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Static versus Cidal Antibiotics

A common belief in clinical practice is that bactericidal ("cidal") antibiotics are more effective than bacteriostatic ("static") antibiotics. Front-line clinicians frequently identify this characteristic as an important factor in selecting between anti-infective agents, even for uncomplicated infectious syndromes. Definitive data that support preferential use of a bactericidal over an appropriately dosed bacteriostatic agent is lacking. This newsletter reviews these concepts, highlights the findings of a recent systematic review, and discusses implications for antimicrobial stewardship practice in community hospitals.

Static versus Cidal: What Does That Mean?

The terms bacteriostatic and bactericidal are based on an *in vitro*, laboratory definition that uses two measurements of the antibiotic's effect on bacterial growth and death: minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) (See **Box**). An antibiotic is classified as bactericidal only if the ratio of MBC to MIC is ≤ 4, while a bacteriostatic antibiotic has an MBC to MIC ratio of > 4.[1] In 1999, the Clinical Laboratory and Standards Institute (CLSI) released a document detailing methods to be performed to determine bactericidal activity of antimicrobial agents. Prior to that time, more arbitrary definitions were used to assign agents to each of these categories.[2] The Food and Drug Administration (FDA) now requires sponsors to perform studies evaluating mechanism of action and microbial killing effects.[3] **Table 1** lists common bacteriostatic and bactericidal antibiotics used in practice.

Definitions

MIC = concentration that inhibits visible bacterial growth at 24 hours in a set of specific conditions

MBC = concentration that results in a 1,000-fold reduction in bacterial density after 24 hours in these same conditions

Table 1. Commonly Prescribed Bacteriostatic and Bactericidal Antibiotics

BacterioSTATIC	BacteriCIDAL
• Macrolides (azithromycin, clarithromycin) • Clindamycin • Doxycycline • Linezolid • Tigecycline • Trimethoprim • Sulfonamides • Vancomycin*	• Penicillins (ampicillin, amoxicillin, etc.) • Cephalosporins (cefoxitin, cefazolin, etc.) • Fluoroquinolones • Carbapenems • Monobactam (aztreonam) • Daptomycin

*dependent on therapeutic level and pathogen

Vancomycin is a special, and confusing, case. Despite the package insert[4] stating it is bactericidal, this designation is limited to organisms such as *Staphylococcus aureus*, while additional studies show vancomycin demonstrates bacteriostatic activity against other Gram-positive organisms such as enterococci.[5] Importantly, vancomycin drug approval occurred prior to CLSI and FDA requirements for standardized studies evaluating the microbial killing effect of agents. Clinical efficacy and the bactericidal effect of vancomycin is achieved by maintaining optimized therapeutic dosing which requires routine drug monitoring and dose adjustments.[6] In contrast, daptomycin exhibits rapid, bactericidal killing proven by *in vivo*, time-kill studies conducted in rabbits and mice.[5] Although these agents differ in killing activity *in vivo*, daptomycin is considered non-inferior to vancomycin for treatment of many *Staphylococcus aureus* infections such as complicated skin and skin structure infections.[7] This example demonstrates the importance of considering pharmacokinetic properties and therapeutic drug monitoring of agents to ensure optimal dosing for good clinical outcomes. The ultimate guide to treatment of any infection must be clinical outcome.

"Busting the Myth of 'Static vs. Cidal': A Systematic Literature Review"[1]

A recent review evaluated a total of 56 randomized controlled trials comparing bacteriostatic to bactericidal antibiotics. Articles for review were selected via search of available literature within PubMed database using terms for commonly used bacteriostatic agents and "randomized controlled trial." Each article comparing bacteriostatic versus bactericidal agents was included. Forty-nine trials found no significant difference in efficacy between bacteriostatic and bactericidal agents on clinical outcomes. Of those remaining, 6 trials found bacteriostatic agent was superior in efficacy to bactericidal agents. Only 1 trial reported the bactericidal agent was superior when compared to a bacteriostatic agent[8], which may be partially explained by under-dosing of the bacteriostatic agent. Table 2 highlights trials comparing bacteriostatic and bactericidal agents.

Considerations when selecting between bactericidal and bacteriostatic agents:

The authors of the review suggest other drug characteristics such as optimal dosing, pharmacokinetics-pharmacodynamics, and tissue penetration are more clinically relevant factors to consider.[1] A simple question, "what is the appropriate dose and frequency based on indication?" leads to a cascade of clinically relevant, case-specific, considerations that include:

- penetration of drug to site of infection (ex. volume of distribution)
- rate of drug clearance (ex. half-life)
- appropriate therapeutic drug monitoring (ex. vancomycin trough)
- sensitivity of organism(s) to drug (ex. MIC)

The current article poses an argument that the distinction of cidal versus static does not impact clinical outcomes. Specifically, the authors claim that the "majority of studies comparing bacteriostatic and bactericidal agents head-to-head for the treatment of invasive bacterial infections have found no difference in clinical outcomes or mortality."[1] An important limitation in the data reviewed is the lack of trials in patients with invasive infections such as primary bloodstream infections, infective endocarditis, and CNS infections. These invasive infections with high burdens of infection are where cidal activity theoretically may be advantageous to produce rapid kill. Second, Wald-Dickler et al. noted that although randomized controlled trials are considered the gold-standard for clinical research due to minimization of bias, they often exclude severely ill or immunocompromised patients with life-threatening infections. Finally, of the 56 studies reviewed, 32 were non-blinded leading to an increased risk of performance bias. Thus, interpretation of the review's conclusion and trials outlined above should be applied to the disease states studied and not extrapolated to more invasive infections.

Despite the limitations of the review, the results were similar to findings of a previous meta-analysis.[9] Further, most common infections can be appropriately treated with bacteriostatic or bacteriocidal agents. When speaking with providers at community hospitals, often the cidal vs. static discussion is not meaningful.

Bottom Line

As discussed above there are many factors impacting the clinical effectiveness of antibiotics, much more than simply bacteriostatic or bactericidal properties. Identifying antibiotics based on bactericidal or bacteriostatic killing is appropriate for understanding the characteristics of each agent. However, it is minor factor to be considered for clinically sound decision-making. All pharmacokinetic-pharmacodynamic and infection-specific factors should be considered when selecting optimal therapy for each patient.

Table 2. Trials Comparing Bacteriostatic and Bactericidal Agents[1]

Site of Infection	Bacteriostatic Agent	Bactericidal Agent	Number of Trials	Result(s) of Trial(s)
Skin and soft tissue infections	Tigecycline	Vancomycin plus aztreonam	4	No significant difference
	Linezolid	Vancomycin	3	One trial demonstrated superiority for linezolid, two others demonstrated no significant difference
	Doxycycline	Trimethoprim-sulfamethoxazole	1	No significant difference
Nosocomial pneumonia	Linezolid	Vancomycin	1	No significant difference
	Tigecycline	Imipenem	2	No significant difference (one study initially demonstrated superiority for imipenem. Further analysis revealed tigecycline dosing was subtherapeutic)
Community-acquired pneumonia	Azithromycin	Penicillin Cefuroxime	1 2	No significant difference
	Doxycycline	Levofloxacin	1	No significant difference
Aspiration pneumonia in elderly	Clindamycin	Ampicillin-sulbactam or panipenem-betamiprom	1	No significant difference
Intra-abdominal infections	Tigecycline	Imipenem Ceftriaxone plus metronidazole	2 2	No significant difference
	Eravacycline	Ertapenem	2	No significant difference
Febrile Neutropenia	Linezolid	Vancomycin	1	No significant difference

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