What is MIC IQ?

Richard B. Thomson, Jr., Ph.D. Evanston Northwestern Healthcare, Professor of Pathology, Northwestern University Feinberg School of Medicine Chicago, Illinois, USA.

Minimum Inhibitory Concentration

Minimum inhibitory concentration (MIC μg/mL) and MIC breakpoint values for categorization of susceptibility groups are the backbones of in vitro antimicrobial susceptibility testing and clinical interpretation. Understanding the MIC and its relationship to the interpretive breakpoint represents a challenge to microbiologists, pharmacists and clinicians alike. In addition, recognizing unusual antibiograms that may represent laboratory errors or new resistant mechanisms is a skill that microbiologists must acquire and continually update and maintain. MIC testing is a valuable quantitative tool for evaluating the pathogens degree of susceptibility, to detect specific resistance mechanisms and to confirm unusual or erroneous results.

Relativity of Susceptibility

The MIC is the lowest concentration of an antimicrobial agent that visually inhibits growth of a microorganism under defined experimental conditions. The MIC per se is not useful unless it can be compared to the concentration of the agent achieved at the site of infection, i.e. one of the key parameters used in guiding the selection of the interpretive breakpoint. Simply speaking, MIC values lower than the breakpoint are interpreted as susceptible results and those higher as resistant for treatment guidance. Pharmacokinetics refers to the dosing, distribution and half-life of antimicrobial agents i.e. factors that impact the achievable concentrations at various body sites. Since the pharmacokinetics of antimicrobial agents can be different drug to drug, infection site to infection site and patient to patient, so too can breakpoints be significantly different. In other words, two agents with the same MIC value for a pathogen may have totally different interpretations because they have different breakpoints. Furthermore, a lower MIC value for one agent may represent a resistant result, while a higher MIC for another agent may be interpreted as susceptible, simply because of relative differences in breakpoints.

Most clinicians may not fully understand the concept of the MIC being relative to the breakpoint. To complicate matters, even when MIC values and breakpoints are identical for two agents, their efficacies may not be equivalent because of differences in the pharmacodynamics of the drugs. Pharmacodynamics is a measure of the inhibitory and killing ability of an antimicrobial agent relative to its mode of action and achievable concentrations. For example, if two agents interact with a pathogen, both with the same MIC and breakpoint values, and both with susceptible interpretations for the organism, one agent may still kill the organism more quickly than the other. Why and when this occurs depends on pharmacodynamic properties of the agents that can result in time or concentration dependent killing and post-antibiotic effects. Concentration dependent killing is the drugs ability to kill the pathogen more efficiently as the concentration increases. Time dependent killing is the ability to kill as the time of drug exposure increases. Post-antibiotic effect is the continued inhibition of bacterial growth after the antibiotic concentration has fallen below the MIC.

Pharmacodynamic Index

Attempts to integrate pharmacokinetic and pharmacodynamic parameters to optimise the eradication of the pathogen have resulted in the identification of various pharmacodynamic indices (PDIs). An example of such a PDI is the Area Under the Inhibitory Curve (AUIC). The AUIC represents the total amount of drug measured in the serum during a 24-hour period (AUC 24h) divided by the exact MIC for the particular organism; the higher the MIC, the lower the AUIC value. The antimicrobial activity or rather the potential efficacy of different agents against a pathogen can be more efficiently compared using the AUIC values rather than just the MIC alone. Once parameters such as AUIC or time above the MIC (T>MIC) between dosing intervals or maximum concentration above the MIC (Cmax/MIC) are defined, correlations of these data to in vivo pathogen eradication either in animal model studies or clinical trial data will allow for selection of PDI cut-offs to predict clinical outcome. PDIs can be used to predict eradication rates and potential development of resistance during therapy. PDI is felt by some to be an important tool to target the therapy of critical infections and high-risk patients both for selecting the most efficacious drug as well as the dosing regimen to best attain the optimal PDI. A recent prospective observational study by Mohr et al. 2004, elegantly illustrates how PK/PD and PDI modelling can be used to help guide targeted antimicrobial therapy for nosocomial Gram negative infections in critically ill patients.

Since PDIs of antimicrobial agents are becoming more important in the selection of MIC breakpoints, one of the simplest ways to view and use the MIC relative to PDI of various agents is to compare their so-called MIC breakpoint quotients (MBQs), calculated by dividing the MIC breakpoint with the MIC value for a particular pathogen. This is particularly useful for agents with pharmacodynamics characterized by concentration dependent killing. Assuming important parameters such as toxicity have been accounted for in the selection of breakpoints, the lower the MIC and the higher the MBQ, the more efficacious an agent is expected to be (Figure 1). Equally, the lower the MIC and the higher the MBQ, dosages can be adjusted without compromising on the PDI goal e.g. for neonatal infections. So, in the simplest of formats, the MIC value relative to the susceptible breakpoint may become a very practical tool to target and fine-tune antimicrobial therapy.

Are all MIC Methods Equal?

How should we perform antimicrobial susceptibility testing (AST) in clinical microbiology laboratories? Quantitative testing by broth microdilution, automated methods or predefined antibiotic gradients (Etest®, AB BIODISK, Solna, Sweden) all give interpretations with some form of MIC value, or ≥ or ≤ results when dilution ranges are limited. There are systems that provide crude estimations of MIC extrapolates from disk diffusion testing through regression analysis based on the assumption of an inverse linear relationship between the zone diameter and MIC values.

Many AST methods may represent acceptable strategies for routine testing. In spite of this, “full-range” MIC testing may be necessary for many organism-drug combinations with specific resistance mechanisms and for critical infections and...
patients where clinical decisions require an exact MIC value. Full range MIC testing refers to the use of an extended concentration range (≥10 dilutions) such that very susceptible to very resistant organisms are covered. Most MIC systems today are based on abbreviated dilutions across a narrow range to accommodate many drugs on a broth microdilution panel and they generally cover the breakpoint concentrations only.

INDICATIONS FOR REAL MICs
When is an exact on-scale MIC result required? Table 1 provides examples of situations where exact MIC values may be needed. Extended dilution or full-range MIC testing may be needed when routine ASTs provide susceptible, resistant or intermediate category results only, dilution schemes are restricted to the breakpoint range or MIC results do not provide sufficient data for pharmacodynamic targeted dosing considerations. MIC testing is necessary to confirm resistance screens used with staphylococci and enterococci. It is necessary to test viridans streptococci isolated from patients with endocarditis and to quantify pneumococci susceptibility to penicillin, ceftriaxone or cefotaxime and other secondary agents as needed. Currently, anaerobes can primarily be tested with agar-based MIC methods only. MIC testing may also be needed for severe infections caused by multi-drug resistant Gram negative bacteria to allow estimations of pharmacodynamic indices to guide antibiotic selection and dosing regimens. For infrequently encountered pathogens for which no AST method has been validated, an estimate of the in vitro susceptibility in terms of the MIC value is still needed to help guide treatment selection, especially if it involves a serious infection and/or a critical patient. It is necessary, however, to report methods that have not been validated by NCCLS or FDA as “non-standardized or investigational only” and to discuss such results with the patient’s physician. An emerging need in clinical laboratories is the ability to perform antifungal susceptibility testing. Since the establishment of NCCLS reference MIC methods, commercial systems now available provide options for MIC testing.

REVIEWING DAILY RESULTS
Daily review of antimicrobial susceptibility test results can improve reporting accuracy and thus patient care. Laboratory errors and/or new resistance mechanisms can be recognized by assessing unusual results such as vancomycin resistant staphylococci or streptococci, meropenem resistant Bacteroides fragilis group or third generation cephalosporin resistant Haemophilus influenzae. Unusual resistance mechanisms can be detected by studying antibiograms of multi-drug resistant isolates such as imipenem resistant Enterobacteriaceae (potential presence of porin mutations or metallo beta-lactamase) or ceftazidime intermediate or resistant E. coli and Klebsiella spp. (potential presence of an extended spectrum beta-lactamase). Unlikely, unexpected or unusual results should be investigated by repeating the test and confirming results using an alternate MIC method or by submitting the specimen to a reference laboratory for confirmation. Those who review daily results must be familiar with wild-type antibiograms, intrinsic resistances and local susceptibility patterns in order to recognize findings that deviate from the expected. Lists of unexpected results can be found in the NCCLS document M39-A, 2002, and the review by Livermore et al, 2001.

In summary, resistance among human pathogens is continually changing and one must use a variety of in vitro antimicrobial susceptibility testing methods to serve needs imposed by the different species encountered, evolving resistance mechanisms and an increasing population of compromised patients. Today’s clinical microbiology laboratories need to provide MIC testing services and, in many cases, exact MIC values to allow the use of pharmacodynamic indices to target therapy for the individual patient. Selection of the most effective antimicrobial agent and dosing regimen for serious infections will increase the chance of eradicating the pathogen, minimise the risk of resistance selection and decrease mortality and morbidity.
### TABLE 1: EXAMPLES OF SITUATIONS REQUIRING EXACT MICs

<table>
<thead>
<tr>
<th>ORGANISM/ SITUATION</th>
<th>ANTIMICROBIAL AGENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus or CNS¹</td>
<td>Vancomycin</td>
<td>VIS² detection by Etest or broth MIC with vancomycin concentrations from 2.32 µg/mL</td>
</tr>
<tr>
<td>CNS</td>
<td>Oxacillin</td>
<td>MRCNS³ detection with oxacillin Etest or broth MIC with concentrations from 0.12 µg/mL</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Vancomycin</td>
<td>VRE⁴ confirmation/characterization with vancomycin Etest or broth MIC with concentrations up to 64 µg/mL</td>
</tr>
<tr>
<td>Viridans Streptococci</td>
<td>Penicillin</td>
<td>Etest or broth MIC with concentrations from 0.064-µg/mL for penicillin and 0.54 µg/mL for ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone⁵</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Penicillin</td>
<td>Etest or broth MIC with concentrations from 0.064 µg/mL for penicillin and 0.254 µg/mL for ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone⁵</td>
<td></td>
</tr>
<tr>
<td>MDR Gram positives</td>
<td>Secondary panel</td>
<td>Etest or broth MIC with full range dilutions to guide selection of regimen and dosing</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>All</td>
<td>Etest or agar dilution (all organisms) or broth MIC (Bacteroides spp., and few drugs)</td>
</tr>
<tr>
<td>MDR Gram negatives</td>
<td>All</td>
<td>Etest or broth MIC with full range dilutions to guide selection of regimen and dosing</td>
</tr>
<tr>
<td>Unusual pathogens</td>
<td>All</td>
<td>Full range MIC testing may provide &quot;non-standardized&quot; result</td>
</tr>
<tr>
<td>Unexpected results</td>
<td>All</td>
<td>Comparing wildtype antibiograms. Confirm by repeat testing and add Etest or broth MIC and/or submit to reference laboratory</td>
</tr>
<tr>
<td>Yeast and moulds</td>
<td>All</td>
<td>MIC testing (Etest or broth MIC) and/or submit to reference laboratory</td>
</tr>
<tr>
<td>Critical care isolates</td>
<td>Drugs of choices</td>
<td>Etest or broth MIC following interactions between microbiologist, pharmacist and ID physician to guide usage</td>
</tr>
</tbody>
</table>

### ABBREVIATIONS
1. CNS = coagulate negative staphylococci
2. VIS = vancomycin intermediate staphylococci
3. MRCNS = methicillin resistant coagulate negative staphylococci
4. VRE = vancomycin resistant enterococci
5. Ceftriaxone or cefotaxime
6. MDR = multi-drug resistant organisms
7. CAT = Category

### GENERAL REFERENCES

For more information on this article please contact rthomson@enh.org

### DISCLAIMER FOR USA
For clinical laboratories in the USA, this publication does not in any way indicate or imply new in vitro diagnostic uses or changes of procedure for Etest, outside those that are clinically cleared.

---

**SEASONS GREETINGS**
AB BIODISK continued its tradition of donating to deserving causes by giving USD 5000 to Médecins Sans Frontières in 2003. MSF is an international humanitarian aid organisation that provides emergency medical assistance to populations in danger in more than 80 countries.

**PRODUCT UPDATES**
Etest products were CE marked in 2003 to fulfill the requirements of the EU directive for in vitro medical devices. A multi-lingual package insert and a comprehensive table including performance, interpretive criteria and QC ranges now accompany each package. For more product information, the user has access to numerous downloadable Etest technical documents at www.abbiodisk.com

**BIOTOOLS™**
Biotools, a new family of instruments, is now increasingly used by clinical laboratories to simplify the set up of Etest for MIC determinations. More information on Simplex C76™ (automatic Etest applicator), Nema C88™ (vacuum pen applicator) and Retro C80™ (incubator), is available at www.abbiodisk.com

**EAL - Etest Application Laboratory**
AB BIODISK is committed to providing high quality educational support. EAL courses provide a forum for participants from all over the world to learn and interact with each other. The latest course schedule and programmes are available at www.abbiodisk.com

**PARENT COMPANY**
AB BIODISK, Dalvägen 10
S-169 56 Solna, Sweden
T. +46 (8) 730 07 80 F. +46 (8) 83 81 58
etest@abbiodisk www.abbiodisk.com

**USA SUBSIDIARY**
AB BIODISK North America Inc.
200 Central Avenue
Piscataway, NJ 08854-3910 USA
T. (732) 457-0408 F. (732) 457-8980
etest@abbiodiskna.com

Etest® is a registered trademark of AB BIODISK and patented in all major markets.
© AB BIODISK M0000485-BE1044