

Introduction

In this issue of MicroFocus, the information resource brought to you by Dade Behring MicroScan, we concentrate on the basics of the MIC result – what it represents and how it is used for clinical practice. As antimicrobial resistance becomes more prevalent, understanding both the meaning and the value of the information you provide to clinical practitioners becomes increasingly more critical.

Through collaboration between the laboratory and clinical pharmacy, Drs. Thomson and Suseno illustrate their best demonstrated practice approach to applying laboratory MIC data to patient management. The inclusion of several case studies helps clarify the concepts of therapeutic breakpoint, pharmacokinetics and pharmacodynamics. For a more basic introduction of some of these concepts, refer to Dr. Brown's commentary on page 10.

How often have you received a call requesting MIC information on Fortaz® or Zynox® or some other drug, and you have to either scramble for a reference or ask the physician for the generic name before you can respond? Within this issue is an antibiotic reference chart that alphabetically lists common agents by both their generic and trade name. We hope you find this a useful tool in your daily routine.

Once again you have the opportunity to obtain one hour of continuing education credit by completing the evaluation and self-assessment test for the article *Clinical Microbiology and the Antimicrobial Pharmacist: a Synergistic Combination*. In an effort to be more "green" instead of supplying a business reply card, we direct you to the Dade Behring website to complete the required information for CEU credit, as well as to "opt in" so you continue to receive your copy of the MicroFocus newsletter. Please go to www.dadebehring.com and click on Services > Education > Microbiology, then click on the link under Publications. Be sure to include comments on other topics you would like to see explored in upcoming issues of MicroFocus. If you have an interest in becoming an author, please e-mail me directly.

We hope the article and commentary in this issue of MicroFocus help you gain a better understanding of how the data you generate in the microbiology laboratory really impact the course of patient management.

Lynn A. Boyer, MicroFocus Managing Editor
Marketing Manager, MicroScan
lynn_a_boyer@dadebehring.com

Clinical Microbiology and the Antimicrobial Pharmacist: a Synergistic Combination

Richard B. (Tom) Thomson, Jr., Ph.D., ABMM
Department of Pathology and Laboratory Medicine
Evanston Northwestern Healthcare
Professor of Pathology
Northwestern University Feinberg School of Medicine

Mira Suseno, Pharm.D., BCPS
Department of Pharmacy
Evanston Northwestern Healthcare

Evanston Northwestern Healthcare
2650 Ridge Avenue
Evanston, IL 60201

Daily antimicrobial susceptibility testing of potential bacterial pathogens in Clinical Microbiology laboratories may be the most important and highly regulated test in the whole Clinical Laboratory. The evolution of susceptibility testing methods has paralleled the discovery and understanding of bacterial resistance, which itself has paralleled the introduction and use of newer antimicrobials.¹ Although Alexander Fleming is best known for reporting the inhibitory effect of penicillin on solid media by observing an area of inhibition of staphylococcal growth around the mold *Penicillium*, in the 1920s he also pioneered the use of broth dilution, using turbidity as an end point. Small filter paper disks impregnated with antimicrobials were first described in 1947, while the use of agar dilution to determine an MIC was popularized in the early 1950s. The need for an easy, highly standardized antimicrobial testing method was filled in 1966 with the publication of a disk diffusion technique by Bauer, Kirby and coworkers that was soon adopted by most

The evolution of susceptibility testing methods has paralleled the discovery and understanding of bacterial resistance, which itself has paralleled the introduction and use of newer antimicrobials.¹

Clinical Microbiology laboratories. So began the broad application of *in vitro* susceptibility testing to the management of patients with infection. Early methods included disk diffusion, broth dilution and agar dilution, with the automation of dilution testing to take place over the next 20 years.

MIC and Therapeutic Breakpoint

The fundamental concepts behind all *in vitro* susceptibility testing methods are the minimum inhibitory concentration (MIC) and the therapeutic breakpoint (referred to as the clinical cutoff by some).² A standard concentration of microorganism to be tested is inoculated to a gradient of antimicrobial, most commonly antimicrobial diluted in broth, incubated overnight and the MIC end point determined by identifying the lowest concentration of antimicrobial needed to visually inhibit growth. By itself the MIC value cannot be used to determine whether the antimicrobial will or will not work when administered to the patient.³

Various antimicrobials achieve different concentrations in patients, leading to different breakpoints, because of unique pharmacokinetics.

The therapeutic breakpoint, in principle, represents the approximate concentration of antimicrobial at the site of infection in the patient. The MIC value must be less than the therapeutic breakpoint

in order for the antimicrobial to inhibit the pathogen *in vivo*. In the laboratory, the MIC value is interpreted by comparing to the therapeutic breakpoint.^{4,5} An MIC that is less than the therapeutic breakpoint is interpreted as susceptible, one that is approximately equal to the breakpoint as intermediate, and an MIC greater than the therapeutic breakpoint is interpreted as resistant. A clinician reviewing laboratory results will interpret a susceptible report to mean that the isolate should be inhibited by the usually achievable concentrations of antimicrobial agent when the recommended dosage is used for the site of infection. Conversely, a resistant report means that the isolate is not inhibited by the

usual achievable concentrations of antimicrobial at the site of infection or that clinical efficacy has not been demonstrated in treatment studies. An intermediate interpretation is more complicated. The clinical interpretation suggests that the clinician cannot expect this antimicrobial agent to inhibit the isolate as consistently as those with a susceptible interpretation. However, if the antimicrobial dose can be increased safely, or if the infection is located at an anatomic site where the drug is concentrated, the therapeutic breakpoint is increased – the MIC value has not changed but is now lower than the breakpoint, so the interpretation can be considered susceptible.

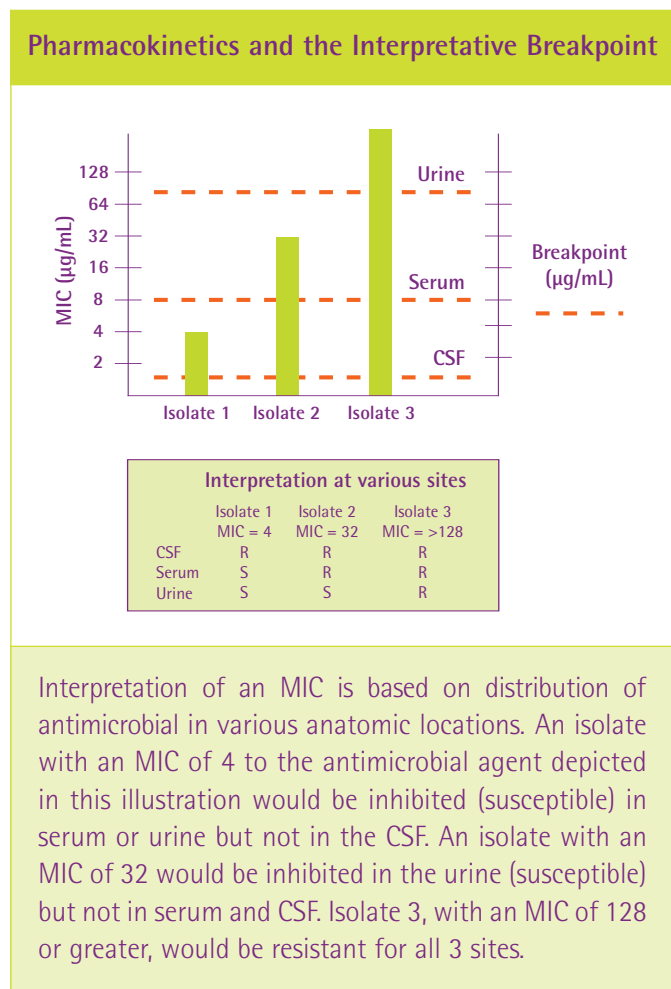
One can test his or her understanding of the MIC test and its interpretation by answering the following question. A patient with a serious infection is examined and found to have a single pathogen. Antimicrobial results are available for 5 different drugs with the following MIC values: Drug A = 1 µg/mL; Drug B = 2 µg/mL; Drug C = 4 µg/mL; Drug D = 8 µg/mL; and Drug E = 16 µg/mL. Assuming no contraindications to any of the 5 antimicrobials, which antimicrobial would be recommended? Surprisingly, most physicians in my hospital answer Drug A, because it has the lowest MIC value. In fact, one cannot answer the question with the data given. The answer can be determined only when both the MIC values and therapeutic breakpoints are known for all 5 antimicrobials. If the breakpoints for Drugs A through D are all 1 µg/mL, and the breakpoint for Drug E is 64 µg/mL, then Drug E with the highest MIC is the best drug to recommend, because it is the only choice with an MIC lower than the breakpoint (interpretation = susceptible).

Pharmacokinetics and Pharmacodynamics

Antimicrobial dosing is managed by the patient's physician and pharmacist. Various antimicrobials achieve different concentrations in patients, leading to different breakpoints, because of unique pharmacokinetics. Pharmacokinetics refers to the distribution and half-life of the drug following particular doses,

impacting concentrations at various body sites. Examples of the MIC value, its comparison to the therapeutic breakpoint, and the impact of pharmacokinetics on the resolution of infection is illustrated in Figure 1.

Figure 1.

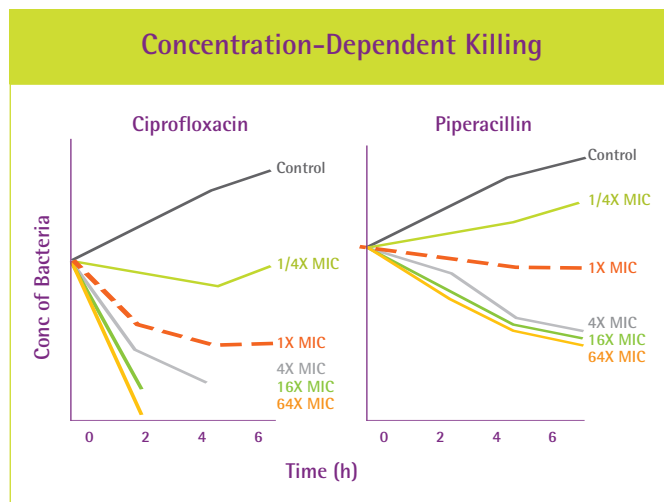


To complicate matters, antimicrobial agents that have similar MIC values and therapeutic breakpoints may not have equal effects. For example, 2 antimicrobials reported as susceptible, both with an MIC value of 2 µg/mL and an interpretative breakpoint of 16 µg/mL, eradicate the infected site of viable bacteria at vastly different rates. One may kill and eliminate the pathogen within 24 hours, while the second antimicrobial requires 3 to 5 days before culture of the infected site is sterile. This occurs as the result of pharmacodynamic differences among drugs. Pharmacodynamics is a

measure of the inhibitory and killing ability of an antimicrobial relative to its mode of action and concentration at the site of infection. Two pharmacodynamic concepts that are most important are concentration-dependent and time-dependent killing. Concentration-dependent killing means that more bacteria are killed as the concentration of antimicrobial agent increases. Time-dependent killing means that more bacteria are killed as the exposure time to antimicrobial increases. Figure 2 demonstrates concentration-dependent killing, while Figure 3 demonstrates time-dependent killing.

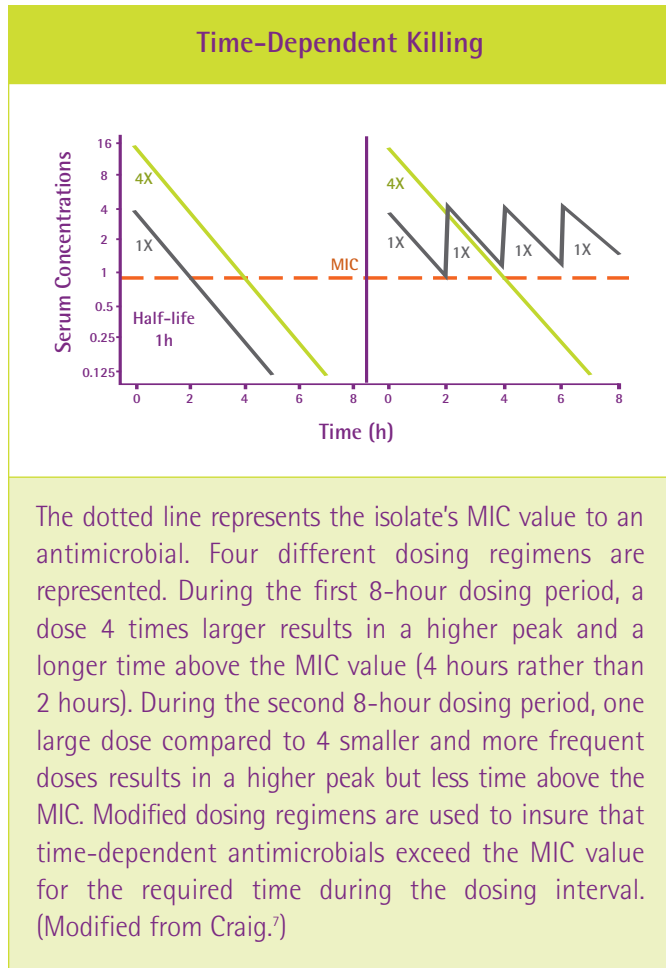
Two pharmacodynamic concepts that are most important are concentration-dependent and time-dependent killing.

Figure 2.



These data represent time kill curves. A pure culture of bacteria is sampled every 2 hours to measure the concentration of bacteria. The control tube represents growth without the addition of the antimicrobial. If the MIC were 1 µg/mL, the concentrations of antimicrobial in each of the 5 tests would be 0.25, 1.0, 4.0, 16, and 64 µg/mL (represented as 1/4 x MIC, 1 x MIC, etc). The fluoroquinolones, such as ciprofloxacin, demonstrate concentration-dependent killing. Each increase in drug concentration results in additional killing of bacteria. The beta-lactams, such as piperacillin, do not show concentration-dependent killing. Additional drug does not result in additional killing. (Redrawn from Craig and Ebert.⁶)

Figure 3.



Antimicrobial Pharmacist

Antimicrobial pharmacists, employed by many hospitals, are able to integrate pharmacokinetic and pharmacodynamic parameters to maximize antimicrobial therapy for seriously ill patients. One approach is to calculate the area under the inhibitory curve (AUC), which combines the effects of concentration- and time-dependent killing. The AUC represents the total amount of antimicrobial measured in a patient's serum during a 24-hour period divided by the MIC of the pathogen from that same patient. By including the total amount of antimicrobial, this calculation encompasses both concentration-dependent killing mechanisms (eg, high peak concentrations with short half-lives) and time-dependent mechanisms (eg, low peaks but long half-lives). Figure 4 illustrates AUC calculations.

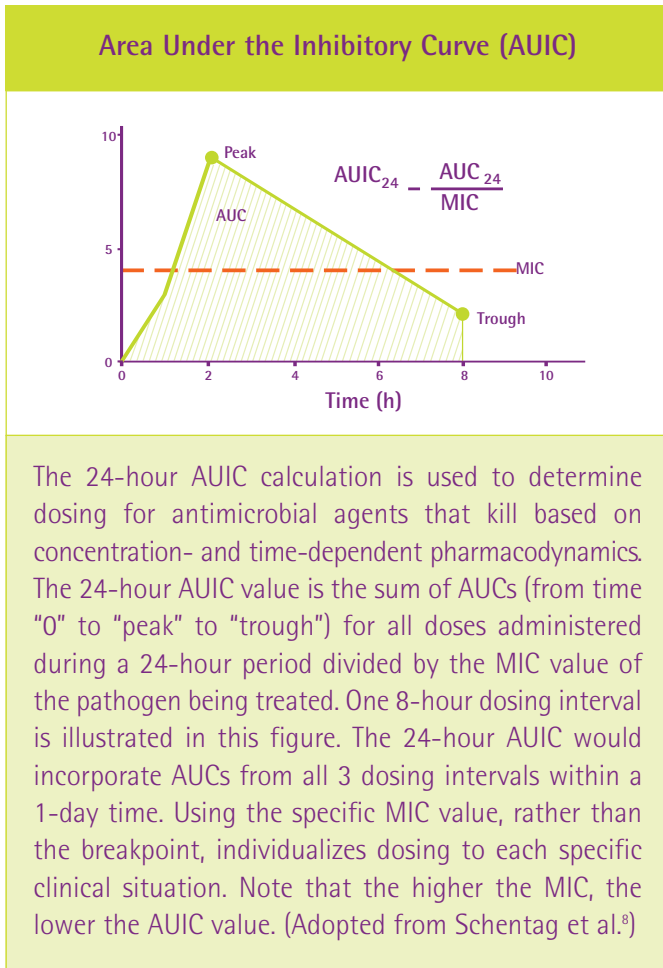
We in the laboratory now recognize that the MIC value, although the most important factor in determining antimicrobial susceptibility, is not the only consideration in antimicrobial selection and dosing. Exchanging information in a timely, sometimes immediate, fashion requires organized interaction between the pharmacist and laboratory. In our institution, the antimicrobial pharmacist attends daily laboratory rounds with the infectious diseases service and the Microbiology Laboratory Director. The knowledge gained by these interactions provides the pharmacist with an understanding of what culture and antimicrobial testing information is available. In addition, the laboratory director and technologists have learned to notify pharmacy with key pieces of antimicrobial information. For example, positive sterile site cultures, such as blood cultures, are reviewed daily with the pharmacy team so they can better oversee empiric therapy. In addition, the suspicion of unusual or infrequent pathogens is phoned in to the antimicrobial pharmacist even though definitive information may not be available for a day or more. The relationship developed during laboratory rounds has resulted in frequent and easy communication with pharmacy.

This interaction is similar to that which laboratories have with infection control professionals. The advent of computer software that matches microbiology reports with pharmacy antimicrobial use data is a significant

The MIC value, although the most important factor in determining antimicrobial susceptibility, is not the only consideration in antimicrobial selection and dosing.

step, but one that is further enhanced by direct communication. Rapid, appropriate therapy is essential to good medical care. Preliminary data included in microbiology reports can be confusing. It is the proper interpretation of preliminary information and unusual findings that is the goal of communication and the reason for synergy between Microbiology and Pharmacy. The following case vignettes illustrate important interactions between laboratory and antimicrobial pharmacist.

Figure 4.



Case 1

Patient ME is a 67-year-old female with a past medical history of hyperlipidemia and gastroesophageal reflux disease (GERD) who is examined in the emergency department (ED) because of complaints of sudden onset

of fever, chills, shakes and cough. The patient's daughter states that her mother was in her usual state of health prior to admission. There has been no recent contact with sick friends or relatives and no significant travel, other

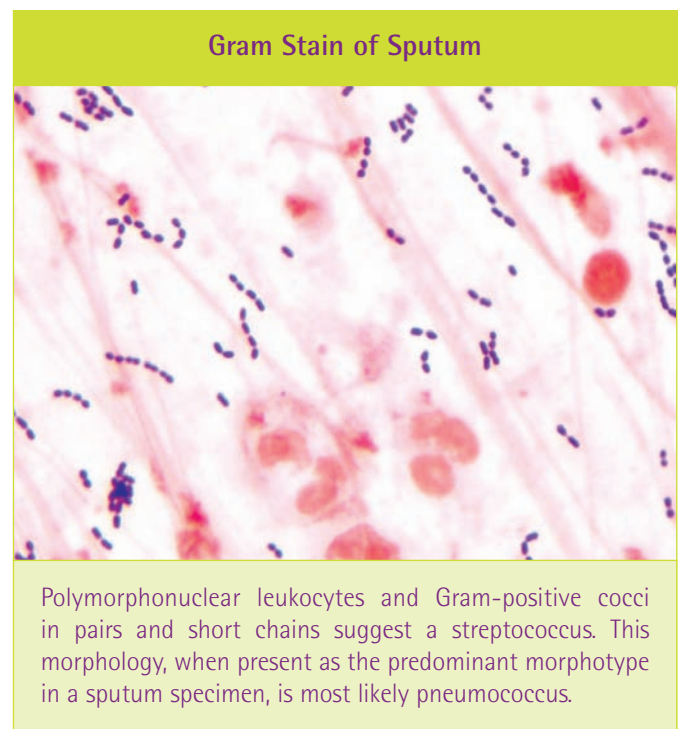
It is the proper interpretation of preliminary information and unusual findings that is the goal of communication and the reason for synergy between Microbiology and Pharmacy.

than recent visits to see her grandchildren. Significant vital signs recorded in the ED included a temperature of 102° F and an oxygen saturation of 93% while receiving 2 liters of oxygen per hour by nasal canula.

Her white blood cell count was 15.7×10^3 per mm^3 with a predominance of neutrophils and 12% bands. A chest X-ray was interpreted as showing right-, middle-, and upper-lobe infiltrates. The patient had no known drug allergies, and was not taking medication at the time of her ED visit that would interfere with usual antimicrobial choices. Her serum creatinine was 1.0 mg/dL with an estimated creatinine clearance of 60 mL/min. Sputum and blood for culture were collected and sent to the Microbiology Laboratory. The patient was admitted to a general medical ward with the diagnosis of community acquired pneumonia and antimicrobial therapy with levofloxacin 500 mg IV daily was initiated.

The sputum Gram stain (Figure 5) was reported a few hours later as "Less than 25 squamous epithelial cells per 10X field, 3+ Polymorphonuclear cells, 4+ Gram-positive cocci in pairs and chains." The following day *Streptococcus pneumoniae* was detected in the sputum culture.

Figure 5.



The Antimicrobial Pharmacist reviewed the patient's empiric antimicrobial regimen, reviewed the Gram stain and conferred with the Microbiology Laboratory

Director, and concluded that the levofloxacin 500 mg daily dose was not appropriate for this patient. The pharmacist recommended that the dose be increased to 750 mg daily.

The current guidelines from the Infectious Diseases Society of America and the American Thoracic Society recommend initial antimicrobial therapy with a beta-lactam antibiotic plus a macrolide or respiratory fluoroquinolone.⁹ If levofloxacin is selected as the respiratory fluoroquinolone, then the recommended daily dose in a patient with normal renal function is 750 mg daily. Why has levofloxacin dosing been increased?

A final consideration for dosing other than generally recommended is drug accumulation and the toxicity with the higher dose.

The predictor of antimicrobial potency for levofloxacin and other fluoroquinolones is AUC.¹⁰ For *S. pneumoniae* an AUC of greater than 30 to 35 in some studies and 40 in others correlates with

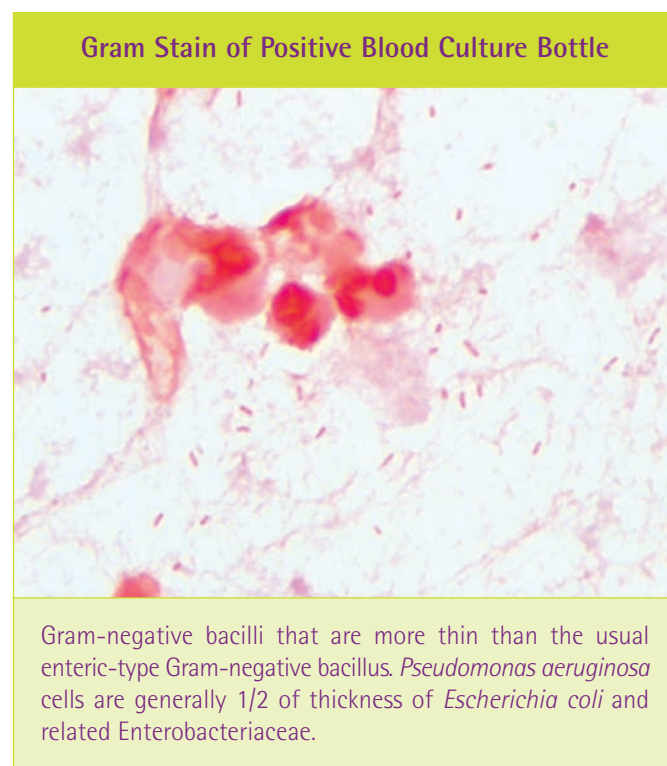
successful outcomes.¹¹ The *S. pneumoniae* from Case 1 had a levofloxacin MIC of 1 µg/mL. The therapeutic breakpoint for levofloxacin and *S. pneumoniae* is 2 µg/mL (CLSI). The isolate was reported as levofloxacin susceptible. Levofloxacin 500 mg/day dosing yields an AUC of 35 (using the concentration of free drug and an MIC of 1 µg/mL). This is less than desired. Alternatively, 750 mg/day dosing gives an AUC of 71, clearly surpassing the minimum recommended. A final consideration is drug accumulation and toxicity with the higher dose. An estimated creatinine clearance of 60 mL/min suggests the patient should clear the drug without side effects. With her dose optimized, she is expected to have microbiologic eradication and clinical cure. A pneumococcal vaccine was ordered prior to discharge.

Case 2

A 39-year-old female is admitted directly from the clinic due to fever. The patient had received chemotherapy for medulloblastoma (a malignant brain tumor) 1 week

ago. She has no other complaints. Her findings were normal except for a temperature of 101.5° F, a peripheral white blood cell count of 0.4×10^3 per mm^3 (45% segmented neutrophils; 17% bands; absolute neutrophil count of 248). A chest X-ray was interpreted as negative and her port-a-cath site showed no erythema or tenderness. The patient was treated empirically with ceftazidime according to the Infectious Diseases Society of America guidelines for empiric therapy in patients with febrile neutropenia.¹² Blood and urine specimens were collected and sent to the laboratory with an order for bacterial culture. Later that evening, the Microbiology Laboratory reported a positive blood culture containing a Gram-negative bacillus in the aerobic blood culture bottle (Figure 6). The patient's doctor was notified, and antimicrobial therapy was broadened with the addition of gentamicin 2 mg/kg every 8 hours. The following morning, the Infectious Disease Pharmacist reviewed the blood culture Gram stain with the microbiologist. Based on this discussion, a change from gentamicin to tobramycin was recommended.

Figure 6.



Aminoglycoside antibiotics have activity against many aerobic and facultative Gram-negative and some Gram-positive bacteria. They exhibit concentration-dependent bactericidal activity.¹³ Favorable clinical response to aminoglycoside therapy is associated with a maximal peak to MIC ratio of at least 10.¹⁴ In addition, a clinical study in patients with Gram-negative bacteremia showed that patients were less likely to die if they achieved initial peak plasma concentration 1 hr post infusion of more than 5 µg/mL for gentamicin or tobramycin.¹⁵

The Gram-negative bacillus is identified as *P. aeruginosa*, with the following antimicrobial susceptibility results: gentamicin MIC = 2.0 µg/mL

interpreted as susceptible, and tobramycin MIC = 0.5 µg/mL interpreted as susceptible. The finding that the tobramycin MIC is lower than the gentamicin MIC for *P. aeruginosa* is normal. When susceptible, tobramycin is always more active than gentamicin. If the peak serum

When susceptible, tobramycin is always more active than gentamicin.... The use of tobramycin or gentamicin insures a peak concentration of more than 5 µg/mL. Tobramycin alone insures a peak-to-MIC ratio of at least 10.

concentration in this patient is 6 to 8 µg/mL, as expected with these agents, the peak to MIC ratio with gentamicin will be between 3 and 4 and with tobramycin between 12 and 16. The use of tobramycin or gentamicin insures a peak concentration of more than 5 µg/mL. Tobramycin alone insures a peak to MIC ratio of at least 10. Therefore, the pharmacist, using Microbiology Laboratory data and pharmacokinetic and pharmacodynamic principles, recommended the change to tobramycin.

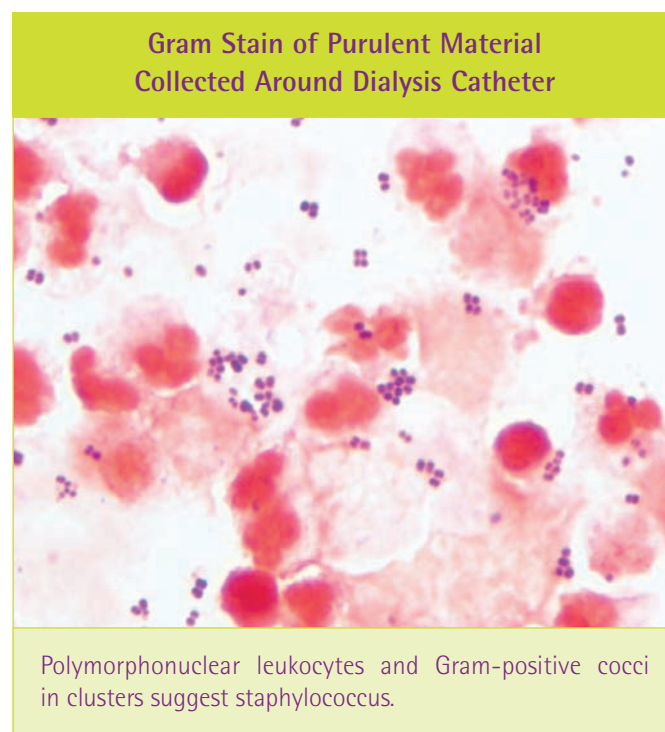
Case 3

A 74-year-old male with a past medical history of coronary artery disease, congestive heart failure, hyperlipidemia, and chronic kidney disease requiring hemodialysis was transported by the Emergency Medical Service to the ED after complaining of shortness of breath and fever after dinner. He also described a

purulent discharge draining from his dialysis catheter site (See Figure 7 for gram stain). The patient was examined and found to have a temperature of 100.6° F, a peripheral white count of 12.4 x 10³ per mm³, and a serum creatinine of 5.3 mg/dL. His chest X-ray showed bilateral pleural effusions and cardiomegaly, consistent with and without change compared to previous testing. Blood for culture was collected and sent to Microbiology along with the hemodialysis catheter that was removed. The patient was treated empirically with vancomycin and ceftazidime for suspected catheter-related bloodstream infection.

The following morning a positive blood culture was reported to show Gram-positive cocci in clusters. Four hours later the Antimicrobial Pharmacist was notified by the Molecular Laboratory that the blood culture isolate was *femA* positive and *mecA* negative by polymerase chain reaction (PCR) testing. At this time, the isolate was identified as methicillin-susceptible *Staphylococcus aureus*, in spite of the fact that no colonies had yet appeared on subculture media. Based on these results, the patient's physician was notified, and antimicrobial

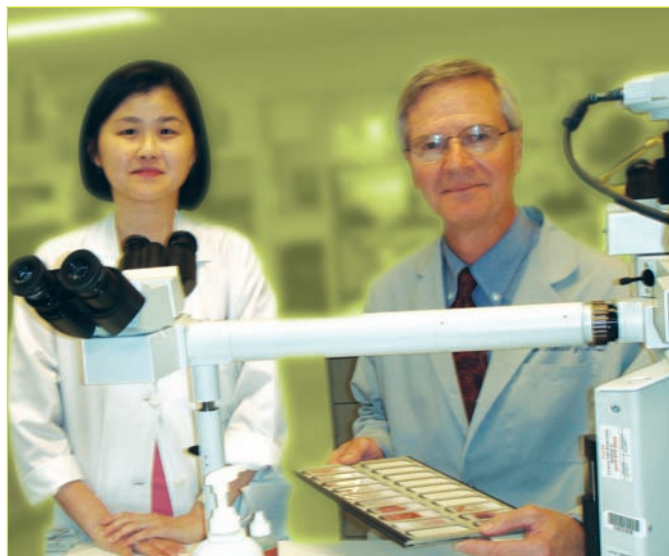
Figure 7.



therapy was changed to nafcillin. The catheter tip culture and susceptibility results were available 2 days later and reported as ">15 colonies of *S. aureus*" that were nafcillin susceptible.

Molecular testing using PCR methods can rapidly detect genes unique to *S. aureus*, such as *femA*, as well as the *mecA* gene, which is responsible for methicillin-resistance among all *Staphylococcus* species. Direct testing of positive blood culture broths showing Gram-positive cocci provides definitive identification and methicillin susceptibility status within hours, allowing directed antimicrobial therapy (therapy directed at the specific pathogen) within hours of the positive culture. This compares to a minimum of 48 hours after culture has turned positive using conventional testing methods. In addition, PCR-based susceptibility testing provided the patient with a better antimicrobial agent. Studies show that anti-staphylococcal penicillins, such as nafcillin or oxacillin, are superior to vancomycin

for the treatment of infections due to methicillin-susceptible *S. aureus*, owing to the fact that they are more rapidly bactericidal.



Drs. Suseno and Thomson assess cases during daily rounds.

Summary Comments

There is more to antimicrobial testing than the MIC result! One must understand pharmacokinetics and the concept of the therapeutic breakpoint to correctly interpret MIC results, and one must learn pharmacodynamic principles to understand how and why antimicrobials do not kill bacteria equally. Laboratory interaction with an Antimicrobial Pharmacist improves selection and dosing of antimicrobials and reduces time to appropriate therapy. For best communication, the Antimicrobial Pharmacist should visit the Microbiology Laboratory each day and be paged with important or unusual antimicrobial susceptibility results. Although conventional MIC and disk testing have served the laboratory and patient well for 40 years, new, more accurate and rapid, and FDA-approved molecular methods will be available in the future. Stay tuned and stay informed.

References:

1. Wheat PF. History and development of antimicrobial susceptibility testing methodology. *J Antimicrob Chemother.* 2001;48(suppl):1-4.
2. Tumidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. *Clin Microbiol Rev.* 2007;20:391-408.
3. Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: general principles and contemporary practices. *Clin Infect Dis.* 1998;26:973-980.
4. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial disk susceptibility tests. *CLSI.* 2006; Approved Standard M2-A9.
5. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. *CLSI.* 2006; Approved Standard M7-A6.
6. Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. *Scand J Infect Dis.* 1990;74(suppl): 63-70.
7. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26:1-12.
8. Schentag JJ, Strenkoski-Nix LC, Nix DE, et al. Pharmacodynamic interactions of antibiotics alone and in combination. *Clin Infect Dis.* 1998; 27:40-46.
9. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America and American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:27-72.
10. Lode H, Borner K, Koeppel P. Pharmacodynamics of fluoroquinolones. *Clin Infect Dis.* 1998;27:33-39.
11. Ambrose PG, Grasela DM, Grasela TH, et al. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. *Antimicrob Agents Chemother.* 2001;45:2793-2797.
12. Hughes WT, Armstrong D, Bodey GP. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34:730-751.
13. Lacy MK, Nicolau DP, Nightingale CH, et al. The pharmacodynamics of aminoglycosides. *Clin Infect Dis.* 1998;27:23-27.
14. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis.* 1987;155:93-99.
15. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis.* 1984;149:443-448.

Self-Assessment Questions

To check your understanding of *Clinical Microbiology and the Antimicrobial Pharmacist: a Synergistic Combination*, please answer the following 5 self-assessment questions.

- 1. The MIC value is the only consideration in anti-microbial selection.**
 - a. True
 - b. False
- 2. What does the therapeutic breakpoint represent?**
 - a. The concentration of antimicrobial agent required to kill an organism
 - b. The antimicrobial agent with the lowest MIC value
 - c. The MIC value representing a susceptible interpretation as assigned by CLSI
 - d. The effective concentration of antimicrobial agent at the site of infection
- 3. Which of the following antimicrobial agents is most likely to be recommended to treat an infection with a single pathogen?**
 - a. Drug A: MIC = 1 µg/mL; therapeutic breakpoint = 1
 - b. Drug B: MIC = 2 µg/mL; therapeutic breakpoint = 1
 - c. Drug C: MIC = 4 µg/mL; therapeutic breakpoint = 8
 - d. Drug D: MIC = 8 µg/mL; therapeutic breakpoint = 8
- 4. Which of the following describes pharmacodynamics?**
 - a. The total distribution of drug within the body based on dosing
 - b. The distribution and half-life of a drug following different doses
 - c. The measure of a drug's effectiveness in the body relative to its mode of action and concentration at the site of infection
 - d. A measurement of total bacteria killed as the concentration of drug increases over time
- 5. What measurement combines the effects of concentration- and time-dependent killing of an antimicrobial agent?**
 - a. Area under the inhibitory curve
 - b. Time above the MIC
 - c. Area under the curve
 - d. Half-life / MIC

Answers will be published in the next issue of MicroFocus and online at www.dadebehring.com.

Answers to "Carbapenemase Activity in the *Enterobacteriaceae*" Self-Assessment Questions published in the MicroFocus Spring 2007 issue.

- Which of the following groups of bacteria known today have the most likely potential to possess carbapenem-inactivating enzymes?
d. *Enterobacteriaceae*, *Stenotrophomonas*, *Pseudomonas*, and *Acinetobacter*
- The incidence of carbapenemase enzymes in enteric gram-negative bacilli is low but is increasing.
a. True
- Closer evaluation for the presence of what resistance mechanism is warranted when a *Klebsiella pneumoniae* isolate shows an increase in ertapenem MIC?
c. KPC
- Can susceptibility or resistance to a carbapenem be predicted based on the results of testing one class representative?
b. False
- Critical issues impacting the accuracy of imipenem susceptibility testing include
e. a (drug instability) and c (low inoculum density)

Commentary: MICs and PK/PD – the Basics for Selection of Antimicrobial Therapy

William J. Brown, Ph.D., D(ABMM), F(AAM)

The continuous evolution and spread of antimicrobial resistance among bacteria and the expanding variety of antimicrobial agents present a challenge to the medical community. The response has led to a team approach in selecting the optimum therapy for the more serious infections. The physician is responsible for the therapy, but relies more and more on the microbiology laboratory and pharmacy for assistance.

The route by which the drug is administered (oral, intramuscular, or intravenous) will determine how fast the drug enters the bloodstream.

Drs. Thomson and Suseno explain this approach and present practical examples of the interaction of the team approach. Laboratorians need to know the more complete picture of antimicrobial therapy and not just the laboratory-measured resistance of an antimicrobial agent and a bacterium. We need to understand what goes into taking the *in vitro* MIC and applying it to the treatment of the patient. To prepare us to more fully comprehend the concepts covered in the article by Drs. Thomson and Suseno, we need to introduce new concepts to clinical microbiologists and technologists. Frequently, we have confined ourselves to only considering the test tube interactions of a bacterial isolate and a series of antibiotic concentrations. To better grasp the therapeutic considerations of antimicrobial therapy, we need to examine the entire dynamic picture of what is occurring inside the patient treated for the infection. Many variables come into play in selecting and dosing antimicrobial therapy. The *in vitro* determined MIC is just the first step. Other questions need to be answered. Can the antibiotic be administered to obtain concentrations at the body site(s) of the infection

that exceed the MIC of the bacterium? How much higher than the MIC is the antibiotic concentration? How long does the drug concentration remain higher than the MIC?

The distribution of the antimicrobial drug throughout the body, as well as the *in vivo* interaction of the drug and the etiological agent of the infection, are the basics of pharmacokinetics (PK) and pharmacodynamics (PD).

What happens to the antimicrobial drug after it is administered to the patient? The route by which the drug is administered (oral, intramuscular, or intravenous) will determine how fast the drug enters the bloodstream. Also important is how much of the drug is given. The blood level will increase with higher doses (eg, 0.25, 0.5, 1.0 or 2.0 grams will yield correspondingly higher concentrations of the drug). For example, a 0.5-gram oral dose will produce a lower blood level and take longer to reach its maximum (or peak) in the blood than administering 2 grams intravenously. Another critical factor is that the antimicrobial drug is not evenly distributed throughout the body (physiological compartmentalization). Each drug has unique features that determine if it is concentrated in some organs or



William J. Brown, Ph.D.,
D(ABMM), F(AAM)

To better grasp the therapeutic considerations of antimicrobial therapy, we need to examine the entire dynamic picture of what is occurring inside the patient treated for the infection.

fluids and extruded from other areas (eg, does it gain entrance to the CNS or is it blocked by the blood-brain barrier). These interactions of the drug and distribution in the body are referred to as the *pharmacokinetics* of an antimicrobial agent.

The interaction of the antimicrobial drug and the microorganism in the patient is referred to as pharmacodynamics. How does the concentration of the antimicrobial drug interact with the microorganism? This is where the MIC comes into play. For successful therapy, the pharmacokinetics have to have resulted in an *in vivo* level of the drug that is higher than the MIC. But how much higher or how long must it remain above the MIC? These are the pharmacodynamic factors that must be taken into consideration in optimizing the antimicrobial therapy. With some antibiotic classes, for example, aminoglycosides and fluoroquinolones (eg, gentamicin and ciprofloxacin, respectively), the important pharmacodynamic principle is a high concentration of the drug above the MIC at the site of the infection (concentration-dependent). The application of PK/PD principles has resulted in a change in how aminoglycosides are administered. Rather than dosing every 8 or 12 hours, they are frequently given just once per day but at a higher dose. This will cause a higher level of drug in the patient and

exceed the MIC by a greater amount. This works for concentration-dependent drugs. Other drugs require a different pharmacodynamic principle of keeping the antimicrobial drug concentration above the MIC for a long time (time-dependent), such as beta-lactam drugs (eg, penicillins and cephalosporins).

The MIC and how the PK and PD factors and their interactions contribute to the therapeutic breakpoint are clearly introduced for laboratory personnel in the main article in this issue of *MicroFocus*. Simply stated, treatment with an antibiotic achieves an effective concentration at the site of infection. A susceptible MIC result must be lower than this concentration. Although many factors go into establishing this effective breakpoint, the concept is straightforward: the concentration of antibiotic at the site of infection must exceed the MIC. This is not a complete coverage of antimicrobial pharmacology, nor is it intended to be. We want to introduce microbiology personnel to how MIC data are applied and how they can better serve as a resource to physicians and pharmacy colleagues.

For successful therapy, the pharmacokinetics have to have resulted in an *in vivo* level of the drug that is higher than the MIC.

Don't forget!

Log on to www.dadebehring.com (Services > Education > Microbiology) to

- Opt in to continue to receive your copy of **MicroFocus A MACRO LOOK AT MICRO ISSUES**
- Complete required information to obtain 1 CEU credit for *Clinical Microbiology and the Antimicrobial Pharmacist: a Synergistic Combination*

First Class Mail
US Postage
PAID
Wilmington, DE
Permit No. 1858



Zero in on Emerging Resistance

MicroScan
Resistance has met its match

Experience MicroScan®'s exciting educational opportunities by visiting www.dadebehring.com

Once you arrive, you will find several different educational tools aimed at spotlighting emerging issues in the complex and changing field of microbiology, including the following:

- 2007 MicroFocus Journal, Volume 3
- CLSI M100-S17 Checklist
- 2006 MicroFocus Journal, Volumes 1 & 2
- 2006 ASM Booth Presentations – Review all 10 presentations to acquire 5 CEU credits!

Coming soon:

- 2007 Fall Series Diagnostic Conference Presentations – ask your Sales Representative for details!

MicroScan – trusted solutions to meet today's changing world of microbiology.

Zyvox® is a registered trademark of Pfizer Inc.

Fortaz® is a registered trademark of GlaxoSmithKline.

© 10/2007 Dade Behring Inc.
MO0282

DADE BEHRING, INC
MicroScan® Microbiology Systems
1717 Deerfield Rd.
Deerfield, IL 60015
1-800-242-DADE (3233), option 3,2
www.dadebehring.com

DADE BEHRING
Every minute of every day®