had not shown clinical improvement with ceftriaxone therapy.^{5,7,9} Despite the discomfort of an injection to a child, most parents found the efficiency of single-dose therapy more desirable than a multi-dose 10-day regimen.

In spite of the benefit of a single-dose regimen, some IM therapy regimen costs can be prohibitive. Ceftriaxone, in particular, costs considerably more than amoxicillin.

Antimicrobial Resistance. Another factor that should be considered when choosing an antibiotic is increasing antimicrobial resistance. Concern has arisen recently that the frequent or unnecessary use of the broad-spectrum antibiotics could lead to increased antimicrobial resistance, particularly among pneumococci, the most common cause of pediatric acute otitis media.¹⁰ However, there is no evidence that the use of ceftriaxone selects for ceftriaxone-resistant pneumococci more readily than the use of other beta-lactam antibiotics, such as amoxicillin.

Increasing concern about antimicrobial resistance has led the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group of the Centers for Disease Control to develop new guidelines for the management of acute otitis media.¹⁰ Oral amoxicillin remained the first choice among antibiotics, although a higher dose (up to 90 mg/kg/day) was recommended, especially in geographic locations with

high pneumococcal resistance. For clinically defined treatment failures, second-line and third-line agents, including amoxicillin/clavulanate, cefuroxime, and IM ceftriaxone, were recommended. Although ceftriaxone does have a good spectrum of activity against most penicillin-resistant *S. pneumoniae* (PRSP) and beta-lactamase producing organisms, such as *H. influenzae* and *M. catarrhalis*, reservations have been expressed about the routine use of ceftriaxone as a second-line agent, especially when PRSP has not been confirmed and oral alternatives are available.¹¹ Yet, there are situations in which an IM agent has an advantage over oral antibiotics. These include when a child refuses to take oral medications, has decreased gastrointestinal absorption due to significant vomiting or diarrhea, or has a risk of poor compliance with therapy (Table 1).⁵⁻⁸ In addition, in an infant or young child who appears to have a severe case of otitis media but does not require hospitalization, IM ceftriaxone may be considered for treatment of both the otitis media and a possible accompanying occult bacteremia.^{5,8,9,12,13}

Additional Uses. These guidelines for ceftriaxone therapy in otitis media could also be used for the treatment of other upper respiratory tract infections. Five percent to 10% of viral upper respiratory infections are complicated by acute bacterial sinusitis.¹⁴ Studies on acute sinusitis in children have demonstrated that the major etiologic pathogens are *S. pneumoniae* in 30% to 40% of cases, *H. influenzae* and *M. catarrhalis* each in 20%, and viruses in 10%.^{14,15} As both the pathogenesis and microbiology of sinusitis are similar to those of acute otitis media, similar conditions for the use of ceftriaxone could be applied. It should be noted that ceftriaxone is not approved by the FDA for the treatment of sinusitis. Wald¹⁴ suggests that a patient with toxicity or inability to

take oral medications could be hospitalized and treated with IV cefuroxime, ampicillin/sulbactam, or cefotaxime (if PRSP is suspected). Ceftriaxone, with the same spectrum of activity as that of cefuroxime, can be administered once daily IM or IV and therefore allow a child with sinusitis to be treated with parenteral antibiotics on an outpatient basis.

A unique indication for ceftriaxone is the treatment of pharyngitis caused by *Neisseria gonorrhoea*. Gonococcal pharyngitis is rare in the pediatric population but should be considered in special epidemiological situations, such as a sexually active adolescent or in a case of sexual abuse.^{16,17} A single dose of ceftriaxone (125 mg IM) is sufficient to eradicate the organism and is the recommended initial therapy at all ages.¹⁸ Colonization of the pharynx with *Neisseria meningitidis* can also be eradicated by a dose of ceftriaxone (≤ 12 years old: 125 mg IM; >12 years old: 250 mg IM) as a method of post-exposure prophylaxis for contacts of a patient with meningococemia.¹⁸

The majority of pediatricians will not see a case of gonococcal pharyngitis, but they will often see infections of the pharynx and tonsils, the most common illness in the pediatric field after the common cold and acute otitis media.¹⁹ Although viruses are responsible for most cases of acute pharyngitis,^{16,17,19} 15% to 20% of pediatric cases are due to the Group A beta-hemolytic

Table 1. Circumstances That Preclude the Use of Oral Therapy in a Child

<p>Child:</p> <ul style="list-style-type: none"> Refuses to take oral medications Has decreased gastrointestinal absorption due to persistent vomiting or diarrhea Has a risk of poor compliance with therapy
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Source: References 5-8.

streptococcus (GABHS). Other bacteria, such as Groups C and G streptococci and *Arcanobacterium hemolyticum*, are gaining increased recognition as pathogens in the pharynx, but none have an incidence as great as that of GABHS.^{16,17,19} More importantly, GABHS pharyngotonsillitis can lead to the development of poststreptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease.

Past and Present Use of Penicillin

As early as 1880, Fowler recognized an association between tonsillitis and rheumatic fever.²⁰ However, it wasn't until 1931 that Coburn and Collis identified the organism responsible for both the throat infections and the subsequent rheumatic fever as a hemolytic streptococcus. There was no definitive therapy available for streptococcal pharyngotonsillitis until the introduction of sulfonamides in the late 1930s. Penicillin was discovered in 1929 by Fleming, and by 1940 it was found to be an effective therapy for streptococcal infections.²⁰

Initially, penicillin was given intravenously, intramuscularly, or subcutaneously, but the intramuscular injection resulted in significant pain and local injury, and a therapeutic level lasted for only 30 minutes. In 1948, the first intramuscular repository form of penicillin (procaine penicillin G) became available, with a dosing interval of 24 hours. Later, the suspension of procaine penicillin G in peanut oil with 2% aluminum monostearate allowed dosing every 2 to 3 days.²¹ This form of procaine penicillin was used in the definitive, large-scale, randomized trial of penicillin G versus placebo control in the treatment of exudative pharyngitis by Denny, Wannamaker, Brink, Rammelkamp, and Custer.²² They were able to demonstrate a significant decrease in acute rheumatic fever and GABHS carriage following penicillin treatment.

In 1952, benzathine penicillin G (BPG), an intramuscular repository form that generated therapeutic levels for 4 weeks, was introduced and became the standard for the treatment of streptococcal pharyngitis and for prophylaxis against recurrent streptococcal infections.²¹ BPG is the aqueous solution of the N, N'-dibenzylethylenediamine dipenicillin G salt obtained by the combination of ammonium base and penicillin G. It slowly releases penicillin G into the area of injection, producing low but persistent serum concentrations.²³

Although BPG was effective in preventing recurrent rheumatic fever, it was associated with significant local reactions of pain and tenderness at the injection site. By mixing the standard pediatric dose of benzathine (600,000 units) with the same dose of procaine penicillin G, Krugman in 1958 was able to reduce the local reaction.²¹ This mixture was approved by the American Heart Association (AHA) for use in children weighing less than 60 lbs. However, this dose of BPG was thought to be too low for larger children.

In 1976, a study demonstrated that 900,000 units of BPG mixed with 300,000 units of procaine penicillin G reduced the local reaction, produced adequate serum concentrations, and had a similar efficacy to the standard benzathine dose in eradication of GABHS.²⁴ This regimen was subsequently approved for the treatment of GABHS pharyngitis in children weighing 60 to 140 lbs. However, for larger children and adolescents weighing more than 140 lbs, the AHA continues to recommend a dose of 1.2 million units of BPG.²⁵

Current IM Forms. The currently used IM forms of penicillin are BPG (Bicillin® L-A) and the benzathine 900,000 U/procaine penicillin 300,000 U combination as described above (Bicillin® C-R 900/300) (Table 2). Both forms are released slowly into

the muscle from the injection site and hydrolyzed to penicillin G, resulting in prolonged serum concentrations. BPG is approved by the FDA for the treatment of moderately severe infections caused by penicillin-susceptible organisms, including pneumonia and otitis media due to susceptible *Streptococcus pneumoniae*.²⁶ However, pediatric cases of pneumonia and otitis media are often treated without identifying an etiologic organism; therefore, these conditions often are treated with a broader spectrum antibiotic and require higher tissue levels than those achievable with BPG. As a result, BPG is rarely used for these indications.

Debate Over Failure Rates. IM BPG remains a standard therapy for GABHS pharyngitis and is often used in the treatment of upper respiratory tract and skin infections due to streptococci. For years its efficacy was undisputed, and bacteriologic failure rates were less than 10%, but in the 1980s, concern arose over BPG's continued efficacy.

In 1985, Kaplan²⁷ reviewed studies conducted in the same region and found that there had been a slight rise in failure rates from 6% in the 1950s, to 8% in 1964, to 19% during an outbreak from 1977 to 1979. Since many of the patients with bacteriologic "failure" developed no serologic response to GABHS, Kaplan concluded that they were probably streptococcal carriers rather than true failures of therapy and therefore were at low risk for developing acute rheumatic fever. Feldman and associates²⁸ likewise noted that the failure rate for BPG, which had been less than 10% in the 1950s and 1960s, had been reported as greater than 10% since the 1970s. However, the researchers questioned the adequacy of the doses of BPG used in these trials as well as the inclusion of possible streptococcal carriers. In their prospective trial of BPG at appropriate doses for the treatment of

streptococcal pharyngitis, Feldman and associates demonstrated a bacteriologic failure rate of 12%.²⁸ This rate, although higher than that of earlier studies possibly due to the inclusion of chronic GABHS carriers, was still less than some reported rates of 20%. A recent large, multicenter, randomized trial suggests that the percentage of BPG treatment failures may have risen even higher, but the significance and interpretation of these results remains to be completely explained.²⁹

Many other antimicrobial agents have been evaluated for the treatment of streptococcal pharyngitis, but it is important to note that only procaine and BPG were studied in prospective, randomized, placebo-controlled trials, and only procaine penicillin G in peanut oil was proven to prevent acute rheumatic fever.^{22,30} In a later trial with BPG, definite acute rheumatic fever developed in 2 of the 109 placebo recipients but not in any of the 257 penicillin-treated patients. (It should be noted that this difference was not statistically significant [$P = 0.088$, Fisher's exact test]).³⁰ Oral antibiotics have been compared with IM penicillin only in their ability to eradicate GABHS. As oral penicillin V became widely used for GABHS pharyngitis, a number of studies were conducted comparing its efficacy with that of new oral cephalosporins.

Pichichero's review and meta-analysis of these studies concluded that the cephalosporins had lower bacteriologic and clinical failure rates (8% and 5%) than penicillin (18% and 14%) and therefore were more effective.

Table 2. Currently Used Intramuscular Forms of Penicillin

■ Benzathine penicillin G
■ Benzathine 900,000 U/procaine penicillin 300,000 U

tive.³¹ Pichichero believed the higher costs of the cephalosporins would be offset by the reduced repeat visits and treatment courses for therapy failures. Several of the same studies were reviewed by various experts who noted the paucity of prospective, randomized trials; the lack of serotyping to determine new infections versus failures; the inclusion of possible carriers or reacquisitions; and the lack of compliance information.³²⁻³⁴ In the studies that did use serotyping, the bacteriologic failure rate for oral penicillin from 1953 to 1979 was 10.5% at 14 days posttherapy. From 1980 to 1993, the rate increased slightly to 12% at 14 days posttherapy, therefore, the rate difference was 4% to 6% between penicillin and the cephalosporins.^{32,33} Overall, these experts concluded that there was no evidence for a decrease in penicillin's efficacy and that penicillin remained the drug of choice for the treatment of streptococcal pharyngitis because of its cost, safety, narrow spectrum, and effectiveness.

Current Indications. The most recent statement by the AHA's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease in 1995 reaffirmed penicillin as the antimicrobial agent of choice for the treatment of GABHS pharyngitis except in individuals with a history of penicillin allergy.²⁵ Although penicillin V is the oral antibiotic of choice, IM BPG is preferred for patients with a personal or family history of rheumatic fever or rheumatic heart disease, and for those who are likely to have difficulty in compliance with therapy or who are at higher risk for developing rheumatic fever (eg, those in crowded living conditions). In these situations, ensuring compliance and eradication of GABHS from the pharynx is more critical, and bacteriologic failure has occurred more frequently with oral penicillin V than with BPG.²⁵

In addition to treatment of GABHS pharyngitis, BPG is also used for con-

tinuous prophylaxis against recurrent streptococcal infections and rheumatic fever in patients who have rheumatic heart disease or have had a previous episode of rheumatic fever. Since the 1940s, there has been a steady decline in the incidence of acute rheumatic fever (ARF). At the time of the Denny study,²² there were 200,000 to 250,000 new cases of ARF a year in the United States, but from 1977 to 1981, Bisno³⁵ reported an incidence rate of only 0.5 to 1.8 cases per 100,000 population. Although this decline began before antibiotics were introduced, likely as a result of improved socioeconomic conditions, antibiotics appear to have played a significant role.

The AHA recommends that any patient with ARF and carditis with persistent valvular disease be treated with BPG until at least 40 years of age and at least 10 years have passed since the last episode, whichever is longer. Patients with ARF and carditis but no valvular disease should continue therapy for at least 10 years and well into adulthood, and patients with ARF but no carditis should be treated for at least 5 years and until 21 years of age.²⁵ While the AHA recommends a dosing interval of every 4 weeks (every 3 weeks if the patient is at high risk or in an area of endemic ARF), some concern has arisen recently over the adequacy of this regimen.

Lue and associates³⁶ conducted a randomized controlled trial with 249 patients in Taiwan evaluating both 3- and 4-week BPG regimens for ARF prophylaxis. They found that only 48% of patients had a serum penicillin level greater than or equal to 0.02 mg/mL at 4 weeks postinjection, as opposed to 65% of patients at 3 weeks. In addition, the researchers showed that, when compared with the 4-week regimen, the 3-week regimen resulted in a significantly greater decrease in streptococcal infections and ARF due to prophylax-

is failure, suggesting that the dosing interval of 3 weeks is more effective.³⁶ An Egyptian prospective study³⁷ comparing 2- and 4-week dosing intervals found no difference in the rate of streptococcal infections, but did discover a lower rate of rheumatic fever recurrences in the group receiving BPG every 2 weeks.

The feasibility of BPG administration every 2 or 3 weeks for 10 to 20 years is doubtful, especially in developing countries. For this reason, Currie³⁸ studied the use of higher doses of BPG rather than shorter intervals. Although these doses led to more prolonged serum penicillin levels, there are currently insufficient data to suggest any dosing of BPG other than that recommended by the AHA.

Summary

The frequency of upper respiratory tract infections in the pediatric population assures that pediatricians will encounter these illnesses on a daily basis. A large number of patients will have a viral infection, but for those with otitis media, sinusitis, or pharyngitis of suspected or proved bacterial etiology, physicians will have to choose the most appropriate therapy. When an oral antibiotic cannot be used because the child will not tolerate oral therapy or has questionable compliance, an intramuscular agent provides an alternative method of antimicrobial delivery in outpatient management. The advantages of intramuscular therapy include confirmed administration of medication, ease of a single-dose regimen, and deliverance of parenteral antibiotics. In specific situations, ceftriaxone IM can be indicated for the treatment of otitis media, sinusitis, and pharyngitis. For the treatment of streptococcal pharyngitis, IM BPG remains the standard therapy and is the only agent recommended for routine prophylaxis against recurrence of rheumatic fever.

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