ANTIBIOTIC THERAPY IN DIABETIC PATIENTS

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Introduction

Choosing an antibiotic for the diabetic patient has always required careful consideration. The myriad of complicating factors associated with diabetes combined with the recent marked increased in the number of available antibiotics has made this task increasingly difficult. A discussion of the considerations involved in instituting appropriate antibiotic therapy in the diabetic is presented below.

Patient Factors

Diabetic patients have an impaired ability to resist infection. Many theories have been presented in attempting to explain the increased incidence of infection. The combination of defective immune systems, neuropathy, and impaired circulation all contribute to the prevalent occurrence of foot infections seen in these patients (1-4).

Assessment of renal function is helpful in the diabetic patient since most of the antibiotics are cleared by filtration or excretion by the kidneys. Pre-existing renal disease increases the likelihood of additional damage to the kidneys by nephrotoxic drugs such as the aminoglycosides. Dosage adjustment or choosing hepatically excreted drugs may be prudent in some patients with advanced renal disease.

The ability of the antibiotic to penetrate into infected tissues depends almost entirely on the circulation to the area. In diabetic patients one commonly finds severe vascular disease which will greatly impair the delivery of antibiotics to the distal lower extremity. For this reason, debridement of necrotic and poorly perfused tissues cannot be over emphasized. Exposure of anaerobic organisms to air is a most effective therapy.

Rayfield and associates discussed the importance of intensive control of hyperglycemia in preventing the complications of diabetes (5). Infection often markedly elevates serum glucose levels in the diabetic patient. Tight glucose control should be a part of management as much as antibiotics and debridement, since elevated glucose levels appear to impair the body's ability to clear infection. Long term aggressive insulin control should continue to be pursued after the infection has been eradicated.

Pathogen Identification

Before beginning any antibiotic in a patient with an infection, an exhaustive attempt to identify the organism(s) present should be made. Even the severely septic patient should have blood and wound cultures performed prior to infusing any antibiotic.

Gram Stain

Gram staining of wound drainage can be helpful in determining whether an infection is being caused by a single agent versus a combination of gram positive and gram negative organisms. Mixed gram stain results of sinus tracts or ulcerations, though unreliable can be helpful when acute infection requires a response, but final culture results are not yet available.

Bacterial Culture

Acquiring a reliable culture is essential. The chronic ulceration which suddenly or insidiously progresses to infection will undoubtedly be colonized with organisms which will actually be playing a minor role, if any, in the infective process. Determining which organisms are involved in this situation is often an arduous but worthwhile task. Superficial debridement and normal saline irrigation of the wound prior to obtaining a specimen for culture may be helpful if a non-operatively obtained culture is indicated. The physician who is responsible for obtaining the culture results should carefully describe and document the means of obtaining the culture. This will enable proper evaluation of the reliability of the culture results.

Culturing of deep tissues is the method of choice. Surgical debridement with biopsy cultures of deeper soft tissue and bone will usually yield the most reliable culture. Prior superficial wound culture should also be performed in the event that deeper cultures result in no growth of bacteria. These less reliable cultures will at least provide an indication of the organisms present.

Poor correlation of superficial sinus tract cultures with deeper reliable cultures was demonstrated by Wheat and associates in 1986 (6). They suggested a three step approach for the microbiological assessment of diabetic foot infections.

1. Specimens should be processed both aerobically and anaerobically since these infections are often polymicrobic. The importance of prompt transport of the specimen in a syringe or other anaerobic transport device was stressed.

2. Aspirates of abscesses or bullous lesions should be submitted along with exudate from draining sinuses. The aspirates were felt to provide a more reliable culture source.
3. Biopsy of deep soft tissues or bone should be submitted for culture when necrotizing soft-tissue infections or osteomyelitis is present.

In a classic study by Mackowiak and associates cultures of sinus tracts were compared with operative specimens in patients with chronic osteomyelitis (7). They found that isolation of any organism other than staph aureus from the sinus did not correlate with the true bone pathogen. A significant percentage of patients (88%) had a single agent cultured from their operative specimens.

Clinical Assessment

Clinical evaluation in conjunction with laboratory findings should play a large role in the decision-making process of choosing an antibiotic regime.

The odor of the wound alone will often aid significantly in arriving at a diagnosis. A fetid feculant odor is suggestive of the presence of bacteroides and other anaerobic organisms. The greenish purulence of pseudomonas has a sickly, sweet smell which is easily recognized once encountered.

The chronically open wound which has become acutely infected with rapid onset and progression of cellulitis, suggests the presence of gram positive cocci (Staphylococcus or Streptococcus).

Empiric Antibiotic Therapy

Once gram stain and culture specimens have been obtained, antibiotic therapy may be instituted. It should be stressed that if incision and drainage is planned it should be performed as soon as is feasible with deep culturing of tissues performed before antibiotics are administered. Unfortunately, some situations will not permit delaying antibiotics due to overwhelming sepsis or unavoidable delay in surgical therapy. However, in cases of chronic osteomyelitis delaying antibiotics for several hours to days while awaiting deep culture is not unreasonable.

Empiric therapy should be based on the clinical presentation, gram stain results, prior antibiotic therapy, and previous culture results of the same site (if available). Patients who present with a progressive infectious process despite taking oral antibiotic such as Cephalexin or Cefadroxil may indicate infection by resistant organisms.

The acute situation, e.g. the puncture wound, which results in rapid abscess formation and cellulitis is suggestive of Staphylococcal or Streptococcal infection. Empiric therapy should begin with oral penicillinase resistant penicillins such as Dicloxacillin. Oral cephalosporin such as cefadroxil and cephalexin have inferior MIC values against Staphylococcus. Ciprofloxacin, a new quinolone antibiotic, whose release is imminent covers staph, strep, and most gram negative organisms. This may prove to be a better choice for puncture wounds which often contain Pseudomonas.

Late pseudomonas infection is indicated by the patient presenting seven to ten days post-puncture wound with exacerbation of symptoms despite appropriate oral prophylaxis for S. aureus. Gram-staining of purulence revealing the presence of gram negative rods combined with the above history merits antibiotic coverage for the presence of P. aeruginosa. An aminoglycoside combined with cephazolin for gram positive coverage could be later altered after reliable culture results are obtained. Ciprofloxacin may prove to be an oral alternative to this regimen in the near future (8).

In most chronic infections, broad spectrum antibiotic coverage for gram negative bacilli, staphylococcus, and possibly anaerobes will be necessary. The unique presentation of each infectious process precludes a formula approach to determining the most appropriate antibiotic regime. However, some suggestions will be presented to use as a guideline in instituting therapy. Emphasis will be placed on individualizing the antibiotic regime.

Antibiotic Regimes

There are many appropriate antibiotic regimes for almost any situation. Choosing the specific agent should first consider the sensitivities of the organisms responsible for the infection. Additional factors, which should affect your antibiotic choice include complicating health conditions, ease of administration, drug allergies, and toxicity, and cost of therapy.

Antibiotic Susceptibility and Resistance

Since the goal in administering any antibiotic is to rid the body of an infecting organism, in vitro testing should be used to assess the ability of antibiotic to kill the organism. While in vitro studies do not fully reflect the complex interaction between host, drug, and microorganism, poor antimicrobial activity is certain to lead to poor results.

One widely available method of assessing antimicrobial susceptibility is to measure the minimum inhibitory concentration (MIC). The MIC for a particular microorganism is defined as the lowest concentration of an antibiotic that will inhibit, but not necessarily kill, the organism. The MIC is given in units of micrograms per millileter and is based on serial dilution of the antibiotic. The "breakpoint" is the dilution at which the microorganisms are inhibited. Some laboratories will interpret the concentrations by designating the numerical value as a reflection of achievable serum levels. An organism is graded as being susceptible (+ + +), intermediate (+ +), or resistant (+) based on whether inhibition occurs at easily achievable serum levels, high serum levels only, or the organism is not inhibited at usually achievable serum levels, respectively.

In Vitro Susceptibility of Staphylococci and Streptococci to Cephalosporins and Newer Beta-Lactam Antibiotics

Antimicrobial Agent	Staphylococci						Streptococci					
	Methicillin-Susceptible S. aureus		Methicillin-Resistant S. aureus		Coagulase-Negative Staphylococci		Enterococci		S. pneumoniae		S. pyogenes	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Ceftazidime	8*	16	128	128	32	32	>256	>256	0.25	0.5	0.12	0.12
Cefotaxime	2	2	16	128	1	8	256	>256	0.01	0.06	≤0.008	0.03
Ceftizoxime	4	8	>256	>256	1	>32	>256	>256	≤0.01	0.25	≤0.01	≤0.01
Moxalactam	4	8	128	256	8	>32	>256	>256	1	1	1	2
Cefoperazone	2	4	64	>256	4	8	32	32	0.12	0.25	0.12	0.12
Ceftriaxone	2	4	32	256	0.12	0.5	256	>256	0.25	0.5	0.01	0.03
Imipenem	0.008	0.008	1†	2†	0.01	1	1†	2†	0.01	0.06	0.004	0.004
Aztreonam	>128	>128	>128	>128	>128	>128	>32	>32	>32	>32	8	>32
Cephalothin	≤0.25	0.5	8	32	0.5	32	32	64	≤0.25	≤0.25	≤0.25	≤0.25
Cefamandole	≤0.25	1	8	8	1	32	32	32	≤0.25	≤0.25	≤0.25	≤0.25
Cefoxitin	2	4	32	64	8	64	>64	>64	1	2	0.5	1

*Expressed in μg/ml.

†Minimal bactericidal concentration elevated.

Table 1. In vitro susceptibilities of Staphylococci and Streptococci are shown. Methicillin-Staphylococcus for the most part are susceptible to these agents. Note, however, that except for Imipenem the first generation cephalosporin (Cephalothin) is more active than the second and third generation cephalosporins. (Taken with permission from Thornsberry, 1985).

In Vitro Susceptibility of Enterobacteriaceae to Second and

Antimicrobial Agent	E. coli	C. diversus	C. freundil	E. aerogenes	E. cloacae	E. agglomerans	K. pneumoniae
Ceftazidime	0.12/0.5*	0.25/0.5	0.5/2	0.25/2	0.12/32	0.25/0.5	0.12/0.5
Cefotaxime	0.06/0.12	0.12/0.25	0.25/0.5	0.06/0.5	0.25/32	0.06/0.25	0.06/0.12
Ceftizoxime	0.06/0.12	0.06/0.25	0.25/1	0.12/64	0.5/16	0.03/0.06	≤0.01/0.03
Moxalactam	0.12/0.25	0.12/0.5	0.25/0.5	0.25/2	0.12/8	0.12/0.25	0.12/0.25
Cefoperazone	0.12/32	0.12/0.25	0.5/1	0.25/8	0.5/64	0.25/2	0.25/4
Ceftriaxone	0.03/0.12	0.06/0.12	0.12/0.5	0.06/0.25	0.25/16	0.06/0.25	0.06/0.06
Imipenem	0.12/0.5	0.12/0.12	0.25/0.5	0.12/1	0.12/0.12	0.25/0.5	0.12/0.25
Aztreonam	≤0.06/0.12	≤0.06/0.12	≤0.06/0.25	≤0.06/4	0.25/4	≤0.06/≤0.06	≤0.06/0.12
Cefamandole	0.5/16	1/2	2/8	2/>64	32/>64	2/>64	1/8
Cefoxitin	2/8	2/64	64/>64	>64/>64	>64/>64	16/>64	2/8

NA = not available.

*MIC_{50}/MIC_{90} expressed in μg/ml.

Table 2. This table depicts in vitro activity of beta-lactam drugs against clinically significant Enterobacteriaceal found in diabetic foot infections. Values shown are expressed in mg/ml and represent the MIC50 (50% of organisms inhibited) and the MIC90 (90% inhibition). First seven antibiotics are third generation cephalosporins. Imipenem, Aztreonam, and Cefpirome are newer beta-lactams. Cefamandole and Cefoxitin represent the second generation cephalosporins. (Taken with permission from Thornsberry, 1985.)

MIC determination usually provides an adequate estimation of the in vivo activity of the antibiotic. However, in cases where greater efficacy is needed, such as in osteomyelitis where actual killing of organisms is needed, simple inhibition may be inadequate. For these cases a second determination called minimal bactericidal concentration (MBC) may be useful. MBC determinations are especially important in difficulty to eradicate infections (SBE, osteomyelitis) and with organisms which show high propensity to develop resistance such as P. aeruginosa.

The MBC for a particular agent is the concentration of a particular antibiotic at which 99.9% of a known number of bacteria are killed. In some cases the MBC can be 32 times the MIC indicating tolerance of an organism to the antibiotic. In those cases, the addition of second antimicrobial or change in regimen may be indicated (9).

Many antibiotics are advertised to have activity against clinically important bacteria. It is important to understand the relativity of such susceptibilities to place in perspective the indications for these antibiotics. "Broad spectrum" is of no value if it does not include good activity against the likely pathogens. Thornsberry (1985) published the MIC values for most of the third-generation cephalosporins and other beta-lactam antibiotics (10). Tables 1-4 include his summarized results.

In Vitro Susceptibility of Pseudomonas and Acinetobacter Species to 17 Beta- Lactam Antibiotics

Antimicrobial Agent	P. aeruginosa		Other Pseudomonas		Acinetobacter	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Ceftazidime	2*	4	4	64	8	16
Cefotaxime	16	32	16	256	16	16
Ceftizoxime	32	64	16	256	8	16
Moxalactam	16	32	32	128	32	64
Cefoperazone	4	8	16	128	64	128
Ceftriaxone	16	16	8	256	8	16
Imipenem	1	2	0.5	8	0.25	0.25
Aztreonam	2	8	4	16	16	64
Cefsulodin	2	4	64	>256	32	64
Azlocillin	4	128	Variable		64	64
Carbenicillin	128	>128	128	>128	16	32
Ticarcillin	16	>128	Variable		8	64
Mezlocillin	16	128	Variable		64	>128
Piperacillin	4	64	8	64	16	64

*Expressed in μg/ml.

Table 3. Pseudomonas and Acinetobacter species tend to be highly resistant to beta-lactam antibiotics. As is evidenced by MIC's reported above. Of third generation Cephalosporins, Ceftazidime and Cefoperazone are most active against P. aeruginosa, ceftazidime having about twice the activity or cefaperazone. Acinetobacter and majority of Pseudomonas species show high degree of resistance. (Taken with permission from Thornsberry, 1985.)

Third Generation Cephalosporins and Newer Beta-Lactam Antibiotics

P. mirabilis	P. vulgaris	M. morganil	P. rettgeri	P. stuartil	S. marcescens	Salmonella	Shigella
0.06/0.06	0.06/0.12	0.12/4	0.25/2	1/4	0.25/1	0.25/0.25	0.12/0.25
0.01/0.01	0.06/16	0.06/2	0.06/0.5	0.5/2	0.5/2	0.06/0.06	0.06/0.12
≤0.01/≤0.01	0.03/0.12	2/16	0.01/0.06	0.03/0.25	0.12/2	≤0.12/≤0.12	≤0.12/≤0.12
0.25/0.25	0.25/0.25	0.25/0.25	0.12/0.5	0.25/4	0.25/4	≤0.12/0.25	≤0.12/0.25
0.5/1	1/32	1/4	2/>256	8/32	8/32	0.12/0.12	≤0.12/1
≤0.004/0.008	0.01/0.12	0.03/0.5	0.01/0.5	0.06/0.5	0.5/4	0.06/0.06	≤0.12/≤0.12
4/4	2/2	2/4	2/4	1/2	0.5/1	≤0.12/≤0.12	≤0.12/≤0.12
≤0.06/≤0.06	≤0.06/≤0.06	≤0.06/1	≤0.06/0.12	≤0.06/≤0.06	≤0.06/2	≤0.12/≤0.12	≤0.12/≤0.12
0.5/1	>64/>64	32/64	8/>64	64/>64	>64/>64	NA	NA
2/8	2/8	8/16	4/64	4/64	32/64	NA	NA

In Vitro Susceptibility of Anaerobes to Cephalosporins and Newer Beta-Lactam Antibiotics

Antimicrobial Agent	Bacteroides				Clostridium	
	B. fragilis		Other			
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Ceftazidime	16*	64	2	32	4	>64
Cefotaxime	8	16	1	16	8	>64
Ceftizoxime	4	16	≤0.5	8	16	>64
Moxalactam	1	32	4	16	2	>64
Cefoperazone	32	>64	4	16	1	64
Ceftriaxone	8	32	NA	NA	NA	NA
Imipenem	0.06	2	0.01	0.25	0.06	8
Aztreonam	>32	>32	64	>128	NA	NA
Cefamandole	32	>64	1	16	1	>128
Cefoxitin	4	16	0.25	16	0.5	>128

NA = not available.
*Expressed in μg/ml.

Table 4. Anaerobic organisms are more effectively treated with Cefoxitin than third generation Cephalosporins or other new beta-lactams. Imipenem, however, does have significantly lower MIC values for these organisms. Other antibiotics with excellent anaerobic activity include Metronidazole and Clindamycin and may be more appropriate when anaerobes are main concern. (Take with permission from Thornsberry, 1985.)

Staphylococcus and Streptococci

In a recent study by Wheat and associates the relative prevalence of microorganisms in diabetic foot infections was reported (6). Fifty-four reliable cultures were performed from a total of 103 patients. Staphylococcus species and/or Streptococcus species were isolated from a total of 50 out of 54 cultures (94%). Although lesser frequences have been reported all authors stress the significance of the involvement of these organisms (11, 12). S. aureus along with anaerobic species are the most important pathogens in bacteremic episodes in diabetic patients (13).

Except for the enterococcal group, the presence of Streptococci will not greatly effect the choice of antibiotic in mixed infections since most antibiotic agents employed will adequately cover these organisms. One notable exception is the monobactan, Aztreonan which is ineffective against gram positive organisms.

The importance of enterococcal presence in mixed diabetic foot infections is somewhat controversial. Regimes which ignore less virulent organisms have been suggested by some authors (4, 6). However, if enterococci appear as a single isolated or in combination with very few other organisms, it is prudent to direct treatment at this organism. PCN, Ampicillin, Mezlocillin, and other Ureidopenicillins in conjunction with Gentamycin (14) are the treatments of choice for serious enterococcal infection.

The Cephalosporins have no activity against enterococci. For penicillin allergic patients, Vancomycin may be used. Imipenem may be appropriate in treatment, but Imipenem may have crossover allergy with Penicillins, so if the penacillin allergy was anaphylactoid one must be wary.

S. Aureus can be divided into two groups which have therapeutic significance. Most S. Aureus organisms produce beta-lactamase and require antibiotics which are not degraded by beta-lactamase enzymes. Nafcillin, Oxacillin and the first, second, and third generation cephalosporins will all have some degree of activity against these organisms at achievable blood levels. Oxacillin/nafcillin are highly ef-

fective, but they must be given every 4 hours and are costly. Cefazolin, a first generation cephalosporin has good MICs, good tissue penetration plus low cost, every 8 hour dosing, and excellent safety making it the drug of choice for Methicillin-susceptible S. aureus.

Cefoxitin, a second generation cephalosporin has inferior activity against Methicillin-susceptible S. aureus (Table 1) but the advantage of superior anaerobic and some gram negative activity. However, in the serious diabetic foot infection suggested by anaerobic gram-positive, and gram negative involvement combination therapy with the most active antibiotic agents is appropriately considered.

Of the third generation cephalosporins, cefotaxime provides the best coverage against methicillin-susceptible S. aureus. Cefotaxime is considered by the authors a good monotherapy agent in mild to moderately severe foot infections in which methicillin-sensitive Staphylococcus and enterobacteriaceae are involved. However, as with any regimen sensitivities will guide its selection (Table 1). The newer agent Imipenem may also be a very efficatious choice, but it is costly.

Clindamycin is also an effective agent in the treatment of Methicillin-sensitive staphylococcal infection. The combination of Clindamycin with an aminoglycoside can be effective in treating many of the mixed infections seen in diabetics since anaerobes, most gram negative organisms, and Methicillin-sensitive staphylococcus will be covered with this combination.

Methicillin-resistant Staphylococcus aureus organisms (MRSA) are resistant to all beta-lactam antibiotics. The only drug of choice for MRSA is Vancomycin. Imipenem has been shown to have activity against Methicillin-resistant Staphylococcus, but further study into its clinical usefulness is needed. Finally, the addition of oral Rifampin to other anti-Staphylococcal agents has been shown to be useful in treating resistant organisms. However, rapid development of resistance occurs if Rifampin is used as a single agent.

Gram Negative Organisms

The gram negative organisms historically have proven to be among the most adaptable of the clinically significant bacteria. Development of resistance within this group has been the main impetus for the development of new antibiotic agents. This group includes the enterobacteriaceae—Klebsiella pneumoniae, Serratia marcesans, Proteus mirabilis and vulgaris, Enterobacter, Morganella morganii, Escherichia coli, and Citrobacter species. Pseudomonas species and Acinetobacter species complete the list of significant gram negative organisms. The MIC's for the above bacteria to several beta-lactams are shown in Tables 2 and 3. Most of these organisms are susceptible to the third generation cephalosporins. However, Pseudomonas, Acinetobacter, Serratia, and some Enterobacter species have been known to develop resistance to single agent therapy with beta-lactam antibiotics. In serious infections such as osteomyelitis it is prudent to use a two drug regimen which includes an aminoglycoside when dealing with these agents. The gram negative organisms are often isolated in polymicrobial diabetic foot infections with three to six organisms not being uncommon (6, 11, 12, 15).

The presence of multiple pathogens usually requires an extended spectrum antibiotic. Cefotaxime, the first third generation cephalosporin provides adequate antimicrobial activity against the majority of these pathogens. If Cefotaxime is not adequate, then combination therapy is usually needed. Note that the second generation cephalosporins are for the most part inadequate for mixed infections with these agents. Imipenem provides sufficient inhibition for these organisms, however, with Ps, Serratia, Acinetobacter and enterobacterial cultures, the addition of aminoglycoside to prevent resistance developing while on therapy is prudent.

Note the large differential between the MIC50 and MIC90 for Enterobacter cloacae and Serratia marcescens. This indicates that these organisms have a wide variation in susceptibilities and therefore will often require synergistic antibiotic coverage. This becomes increasingly important in the debilitated host.

Pseudomonas aeruginosa is a commonly recovered organism in the mixed diabetic infection. However, it is a common colonizer of no pathologic significance and often is isolated from an unreliable culture of a chronic ulceration and absent in reliable deep wound culture. Mackowiak and associates stated "The predictive values for Enterobacteriaceae and Pseudomonas aeruginosa, and mixed cultures of Streptococcus species isolated from sinus tracts were all less than 50% (7). Wheat and associates found that in approximately 20 out of 131 infections aminoglycosides would have been unnecessarily used to cover Pseudomonas aeruginosa and Acinetobacter colonizers found only in unreliable culture (6). This has important implications in treating the diabetic foot infection.

Proper use of aminoglycosides requires expensive monitoring of drug levels and renal or otic toxicity. The diabetic patient with renal impairment is at particular risk of toxicity. One should try to avoid unnecessary aminoglycoside use by careful and accurate culturing. This is not to say that aminoglycosides are contraindicated in these patients since appropriate use will often determine the fate of the infected diabetic foot. One should remember nephrotoxity is reversible while amputations are irreversible.

Ceftazidime is the third generation cephalosporin most active against Pseudomonas aerugenosa. Cefoperazone is the second most active against this organism, however, its MICs are approximately twice that of Ceftazidime. Imipenem and Axtreonam are also active against Pseudo-

monas aeruginosa. Cefsulodin is a new parenteral beta-lactam with activity virtually restricted to Pseudomonas aeruginosa. Very few reports on its use in osteomyelitis have been published. Response of diabetic patients with soft tissue infections has been reportedly poor to moderate (16).

Pseudomonas species other than aeruginosa and Acinetobacter species are among the most resistant of the clinically significant organisms. Reliable isolation of these organisms necessitates careful selection of effective combination drug therapy.

Serial culturing of the wound is important in determining not only clearing of the pathogen originally cultured but also will alert the physician to developing superinfection. It is wise to perform consecutive cultures taken two days apart before delayed primary closure of a wound.

Patients placed on aminoglycoside antibiotics require consistent monitoring of therapy. Baseline serum creatinine levels should be checked. Subsequent serum creatinine levels on a daily to every other day basis will provide an indication of renal function. An increase in serum creatinine level of 0.4 mg/dl is indicative of renal damage and suggests the need for adjustments. Concomitant use of aminoglycosides with other nephrotoxic or ototoxic drugs increases the risks of toxicity. Furosimide is a commonly encountered example.

Safe and effective use of aminoglycoside therapy requires obtaining peak and trough levels on therapy (17) (Fig. 1). Trough levels under 2 mcg/ml (8 mg for Amikacin) reduce the risk of toxicity, but without good peak levels the drug is not effective. Peaks of at least 4 mg/ml or preferably 6 mg/ml (20 to 30 for Amikacin), but less than 10 mcg/ml will give the best therapeutic response. When starting an aminoglycoside one should obtain a weight and a serum creatinine. Dosage of 1.5—2.5 mg/kg is appropriate. The intervals should be adjusted starting with the serum creatinine of 1.0 as every 8 hours interval and widening the intervals by multiplying 8 x serum creatinine = interval in hours. Levels should be ordered 30 minutes before and 30 minutes after the third dose to give steady state levels. Adjustments based on these levels can then be performed and remeasured. Haas and Collins review aminoglycoside dosing (18).

Anaerobic Organisms

The rapidly progressing foot infection in diabetic patients which results in fulminant tissue necrosis is most commonly associated with the presence of anaerobic organisms. Acute clostridium myonecrosis and streptococcal necrotizing fasciitis are the most feared anaerobic infectious processes. Bacteroides infections, while often severe, tend to be associated with a more chronic presentation (19). The clinical presentation of a feculent, foul smelling, necrotic infection will require empiric antibiotic therapy directed at these organisms. Subcutaneous gas formation evidenced by radiographic appearance and tissue crepitus is further suggestive, but not pathognеumonic for the presence of anaerobic organisms.

Gram stain evidencing gram positive rods is suggestive of clostridial species infection and is a medical and surgical emergency in the septic patient. High dose penicillin G therapy combined with aggressive surgical debridement and amputation will be necessary in the life saving attempt.

Bacteroides species are the most commonly encountered anaerobes. Susceptibilities are quite variable among this group. Many species are susceptible to the second generation cephalosporin cefoxitin. However, resistance to this agent has been reported requiring careful attention to specific MIC values.

Clindamycin is considered the drug of choice for serious anaerobic infections other than clostridial. Metronidazole is also effective against anaerobic organisms, however, it has the disadvantage of no aerobic coverage, whereas clindamycin is also a very effective anti-staphylococcal agent. Imipenam has been shown to have good activity against many anaerobic strains, however, some bacteroides species are uniformly resistant (Table 4).

Monitoring Therapy

The most important signs of appropriate therapy are clinical improvements. A decrease in localized pain, erythema, edema, and calor outweigh the best laboratory tests. The patient who continues to complain of pain is all too often labeled as a "problem patient". Reevaluation of the therapy should be undertaken when pain seems too persistent, for pain is an early and often sensitive indicator of infection.

Laboratory studies including complete blood count with differential, erythrocyte sedimentation rate or "C" reactive protein can be helpful in monitoring therapy. A decrease in the number of white blood cells is expected as therapy progresses successfully.

An increase in insulin requirements occurs in the infected diabetic patient. For this reason sliding scale supplementation with regular insulin should be employed. Adjusting insulin regimens is a must in treating the diabetic patient suffering from an infection. Optimum glucose control can aid in reducing the duration and intensity of the infective process (5).

The Future in Antibiotic Therapy

At present there is no oral antibiotic which can achieve the tissue levels necessary to treat the serious diabetic foot infection. However, the advent of a new class of antibiotics, fluoroquinolones is on the horizon. The most promising agent at present is Ciprofloxacin. The fluoroquinolones are structurally related to Nalidixic acid. They have a very broad-spectrum of bactericidal activity. The clinical and economic

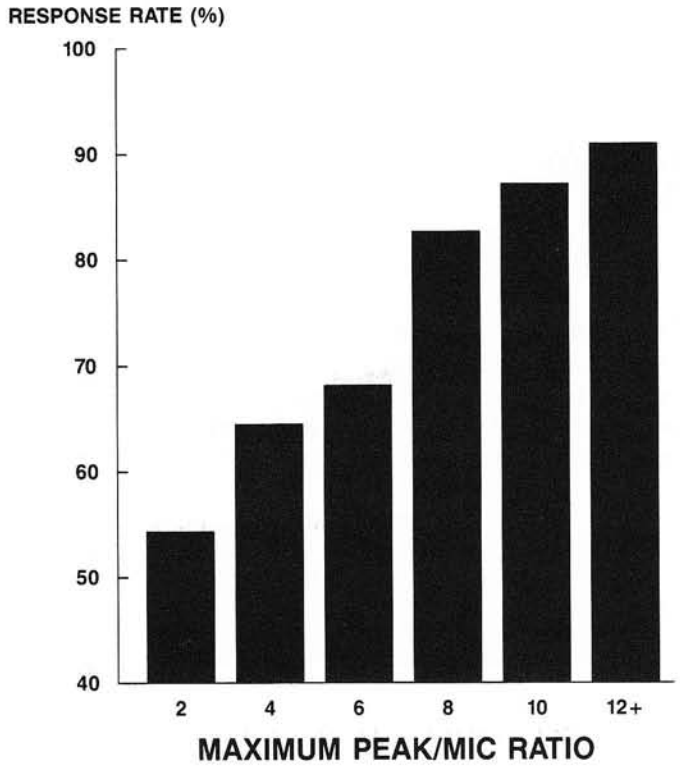

Figure 1. Relationship between the maximal peak level/MIC ratio and the rate of clinical response.

Source: Moore, R.D., et al: Clinical Response to Aminoglycoside Therapy: Importance of the Ratio of Peak Concentration to Minimal Inhibitory Concentration. J Infect Dis 1987; 155 (January): 93-99.

Fig. 1. The maximum peak antibiotic level/minimal inhibitory concentration ratio and its relationship with clinical response as presented by R.D. Moore and associates, 1987.

implications of this new class of antibiotic was discussed in a series of articles by Nev (21) and Scully and associates (22).

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