Bactericidal antibiotics are generally regarded as superior to bacteriostatic agents for treatment of most infections. However, clinical data in support of this viewpoint are lacking except for relatively few infections, namely endocarditis, meningitis, bacteremia in a neutropenic host, and possibly osteomyelitis. Even for these infections most supporting data are drawn from empirical experience, case series, and results from animal models of infection, rather than from well-designed comparative clinical trials. Given this strong presumption of the superiority of bactericidal over bacteriostatic agents, a clinical trial to directly test this hypothesis for the treatment infections where bactericidal activity is likely to make a difference would be considered unethical. Thus, such a clinical trial probably will never be conducted. Our understanding of the importance of this activity must be derived from in vitro studies, experimental animal models, and a rather limited clinical database, some of which is analyzed below.

The Continuum of Bacteriostatic and Bactericidal Activity
Complicating matters is the fact that bacteriostatic or bactericidal activity, although defined as a discrete endpoint (e.g., a 99.9% reduction in bacterial inoculum within a 24h period of exposure), is actually a continuum, such that a 99% reduction very well could be considered bactericidal, albeit at a slower rate (Figure 1).
In addition, bactericidal activity is not an invariable property of an antibiotic; it can depend upon the organism and the growth conditions. For example, *Staphylococcus aureus* is not killed by protein synthesis inhibitors, chloramphenicol and erythromycin, which are classical bacteriostatic agents and which target the ribosome. *Streptococcus pneumoniae*, on the other hand, is intrinsically quite a susceptible organism. It is readily killed by these and other antibiotics that are bacteriostatic against harder bacterial species. Like most bacteria, *S. aureus* and *S. pneumoniae* are killed by cell wall inhibitors, penicillin and vancomycin, as well as by the fluoroquinolones, which are classical bactericidal agents. Yet these agents *in vitro* do not produce a 99.9% kill of enterococci within the 24-hour timeframe, and they are therefore considered to be only bacteriostatic against this organism.

Growth conditions also will affect activity of bactericidal agents. Many antibiotics, and especially beta-lactams, require that cells be growing and dividing in order to have a bactericidal action. Slow growth impairs bactericidal activity. Conditions in the host at the site of infection that favor no growth or slow growth of bacteria will negate an antibiotic's bactericidal action. Thus, whether a bactericidal or a bacteriostatic effect is achieved can vary depending on not only the antibiotic but also the organism and conditions of growth.

**Bacterial Meningitis**

Proving that bactericidal activity vis-à-vis bacteriostatic activity is clinically more beneficial or essential is surprisingly difficult. Ignoring for the moment the considerable ethical and logistical hurdles of conducting a clinical trial testing this hypothesis, two experimental approaches can be imagined. One would randomize patients to one of two regimen, one bacteriostatic, the other bactericidal, after stratifying them according to type of infection (to assure that bacterial growth conditions are similar between groups) and bacterial etiology (to control for bacterial species). An inherent limitation of this design is that if two different antibiotics, one bactericidal and the other bacteriostatic, are used, it will be impossible to determine whether differences in outcome are because of differences in antibacterial activity or due to other differences that unavoidably will be present whenever chemically different agents are compared.

A more robust experimental design is one in which patients are randomized to receive the same drug that is manipulated to be bactericidal in one treatment arm and bacteriostatic in the other. The classic study of the treatment of pneumococcal meningitis by Lepper and Dowling, although falling well short of the standards for modern clinical trials, employed this latter approach. These investigators compared outcomes for patients with pneumococcal meningitis who were treated either with penicillin 1 million units intravenously every two hours or with a combination of penicillin plus tetracycline at a dose of 500 mg every six hours intravenously. One major shortcoming of the study is the enrollment scheme. There was no randomization; rather, the study included two series of patients, one of which received only penicillin and a second series of patients who were assigned on an alternating basis to one or the other regimen. Nevertheless, the differences between the two groups were compelling.

The penicillin-tetracycline combination of a cell wall agent, the bactericidal activity of which depends on cell growth (penicillin), with a reversible protein synthesis inhibitor that interferes with cell growth (tetracycline), is a classic example of antibiotic antagonism, and the overall activity of such a combination is bacteriostatic. As might be expected, mortality was significantly higher in the penicillin-tetracycline group compared to the penicillin only group: 79% versus 30%. This difference in mortality was not attributable to differences in severity of illness between treatment groups, or an imbalance in assignment of patients with clinical findings (e.g., coma) known to affect outcome adversely. In fact, the patients treated with penicillin were, if anything, at higher risk of poor outcome. The timing of deaths relative to initiation of antimicrobial therapy was strikingly different for the two treatments. Deaths in the penicillin group tended to occur within the first few days of illness, whereas deaths occurred over the course of therapy for the penicillin-tetracycline group, suggesting that there was failure to control the infection in this group. While the unfavorable outcome for patients treated with the combination supports the importance, indeed necessity, of using a bactericidal regimen when treating meningitis, the authors in passing mention their anecdotal success with the use of tetracycline alone. This leaves open the possibility that the poor outcome observed for the combination may not be entirely explained by its being bacteriostatic; rather, there is a specific, mutual antagonism between these two antibiotics that renders both ineffective. Alternatively, tetracycline, classically a bacteriostatic agent, may be sufficiently bactericidal for pneumococci for it to be efficacious in cases of meningitis. Because bactericidal activities of penicillin, tetracycline, and the combination were not assayed, it is not possible to determine which of these possibilities is the more likely.

A second study of the treatment of pneumococcal meningitis that was published in 1961 confirmed the finding of poor outcome of patients treated with penicillin-tetracycline combination (one of seven patients survived) compared to penicillin alone (nine of 20 patients survived). Interestingly, this study also reported that of six patients treated with erythromycin, classically considered a bacteriostatic antibiotic, three survived. While the experiences described in these two clinical studies demonstrate the therapeutic relevance of bactericidal activity in the treatment of bacterial meningitis, the minimum level of activity that was necessary was not well defined. The required level of activity probably varies with the bacterial species and probably the specific isolate, and it may be achievable with agents not meeting the *in vitro* threshold of a 99.9% kill at 24 hours.

**Endocarditis**

Endocarditis is another infection that classically requires use of a bactericidal antibiotic or a combination of antibiotics in order to achieve cure. However, bactericidal activity in the setting of endocarditis is not an all or none phenomenon, as the example of clindamycin for the treatment of staphylococcal endocarditis illustrates. Clindamycin, a reversible protein synthesis inhibitor with the same mechanism of action as erythromycin (creating the potential for cross-resistance), is regarded as a bacteriostatic antibiotic. However, at the upper extreme of serum concentrations achievable with large doses (e.g., 900 mg every 8 hours), its activity approaches the bactericidal threshold. The rabbit model of *S. aureus* endocarditis clindamycin, although less active than penicillin or vancomycin, was effective in reducing numbers of bacteria in vegetations.
In non-comparative clinical trials conducted to determine the efficacy of clindamycin for treatment of patients with staphylococcal endocarditis, cure rates are on the order of 80%.

Emergence of resistance to clindamycin during treatment and failure have been observed with clinical isolates that were erythromycin-resistant. The combined results of numerous clinical trials, case reports, and case series confirm the perceived relative bactericidal activity of penicillins, which are the most active and for which microbiologic or clinical cure rates are 90% or higher. Less rapidly bactericidal agents, such as vancomycin and clindamycin, produce cure rates of 75-80%.

Experience with truly bacteriostatic agents for treatment of endocarditis is extremely limited, comprising only a handful of cases. Nevertheless, even these agents may on occasion be effective; there are case reports of successful therapy of methicillin-resistant Staphylococcus aureus infections, including endocarditis, with minocycline, which exhibits little if any bactericidal activity in vivo against staphylococci. On the other hand, treatment failures with linezolid, a bacteriostatic agent, in cases of S. aureus endocarditis, and quinupristin/dalfopristin, which is bacteriostatic against many macrolide resistant strains, are reminders of the advantage of using an agent with bactericidal activity whenever possible.

The treatment of enterococcal endocarditis is an excellent example of the beneficial clinical impact resulting from bactericidal vis-à-vis bacteriostatic activity. In this instance outcome is improved by converting a marginally bactericidal or bacteriostatic regimen (i.e., one that fails to reach the cutoff of 99.9% kill by 24 hours) into a bactericidal one. Penicillin and vancomycin, the two drugs of choice for treatment of enterococcal infection, in vitro are bactericidal against Enterococcus faecalis or Enterococcus faecium. Historically, cure rates were on the order of 20% when penicillin was used as a single agent. The combination of a cell wall active agent (penicillin or vancomycin) with an aminoglycoside was observed to kill enterococci in vitro. The first demonstration of the clinical relevance of antimicrobial synergism and bactericidal activity was the application of this in vitro observation to the treatment of enterococcal endocarditis. Penicillin in combination with either streptomycin or gentamicin administered for four to six weeks dramatically improved outcome of this infection, resulting in cure rates of approximately 75% and relapse rates of 2-6%.

The superiority of achieving bactericidal activity and not merely bacteriostatic activity in the treatment of endocarditis was thus confirmed.

A recent study, however, serves as a reminder that our understanding of bactericidal activity is incomplete, even for infections in which its superiority seems clearcut. Oliason, et al reported their experience with 93 cases of enterococcal endocarditis, 27 with prosthetic valve involvement, for which the median duration of aminoglycoside combination therapy was 15 days, with early termination due to the occurrence of toxicity. Despite the fact that patients received only half of the recommended dose of aminoglycoside, and that the remaining therapy (ampicillin or vancomycin administered for a median total duration of 42 days) was probably bacteriostatic, the overall cure rate was 81%, the death rate was 16%, and the relapse rate was 3%; results very comparable to those for 4-6 weeks of penicillin-aminoglycoside combination regimens. The ten deaths appeared not to have been a consequence of insufficient doses of aminoglycoside. Patients who died actually received on average more aminoglycoside than those who were cured, and those receiving a week or less of aminoglycoside were no more likely to die than those receiving more aminoglycoside. Seven patients who never received an aminoglycoside were cured; one patient of the three that relapsed received only seven days of aminoglycoside.

Without confirmatory data it would be imprudent to routinely shorten the duration of aminoglycoside therapy, but it may be that once the infection has been controlled and the burden of organisms significantly reduced by a maximally bactericidal regimen, a slowly bactericidal effect may be sufficient to eradicate residual organisms. These data indicate that patients sustaining significant aminoglycoside toxicity need not continue to receive the drug in order to be cured, which can be accomplished with the continuation of single agent (ampicillin or vancomycin), “bacteriostatic” therapy.

Summary and Conclusions

Rigorously designed, randomized trials directly comparing a bactericidal regimen to a bacteriostatic one and demonstrating the superiority of the former over the latter, even for meningitis and endocarditis, are nonexistent. Less well-designed studies and case series, however, indicate that bactericidal agents are critical for a satisfactory outcome. Antibiotics that are the most efficacious for otherwise lethal infections, such as endocarditis or meningitis, usually have significant bactericidal activity in vitro, although the minimum threshold of this activity has not been established. Data are limited concerning outcomes when these infections are treated with classical bacteriostatic agents, but lack or loss of bactericidal activity is associated with poorer outcome; enhancement of this activity generally is associated with better outcome. The superiority of bactericidal agents over bacteriostatic ones may not be generalizable to infections in which host defenses are relatively intact and play more of a role. Nevertheless, bactericidal agents continue to be preferred for the treatment of serious, life threatening infections.
REFERENCES:

**Target Audience:** Practicing physicians, infectious disease physicians, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, and others interested in the treatment of infections caused by resistant Gram-positive pathogens.

**Learning Objectives:** After reading this publication, the reader should be able to:
- Explain the difference between bactericidal and bacteriostatic antibiotic therapy.
- Enumerate the factors which might influence your decision to use bacteriostatic vs. bactericidal antibiotic therapy.

**CME Self Assessment Examination**

See instructions and pertinent information on the reverse before requesting credit.

1. For which of the following infections does clinical data support the utility of bactericidal compared to bacteriostatic antibiotic therapy?
   a) Endocarditis  
   b) Meningitis  
   c) Bacteremia in neutropenic hosts  
   d) Osteomyelitis  
   e) All of the above  
   Answer: ____________

2. Which of the following statements is incorrect?
   a) *Staphylococcus aureus* is not killed by protein synthesis inhibitors such as chloramphenicol and erythromycin.  
   b) *Staphylococcus aureus* and *Streptococcus pneumoniae* are killed by cell wall inhibitors.  
   c) Slow growth of bacteria, such as that which may occur at the site of an infection, may inhibit an antibiotic's otherwise bactericidal properties.  
   d) Bactericidal activity of an antibiotic is an invariable property of that antibiotic  
   Answer: ____________

3. Lepper and Dowling’s experiments using penicillin or penicillin and tetracycline to treat pneumococcal meningitis demonstrated which of the following phenomenon?
   a) Antibiotic tolerance  
   b) Synergistic antibiotic activity  
   c) Antagonistic antibiotic activity  
   d) Additive antibiotic activity  
   Answer: ____________

4. Which of the following statements concerning the treatment of *Enterococcus faecalis* is true?
   a) Cure rates of 20% have been observed when penicillin was used as a single therapeutic agent.  
   b) Cure rates of approximately 75% were seen when penicillin was administered in combination with streptomycin or gentamicin.  
   c) The addition of streptomycin or gentamicin to penicillin takes advantage of synergistic antibiotic activity  
   d) All of the above  
   Answer: ____________

5-6. For each of the following statements 5-6, answer T if the statement is true and F if the statement is false:
   5. _____ The superiority of bactericidal over bacteriostatic antibiotics may not be generalizable to infections in which host defenses are intact and active at the site of infection.  
   Answer: ____________

   6. _____ While our understanding of the importance of bactericidal activity is limited, bactericidal agents are generally preferred for the treatment of serious life threatening infections.  
   Answer: ____________

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