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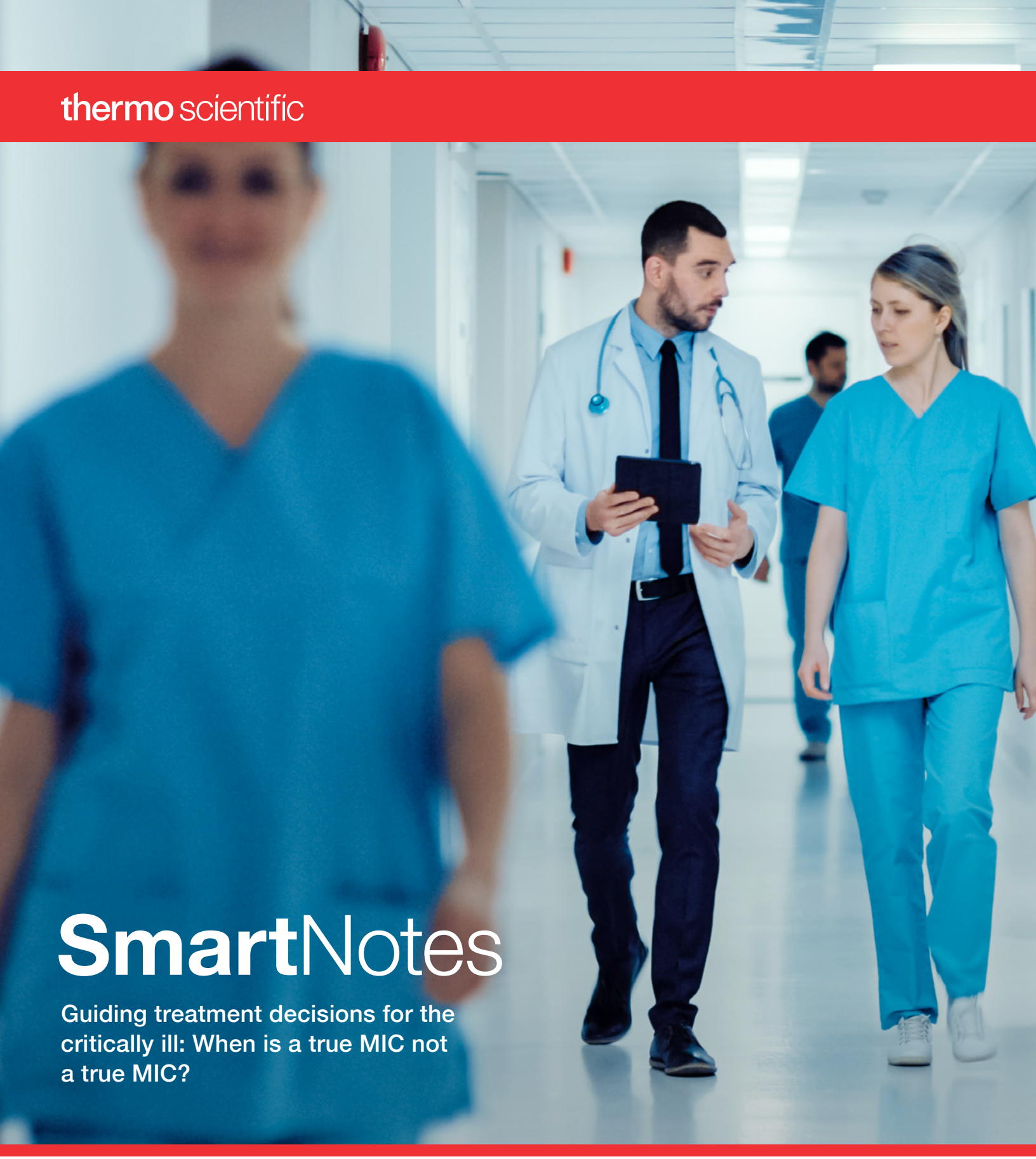

SmartNotes

Guiding treatment decisions for the critically ill: When is a true MIC not a true MIC?

ThermoFisher SCIENTIFIC

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By determining the lowest antimicrobial dose needed to eliminate an infection, minimum inhibitory concentration (MIC) results can play a vital role in patient care and public health alike. They guide clinical decisions towards the best possible individual outcomes and help protect against the devastating consequences of antimicrobial resistance (AMR).

Yet despite the undisputed importance of MIC, there is still uncertainty around the best way to generate results. A number of products have entered the market, all claiming to provide robust, actionable insights. Some of these approaches extrapolate from minimal data points, while others use definitive, observable growth, but are all MIC methods made equal?

In this SmartNote, we explain why an MIC result is too important to fail, outline the difference between extrapolated and definitive results, and talk to leading experts about the role of accurate, robust MIC results in patient care and the fight against AMR.

What is MIC and why does it matter?

An MIC, a quantitative method of antimicrobial susceptibility testing (AST), is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after incubation. It's a value that allows clinicians to tailor antibiotic dosing to the individual infection.

This matters for two very important reasons, according to Jeroen Bursens, Thermo Fisher Scientific Microbiology's EU clinical equipment manager: "MIC calculations can help to protect individual patients and society alike. Inaccurate results negatively affect antimicrobial stewardship programs and may impact the ability to guide optimal clinical decisions," he says.

First, it is a vital tool in the war against AMR, a global threat that is predicted to cause 10 million deaths a year by 2050,[1] explained Cindy Knapp, Thermo Fisher Scientific's director of R&D, AST and pharma. "While some degree of antimicrobial resistance is inevitable, the misuse and overuse of some agents is contributing to resistance and putting lives at risks. Stewardship, in which antimicrobials are used only when necessary, is our best form of defense."

On the individual patient level, antibiotics may be indispensable, but some present a complex risk/benefit profile. One retrospective study suggests that antibiotic-associated adverse drug events (ADEs) are common (20%) among inpatients receiving antibiotics, "some of which may be avoidable with more judicious use of antibiotics", with ADEs ranging from gastrointestinal, dermatologic and musculoskeletal to hemotologic, hepatobilitiary/renal/cardiac and even neurologic in nature.[2]

To extrapolate or to observe?

The Clinical and Laboratory Standards Institute (CLSI)[3] and the International Organization for Standardization (ISO)[4] have detailed the broth dilution procedure as a reference method for determining an MIC of rapidly growing aerobic bacteria. However, these are manual procedures and are largely impractical for routine testing. Instead, most laboratories rely on commercial systems which are based on these methods.

Multiple automated AST systems that generate MIC results are currently on the market. Their main point of difference is the method used to calculate post-incubation growth levels. While some utilize machine learning to extrapolate results from a defined, but potentially incomplete dataset, others streamline microbiological processes to generate observed, definitive results efficiently.

The extrapolation method trains algorithms to understand the growth patterns of target microorganisms under appropriate conditions. Growth is then measured at a set point during incubation, and a statistical model calculates the likely continued growth at endpoint. It can be accurate but is also at risk of limitations – because like any algorithm-based technology, it is only as good as the data it holds.

The models are based on a subset of isolates that may not be relevant to the clinical case in hand. Importantly, they may have limited capacity to recognize new kinetic models of growth, such as those influenced by resistance mechanisms, or the synergy between them. In short, these systems only 'know what they already know'.

"The problem with non-definitive devices is you don't know how the kinetic model becomes influenced by different resistance mechanisms. Resistance mechanisms occur continuously and there is also a lot of synergy between them," Bursens explains. "The curves may have been a good fit for the organisms that were used in the development of the algorithm. But new resistance mechanisms come with new ways for them to interact, and this will have a creep on the accuracy of the result."

Definitive detection, such as that utilized by the Thermo Scientific™ Sensititre™ System, is different. By using a minimum of four two-fold, sequential microbroth dilutions, it closely mirrors the reference method to arrive at robust, observable results at endpoint – even if the isolate behaves unpredictably in the presence of antibiotics.

Interpretations are also an important point of difference. Some systems may record an organism as sensitive (S), intermediate (I) or resistant (R), whereas others, such as the Sensititre System, return definitive MIC values and well as the categorical interpretation defined by user preferences (CLSI, EUCAST or FDA interpretations).

Definitive MIC results and quality patient care

Definitive MIC results support confident clinical decision making. James A. McKinnell, M.D., an academic researcher at Harbor-UCLA Medical Center and infectious disease physician at Torrance Memorial Medical Center, notes: “Each MIC interpretation is unique to the individual organism and the individual drug. As clinicians, we need to pick the agent that is the safest for the patient, and the most effective at killing the bacteria causing the infection. Accurate MIC is the key to this critical decision.”

If an MIC mistakenly categorizes an organism as “sensitive”, the patient could be exposed to potential side effects, with no therapeutic benefit. Importantly, according to Dr. McKinnell, SIR (susceptible-intermediate-resistant) categorical classifications alone may not be enough to make informed decisions in critical care and in-patient populations where the right choice of antibiotic “is the only thing keeping them alive”. Rather, definitive MIC results are vital.

Genetic tests are increasingly utilized to detect antimicrobial resistance markers within the pathogen’s genome. However, the existence or absence of a genetic resistance marker does not always correlate with *in vitro* or *in vivo* activity of the pathogen, Dr. McKinnell explains.

“The absence of detecting known genetic resistance mechanisms is not the same as susceptible,” he says. There are, for example, thousands of mechanisms that can cause carbapenem-resistance, yet molecular detection of resistance markers will only search for the handful that are fully understood. “If you only test for five carbapenem-resistant genes, you are searching in the dark,” he says, adding that only observed growth of a definitive MIC gives a true indication of *in vitro* activity of the pathogen in the presence of an antibiotic.

Clinical application

Definitive MIC values, he argues, allow clinicians to tailor antibiotic treatment regimens to the bacterial pathogen observed in an individual patient. “If I have to use a broader agent, I can do so until such time as I get a culture and susceptibility result back that demonstrates I can adjust the approach,” he says adding that categorical interpretation may only be useful as a guide. “When I am treating an infection, I need an accurate, true assessment of what is going on.”

Dr. McKinnell likens designing effective antimicrobial treatment plans in critical care to “landing a fighter jet on an aircraft carrier in a storm”. “If you don’t do everything perfectly, you will crash – and the outcome here is that the patient dies.” There is a lot to consider, and definitive MIC results are an important part of making a “safe landing” possible.

"I do not just need to know if the organism will die in the test tube; I need to think about whether I will be able to get the appropriate concentration of drug into the affected organ space," explains Dr. McKinnell.

MIC results may, for example, show that the *Escherichia coli* causing a case of meningitis is sensitive to ertapenem. However, the agent's poor penetration of the blood/brain barrier would make it difficult to achieve a concentration adequate to kill the organism. Referring to a case of septic shock, Dr. McKinnell explains: "I may have a drug with a sensitive MIC, but I need to achieve the necessary concentration in the lung, the liver, the brain, the spleen, or even in bone."

Such scenarios often raise considerations of dual mechanism treatment that rely on MIC results that go further than "sensitive", "intermediate", or "resistant". Rather, doctors need accurately measured, definitive MIC range values for various antimicrobial agents, which can be compared to established breakpoints throughout the treatment plan, and guide de-escalation.

MIC in the stewardship equation

Dr. McKinnell and Jerod Nagel, PharmD, clinical pharmacist and specialist in infectious diseases at University of Michigan Hospitals, both highlight that MIC is just one element of the drug selection equation. Factors such as the infection location and severity, and certain patient characteristics, for instance immunosuppression, comorbidities, or obesity, can all influence the most appropriate choice of agent and dosing strategy.

One important consideration in administration planning is the interplay between the MIC and the drug's pharmacokinetic and pharmacodynamic (PK/PD) profile. Some agents, Dr. Nagel explains, are most effective at a high peak/MIC ratio, indicating aggressive dosing. For others, the measure for success may be time above the MIC, necessitating extended infusion or more frequent dosing, or area under the curve (AUC)/MIC ratio.

In non-complex cases, combining all that information with an S, I, or R categorical interpretation of a MIC result may be enough to make the right decision. But in a world of increasing resistance, things are not always that straightforward. "If you have an infection with a lot of 'R' or 'I' on the report , or the patient has allergies or intolerances that eliminate a lot of your options, you need to look at the MICs in relation to each other," notes Dr. Nagel.

Predicting resistance mechanisms

Definitive MIC values can help clinicians to predict resistance mechanisms. They can then use that information to select an agent with the most appropriate mode of action.

Using the example of *Pseudomonas*, Dr. Nagel highlights three main resistance mechanisms, each of which affects the bacteria's susceptibility to different agents in different ways **(see table 1)**. It means that clinicians can find clues by looking at the MIC values in relation to each other, he explains.

Table 1: Antibiotic impact on common Pseudomonas resistance mechanisms

AmpC = ampicillinase; MexAB = MexAB-OprM

Antibiotic	AmpC hyperproduction (beta-lactamase)	MexAB upregulation (effiux pump)	OprD downregulation (porin channel)
Piperacillin-tazobactam	Elevated MICs, but usually resistant	Elevated MICs, or resistance	No Impact on MIC
Cefepime	Elevated MICs, resistance possible	Elevated MICs, or resistance	No Impact on MIC
Ceftazidime	Resistance (usually)	Elevated MICs, or resistance	No Impact on MIC
Aztreonam	Resistance (usually)	Elevated MICs, or resistance	No Impact on MIC
Imipenem	Elevated MICs, but susceptibility retained	No Impact on MIC	Resistance usually seen
Meropenem	No Impact on MIC	Elevated MICs (alone unlikely to cause resistance)	Elevated MICs (alone unlikely to cause resistance)

More than half of *Pseudomonas* spp. have more than one resistance mechanism, which can severely limit options by rendering most first-line treatments ineffective.

Full MIC range details can also guide decisions when results show more than one agent could be effective, or, in cases of multiple resistance mechanisms, all are categorized as R. When there is a choice, clinicians can select the one with the lowest MIC relative to the published breakpoints to protect these newer drugs from emerging resistance.

It is extremely challenging when the opposite is true, and healthcare teams are faced with pan-resistant organisms. Dr. Nagel says the data on multidrug resistance and combination therapy are being updated all the time.

Outlining his current approach, he explains: "I look at the MIC in relation to the breakpoint, I compare it to the other agents, and I try to examine the likelihood of hitting the PK/PD target if I use the standard or potentially a modified dosing strategy."

Definitive, accurate, reliable

Thermo Fisher Scientific is committed to supporting our customers' antimicrobial stewardship efforts and protecting public health.

Our Sensititre System generates definitive MIC results that clinicians can rely on. The solution is fully validated, with gold standard-level accuracy[4] to provide laboratories with reliable, robust results which may guide vital clinical decisions.

In addition, we are dedicated, through our collaboration with pharmaceutical companies, to supporting the development of new antimicrobials and expediting their incorporation into our antimicrobial susceptibility testing portfolio. This is how the Sensititre System strives to be first-to-market with the latest antimicrobials.

> *"When a new drug comes to market, I need it right away. If it takes someone six months to get a drug onto a system or get it approved, that's six months in which I am working in the dark,"* - Dr. McKinnell

The Sensititre System:

- Offers a wide range of standard AST plates, which allow clinicians to make critical choices for antibiotic selection and dosing to support optimized patient outcomes
- BMD platform allows the flexibility to quickly implement breakpoint changes by FDA, CLSI and EUCAST
- Provides accurate susceptibility testing for new antimicrobials, including imipenem/relebactam, eravacycline, omadacycline and plazomicin, eliminating the need for testing via other methods, and allowing prescribers to select timely effective therapy for multi-drug resistant pathogens.

For more information on the Sensititre System, and to subscribe to our susceptibility testing, empowered newsletter, visit **thermofisher.com/AST.**

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