JASPI

Journal of Antimicrobial Stewardship Practices and Infectious diseases

September 2025/ Volume 3/Issue 3

Narrative Review

The Breakpoint MIC Quotient: A Critical Review of a Novel Tool for Antimicrobial Therapy

Elantamilan Durairaj[1], Jyotismita Rajbongshi[2], Mangayarkarasi V[1]*

1- Department of Microbiology, AIIMS, Madurai, Ramanathapuram, 623503, Tamil Nadu
2-Department of Microbiology, ESIC Medical College & PGIMSR, KK Nagar, 600078, Chennai.

* **Corresponding author:** Dr Mangayarkarasi V, Professor & Head, Department of Microbiology, AIIMS, Madurai, Ramanathapuram, 623503, Tamil Nadu, India.
Email:microbiology.aiimsmadurai@gmail.com

ABSTRACT

Introduction: The "Breakpoint MIC Quotient" (BMQ), defined as the ratio of an isolate's minimum inhibitory concentration (MIC) to the susceptible clinical breakpoint for a given drug–pathogen pair, has been proposed as a simple surrogate of pharmacokinetic/pharmacodynamic (PK/PD) target attainment and therapeutic margin. Although formal definitions are lacking, the BMQ and related indices (e.g., Breakpoint/MIC) are grounded in PK/PD principles and aim to provide a simplified surrogate for estimating the probability of achieving therapeutic success.

Methods: We critically examined available literature describing the concept, rationale, and clinical correlates of the BMQ, focusing on its role in antimicrobial therapy decision-making. Illustrative studies involving Gram-negative and Gram-positive infections were reviewed to explore its relevance and limitations.

Results: Evidence suggests that higher MICs, even within the susceptible range, may narrow the therapeutic margin and increase the risk of treatment failure. Clinical studies, such as those involving cefepime against *Pseudomonas aeruginosa* and vancomycin against MRSA, show associations between elevated MICs and poorer outcomes, including increased mortality. Quantitative assessments using the BMQ may support antimicrobial optimization through higher dosing or prolonged infusions in severe or high-risk infections. However, limitations include oversimplification of host-pathogen interactions, variability in MIC testing (±1 $\log_2$ dilution), dependence on accurate breakpoints, and reduced applicability in scenarios like biofilm-associated or heteroresistant infections.

Conclusions: The BMQ is a promising conceptual tool for risk stratification and antimicrobial stewardship. While it may inform individualized therapy, its clinical utility requires standardization and validation through well-designed prospective clinical trials before widespread adoption.

KEYWORDS: BMQ, Minimum Inhibitory Concentration,; Antimicrobial Susceptibility Testing; Pharmacokinetics / Pharmacodynamics; Clinical Breakpoints

INTRODUCTION

Antimicrobial Susceptibility Testing (AST) is a fundamental component of infectious disease management, providing critical information for guiding effective antimicrobial therapy. At the heart of AST lies the Minimum Inhibitory Concentration (MIC), defined as the lowest concentration of an antimicrobial agent that inhibits the visible *in vitro* growth of a microorganism after a specified incubation period. The MIC serves as the basic quantitative measure of an antibiotic's activity against a specific pathogen. Generally, a low MIC value suggests that the

Citation: Durairaj E, Rajbongshi J, V M.The Breakpoint MIC Quotient: A Critical Review of a Novel Tool for Antimicrobial Therapy. JASPI. 2025;3(3):22-31

microorganism is susceptible to relatively low concentrations of the antimicrobial, whereas a high MIC value indicates the potential for resistance.[1]

To translate these quantitative MIC values into clinically actionable categories, clinical breakpoints are established. These are specific MIC values (or corresponding disk diffusion zone diameters) used to classify an organism as susceptible (S), susceptible Dose-Dependent (SDD), intermediate (I), or resistant (R) to a particular antimicrobial agent. It is important to recognize that these breakpoints are not arbitrary; they are meticulously determined by international and national committees, such as the Clinical & Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and vary depending on both the antimicrobial agent and the specific microorganism.[1-3] The determination of clinical breakpoints integrates diverse data sources, including distributions of MICs for large numbers of bacterial strains (both wild-type and those with known resistance mechanisms), epidemiological cut-off values (ECVs or ECOFFs) that differentiate wild-type isolates from those with acquired resistance, pharmacokinetic and pharmacodynamic (PK/PD) data relating drug exposure to bacterial killing, and, crucially, clinical outcome data from patients treated for specific drug-bug combinations.[4,5] A report of "susceptible" generally implies a high likelihood of therapeutic success when the antimicrobial is administered using a standard dosing regimen.[1]

The entire framework of S/I/R categorisation while immensely practical for guiding routine therapy, represents an interpretive layer applied over the continuous, quantitative MIC data. This simplification is a key strength, offering ease of use for clinicians. However, it also presents a potential limitation, as the specific information contained within the precise MIC value can be lost. For instance, an organism with an MIC just below the susceptible breakpoint is categorized identically to an organism with an MIC many dilutions lower, yet the pharmacodynamic reserve and the probability of achieving effective drug concentrations at the site of infection might be substantially different. This inherent simplification in the S/I/R system lays the groundwork for exploring more granular interpretations of susceptibility data.

In an era characterized by the escalating threat of antimicrobial resistance (AMR) and the increasing prevalence of difficult-to-treat infections, the limitations of relying solely on S/I/R categorizations have become more apparent. There is a growing recognition that the quantitative MIC value itself, beyond its qualitative interpretation, may offer valuable insights for optimizing and individualizing antimicrobial therapy.[4] Indeed, studies have demonstrated that for certain pathogen-drug combinations, the actual MIC value can predict patient outcomes with greater accuracy than the broader categorical classifications (S, I, R) alone. For example, research involving cefepime treatment for *Pseudomonas aeruginosa* infections has shown that MIC values, even those falling within the "susceptible" range, can correlate with significantly different clinical outcomes.[6]

This drive for enhanced interpretation stems from the clinical observation that "susceptible" does not invariably mean "equally susceptible." An organism with an MIC at the upper limit of the susceptible range poses a different pharmacodynamic challenge compared to one with an MIC significantly below that threshold. This disparity is not adequately captured by the simple "S" designation. Consequently, there is an unmet need for tools or indices that can assist clinicians in gauging the degree of susceptibility or the margin of safety, particularly when managing high-risk patients, infections with high bacterial burdens, or infections caused by organisms nearing resistance. The global challenge of AMR further intensifies this need, compelling clinicians to maximize the efficacy of existing antimicrobial agents through more precise and informed therapeutic strategies. In this regard, this review was undertaken to critically review the role of a novel quotient that is becoming increasingly used in AST reports.

METHODOLOGY

We conducted a narrative review of peer-reviewed literature and authoritative guidance indexed in PubMed and Embase from January 2010 through June, 2025, using terms such as "breakpoint MIC quotient," "MIC-to-breakpoint ratio," "efficacy ratio," "AUC/MIC," "probability of target attainment," "CLSI/EUCAST breakpoints," and "MIC creep." We prioritized adult clinical outcome studies, PK/PD modelling and target-attainment analyses, and standards or guidance from CLSI, EUCAST, and the U.S. FDA; pediatric data and non-bacterial pathogens were included selectively when mechanistically informative. Reference lists of included articles and guidelines were hand-searched to identify additional sources; English-language sources were included, and non-peer-reviewed content was limited to regulatory or standards documents. This is a narrative (not systematic) review, and no formal risk-of-bias assessment or meta-analysis was performed.

ISSN: 3048-4510 (Online)
DOI: 10.62541/jaspi089

DEFINING - "BREAKPOINT MIC QUOTIENT" IN AST

A comprehensive search of the peer-reviewed literature did not yield a universally accepted, formal definition or standardized formulation for the term "Breakpoint MIC Quotient (BMQ)" as a distinct clinical index in antimicrobial susceptibility testing. Being an emerging concept, the term "Breakpoint to MIC Quotient" (BMQ) is used in a few texts, although few other texts use different terms such as the "MIC-to-breakpoint ratio", "Efficacy Ratio" and "Therapeutic index".[7,10]

In all these texts, organism's measured MIC is compared with the established susceptible clinical breakpoint for that specific drug-organism combination. For instance, a ratio could be expressed as: "Ratio = Breakpoint susceptible / observed MIC organism". A value approaching 1 would indicate an MIC close to the susceptible breakpoint, while a smaller fraction would suggest an MIC well below the breakpoint. Alternatively, the reciprocal (Breakpoint/MIC) could be used, where a larger value would be more favorable. The choice of which breakpoint category to use (e.g., susceptible vs. resistant) would also need careful consideration and standardization. The lack of a formal definition implies that if this concept is being utilized, it is likely on an informal basis or represents an area where a standardized tool is conceptually desired but not yet developed or widely adopted. The focus of this review, therefore, shifts to the underlying principle: the quantitative comparison of an MIC to its breakpoint and the implications thereof.

EMERGENCE OF BMQ USAGE

The fundamental concept of comparing an organism's MIC to an established breakpoint is, of course, not new; it is the very basis of the S/I/R categorization system used in AST for decades. However, the explicit focus on the *clinical significance* of where an MIC value falls *quantitatively relative* to its breakpoint, particularly for MICs within the "susceptible" range, appears to be a more contemporary development. This heightened interest is likely driven by an improved understanding of PK/PD principles and the increasing challenges posed by AMR. Evidence suggesting that "high" susceptible MICs (i.e., MICs close to the susceptible breakpoint) can be associated with poorer clinical outcomes has spurred greater attention to the actual MIC value.[6,11,12] One study notes that actual MICs have predicted patient outcomes more accurately than did the categorical classification, highlighting this evolving appreciation for the quantitative MIC.[6] Thus, while the act of comparing MIC to breakpoint is old, the formalization or explicit use of a ratio derived from this comparison as a supplementary interpretive tool seems to be an emerging or less-defined area, reflecting a more recent appreciation for the nuances within susceptibility categories.

THEORETICAL BASIS: RELATIONSHIP TO PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) PRINCIPLES

Any utility of an MIC/breakpoint ratio is fundamentally rooted in pharmacokinetic/pharmacodynamic (PK/PD) principles. Clinical breakpoints, when appropriately established, are themselves determined with consideration of PK/PD targets. A susceptible breakpoint implies that for organisms with MICs at or below this value, standard antimicrobial dosing regimens are expected to achieve the necessary PK/PD targets for efficacy (e.g., fT>MIC for beta-lactams, fAUC/MIC for fluoroquinolones and vancomycin, or fCmax/MIC for aminoglycosides).[4,13,14]

A Breakpoint MIC Quotient or an MIC-to-breakpoint ratio can therefore be conceptualized as a surrogate or simplified indicator of the likelihood of achieving these critical PK/PD targets.

- A low MIC relative to the breakpoint (resulting in a low MIC/Breakpoint ratio, e.g., 0.125 if MIC=1 mg/L and Breakpoint=8 mg/L) would suggest a greater probability of attaining the desired PK/PD target, potentially with a wider margin of safety. This implies a more robust likelihood of therapeutic success.

- A high MIC relative to the breakpoint (a ratio approaching 1, e.g., MIC=8 mg/L and Breakpoint=8 mg/L) indicates that the MIC is at the upper limit of susceptibility. This suggests a narrower margin for achieving PK/PD targets. In such cases, standard dosing might be insufficient, especially in patients with altered pharmacokinetics (e.g., critically ill patients with augmented renal clearance) or at infection sites with suboptimal drug penetration. This scenario could correlate with a higher risk of therapeutic failure or the need for optimized dosing strategies.[6,12]

The specific PK/PD index that best predicts efficacy varies by antibiotic class.[13] For time-dependent antibiotics like beta-lactams, the crucial parameter is the duration for which the free drug concentration remains above the MIC (fT>MIC). For concentration-dependent antibiotics like aminoglycosides, the ratio of peak free concentration to MIC (fCmax/MIC) is paramount, while for drugs like fluoroquinolones and vancomycin, the ratio of the area

under the free drug concentration-time curve to MIC (fAUC/MIC) is often the key determinant of efficacy.[4,14] An MIC-to-breakpoint ratio attempts to provide a simplified, readily calculable value that offers a general sense of this pharmacodynamic situation without requiring complex PK modelling or therapeutic drug monitoring for every patient. Its utility hinges on how well this simple ratio reflects the true probability of PK/PD target attainment across diverse drugs, pathogens, and patient populations, considering that the breakpoint itself is ideally set to ensure target attainment for MICs at that level with standard dosing. An MIC significantly lower than the breakpoint should, therefore, imply a higher probability of target attainment or a greater buffer against inter-patient pharmacokinetic variability.

CLINICAL RELEVANCE AND PREDICTIVE VALUE OF MICS RELATIVE TO BREAKPOINTS

The clinical interpretation of MIC values, particularly their magnitude in relation to established breakpoints, has garnered significant attention due to emerging evidence linking these quantitative measures to therapeutic outcomes. This clinical relevance of such comparisons is explored below and a summary of the explored studies is presented in Table 1.

Table 1: Summary of studies on the clinical impact of MIC values relative to breakpoints

Study (Author, Year)	Organism(s) & Antimicrobial(s)	MICs/Ratios investigated	Key Findings
Su et al. (2017)[6]	*P. aeruginosa* & Cefepime	Cefepime MIC <4 mg/L vs. ≥4 mg/L (susceptible breakpoint ≤8 mg/L)	MIC ≥4 mg/L associated with significantly lower 30-day survival (23.5% vs. 72.6%, p<0.0001) and was an independent risk factor for mortality. Maximal cefepime dose did not improve outcomes if MIC ≥4 mg/L.
Kullar et al. (2011)[12]	MRSA & Vancomycin	Vancomycin MIC >1 mg/L by Etest; Vancomycin AUC_{24h}/MIC<421	Vancomycin MIC >1 mg/L was an independent predictor of treatment failure. AUC24h/MIC<421 associated with significantly higher failure rates (61.2% vs. 48.6%, p=.038).
Arshad et al. (2020)[11]	MRSA & Vancomycin	Vancomycin MIC creep; MICs ≥1.5µg/mL (within susceptible range)	Review indicates that higher vancomycin MICs, even within susceptible limits (e.g., ≥1.5µg/mL), are associated with treatment failure, increased morbidity, and relapse. Study observed increasing geometric mean MIC over time.
FDA (2024)[16]	*P. aeruginosa* & Piperacillin-Tazobactam	Piperacillin-Tazobactam MICs ≥32/4 µg/mL	MICs ≥32/4 µg/mL associated with a clinical failure signal, unacceptably low Probability of Target Attainment (PTA), and increased mortality. Led to breakpoint revisions and recommendations for extended infusions for MICs of 16/4 µg/mL (SDD category).
Hill H (Thesis, Univ. of Liverpool) [18]	Gram-negative bacteria & Ciprofloxacin	Relatively higher MICs within the susceptible range; AUC_{24h}/MIC targets	Relatively higher MICs within susceptible range associated with greater risk of treatment failure (though not statistically significant in this study due to low incidence). Higher AUC_{24h}/MIC targets (>250) may be required for serious infections.
Zelenitsky et al (2010)[17]	Enterobacteriaceae & Ciprofloxacin	Ciprofloxacin AUC_{24}/MIC	An AUC_{24}/MIC breakpoint of 250 showed significantly higher cure rates (91.4% vs 28.6%) in patients with values above and below this threshold, respectively (P=0.001). Treatment failure risk was 28 times higher in those who don't achieve AUC_{24}/MIC ≥250 (P=0.011)

ISSN: 3048-4510 (Online)
DOI: 10.62541/jaspi089

Correlation with clinical outcomes: evidence for predicting therapeutic success or failure

Several studies have demonstrated that MIC values, even those categorized as "susceptible," can correlate with clinical success or failure, especially when the MIC approaches the breakpoint.

- Cefepime for *Pseudomonas aeruginosa*: A notable study by Su et al. (2017) investigated outcomes in patients with cefepime-susceptible *P. aeruginosa* bacteremia. Despite a CLSI susceptibility breakpoint of ≤8 mg/L, patients with isolates having a cefepime MIC <4 mg/L experienced significantly higher 30-day survival rates (72.6%) compared to those with MICs ≥4 mg/L (23.5%; p<0.0001). Furthermore, a cefepime MIC ≥4 mg/L was identified as an independent risk factor for mortality. This finding strongly suggests that within the "susceptible" range, the actual MIC value carries prognostic weight.[6]

- **Vancomycin for Methicillin-Resistant *Staphylococcus aureus* (MRSA):** The phenomenon of "vancomycin MIC creep"—a gradual increase in vancomycin MICs for MRSA isolates over time, even while remaining within the susceptible range—has raised concerns. Arshad et al. (2020) reviewed this issue, noting that higher vancomycin MICs (e.g., ≥1.5µg/mL), even if technically susceptible, have been associated with increased rates of treatment failure, morbidity, and relapse in MRSA infections.[11,15] Supporting this, Kullar et al. (2011) found that in patients with MRSA bacteremia, a vancomycin MIC >1 mg/L (as determined by E-test) was an independent predictor of vancomycin treatment failure. Their study also highlighted the importance of the PK/PD index AUC_{24h}/MIC, with ratios <421 being associated with significantly higher rates of failure.[12]

- Piperacillin-Tazobactam for *Pseudomonas aeruginosa*: Regulatory bodies have also acknowledged the impact of MIC values near breakpoints. The U.S. Food and Drug Administration (FDA) rationale for revising piperacillin-tazobactam breakpoints for *P. aeruginosa* cited a clinical failure signal for isolates with MICs ≥32/4 µg/mL. These MICs were associated with an unacceptably low probability of target attainment (PTA) and increased mortality, leading to adjustments in breakpoint definitions.[16]

- General Observations: For ciprofloxacin, it has been suggested that higher AUC_{24h}/MIC targets (e.g., >250) may be necessary for serious infections, and that relatively higher MICs within the susceptible category were linked to an increased risk of treatment failure.[17,18]

These examples consistently indicate that the categorical interpretation of "susceptible" may not fully capture the spectrum of clinical risk. An MIC value that is high yet still classified as susceptible can result in a less favorable outcome compared to a significantly lower MIC. This implies that a more granular measure, such as an MIC-to-breakpoint ratio, could serve as a valuable "warning flag," prompting clinicians to consider the potential for reduced efficacy even when faced with a "susceptible" report. Moreover, as a clinician, among multiple susceptible antimicrobials, which one to choose for the patient is still remains a mystery and this may be one of the driver for AMR and can be answered with BMQ.

APPLICATION IN GUIDING ANTIMICROBIAL DOSING AND REGIMEN OPTIMIZATION

Understanding the MIC relative to its breakpoint is not merely prognostic; it can actively inform therapeutic decisions, particularly regarding dosing strategies.

When an organism's MIC is high but still within the susceptible range, clinicians may consider several approaches to optimize therapy:

- **Higher Doses**: Administering higher doses of the antimicrobial (within safe limits) can increase drug exposure and improve the likelihood of achieving PK/PD targets.

- **Extended or Continuous Infusions**: For time-dependent antibiotics like beta-lactams, prolonging the infusion time (extended infusion) or administering the drug continuously can maximize the fT>MIC, which is particularly beneficial when MICs are elevated.[19] The FDA's revised guidance for piperacillin-tazobactam, for instance, recommends extended infusions to improve PTA for *P. aeruginosa* isolates with MICs of 16/4 µg/mL.[16]

- **PK/PD Target-Based Dosing**: For drugs like vancomycin, achieving a specific PK/PD target (e.g., an AUC/MIC ratio ≥400) is associated with improved outcomes, especially when dealing with higher MICs.[12]

However, the study by Su et al. (2017) on cefepime for *P. aeruginosa* also provides a crucial caveat: while a maximal cefepime dose was protective for isolates with

MICs <4 mg/L, it did not improve outcomes if the MIC was ≥4 mg/L. This suggests that there are limits to dose escalation, and if the MIC is too high (even if technically "susceptible"), simply increasing the dose may not overcome the reduced activity.[6]

The existence of the "susceptible dose-dependent" (SDD) category (utilized by CLSI) or EUCAST's "susceptible, increased exposure" (I) [A1] category inherently acknowledges the link between MIC level and the need for adjusted (often higher or optimized) dosing regimens to achieve clinical efficacy.[2,3,16] An MIC-to-breakpoint ratio could potentially offer a more continuous scale to refine such decisions, moving beyond discrete categories to provide a finer gradient of pharmacodynamic challenge.

POTENTIAL UTILITY IN SPECIFIC CLINICAL SCENARIOS

The value of a more refined interpretation of MICs, such as that offered by an MIC-to-breakpoint ratio, is likely amplified in specific clinical situations where the margin for therapeutic error is minimal:

- **Severe infections**: In patients with life-threatening conditions like bacteremia, sepsis, or severe pneumonia, achieving rapid and effective bacterial eradication is paramount. In these contexts, an MIC that is "susceptible but high" might be less tolerable, prompting more aggressive or alternative therapeutic strategies.[6]

- **Difficult-to-Treat organisms**: For pathogens notorious for their intrinsic or acquired resistance, such as *Pseudomonas aeruginosa* [6,16,20] or MRSA,[11,12] where therapeutic options can be limited, a precise understanding of the degree of susceptibility is vital for selecting the most appropriate and effective agent.

- **Immunocompromised patients**: Individuals with weakened immune systems rely more heavily on the bactericidal activity of antibiotics. For these patients, achieving robust PK/PD targets is crucial, making the MIC relative to the breakpoint a more critical consideration.

- **Infections at sites with poor drug penetration**: If an infection is located in a body compartment where antimicrobial penetration is limited (e.g., cerebrospinal fluid, abscesses, bone), higher systemic exposures are often required to achieve therapeutic concentrations at the site. In such cases, an MIC approaching the breakpoint for systemic concentrations may signal a high risk of failure due to insufficient local drug levels.

For a straightforward urinary tract infection in an otherwise healthy individual, a simple "susceptible" report is often adequate. However, for a complex case like ventilator-associated pneumonia caused by *P. aeruginosa* in an intensive care unit patient, knowing that the organism's MIC is "susceptible but high" (i.e., yielding a high MIC-to-breakpoint ratio) could significantly influence the choice of antibiotic, dosing regimen, or consideration of combination therapy.

ROLE IN ANTIMICROBIAL STEWARDSHIP: INFORMING DE-ESCALATION OR TARGETED THERAPY

The principles underlying an MIC-to-breakpoint ratio can also contribute to antimicrobial stewardship efforts.

- **Confidence in De-escalation**: A low MIC relative to the breakpoint (indicating a low, favorable ratio) for a narrower-spectrum antibiotic might provide greater confidence for de-escalating from broader empirical therapy, assuming the narrower agent is clinically appropriate for the infection type and site.

- **Re-evaluation of "susceptible" choices**: Conversely, if a chosen antibiotic, though reported as "susceptible," yields a high MIC-to-breakpoint ratio, stewardship programs might be prompted to re-evaluate if it is truly the optimal agent. An alternative "susceptible" agent with a more favorable (lower) ratio might be preferred, assuming other factors like spectrum of activity, toxicity profile, and cost are comparable.

- **Informing reporting strategies**: Cascade or selective reporting strategies, which are employed by microbiology laboratories to promote the judicious use of antimicrobials by preferentially reporting narrower-spectrum or more appropriate agents, could potentially incorporate logic based on MIC-to-breakpoint ratios.[21] For example, broader-spectrum agents might only be reported if narrower-spectrum options have unfavorable ratios or are resistant.

While current stewardship reporting strategies do not explicitly use a formal "Breakpoint MIC Quotient," the underlying principle of guiding antibiotic choice based on a better understanding of susceptibility aligns well with stewardship goals. An MIC-to-breakpoint ratio could add a quantitative dimension to these decisions, helping to refine de-escalation pathways and optimize antibiotic

Submit a Manuscript: https://jaspi.saspi.in/ ISSN: 3048-4510 (Online)
SASPI: https://saspi.in/ DOI: 10.62541/jaspi089

selection by providing a measure of the "pharmacodynamic reserve" or "margin of safety" for a given drug-bug combination.

ADVANTAGES OF EMPLOYING A BREAKPOINT MIC QUOTIENT OR SIMILAR RATIOS

The exploration of an MIC-to-breakpoint ratio or a similar quotient is driven by the potential benefits it could offer in refining antimicrobial therapy.

Potential for simplified interpretation of complex PK/PD data at the bedside

Comprehensive PK/PD modeling and routine therapeutic drug monitoring (TDM) are powerful tools for optimizing antibiotic therapy but are not universally available or easily implemented for every patient in all healthcare settings due to logistical constraints, cost, and the need for specialized expertise.[19] A simple, calculable ratio, such as MIC divided by the susceptible breakpoint, could offer a more accessible, although approximate, indicator of the underlying pharmacodynamic situation and the likelihood of achieving therapeutic targets. Such an index has the potential to bridge the gap between sophisticated PK/PD science conducted in research settings and the practical, time-sensitive decisions made at the patient's bedside.[19]

Enhanced risk stratification for patients

As detailed earlier, accumulating evidence suggests that patients infected with organisms demonstrating "high-susceptible" MICs—that is, MICs that are close to the susceptible breakpoint, which would yield a high MIC-to-breakpoint ratio—may be at an increased risk of adverse clinical outcomes, including treatment failure or mortality.[6,11,12] A numerically expressed MIC-to-breakpoint ratio could serve as a tool to more formally identify these higher-risk patients, even when the standard laboratory report categorizes the isolate as "susceptible." This early identification could prompt clinicians to institute more intensive monitoring, consider combination therapy if appropriate, or evaluate alternative treatment strategies with more favorable pharmacodynamic profiles.

Facilitating better therapeutic decisions beyond simple S/I/R categories

An MIC-to-breakpoint ratio could empower clinicians to "read between the lines" of a standard susceptibility report, promoting a better approach to therapeutic decisions. Quantitative MICs, when considered in this context, allow for greater individualization of therapy.[4] For instance, when choosing between multiple antimicrobial agents to which an organism is reported as "susceptible," the agent demonstrating a more advantageous (i.e., lower) MIC-to-breakpoint ratio might be preferred, assuming all other factors such as spectrum of activity, toxicity, and site penetration are comparable. Also, if an MIC-to-breakpoint ratio is high (e.g., the MIC is very close to the susceptible breakpoint), it might encourage clinicians to consider optimized dosing regimens, such as higher approved doses or extended infusions for time-dependent drugs like beta-lactams, to maximize the probability of achieving PK/PD targets.[16,19]

DISADVANTAGES, LIMITATIONS, AND CHALLENGES OF A BREAKPOINT MIC QUOTIENT OR SIMILAR RATIOS

Despite the potential advantages, the concept of using an MIC-to-breakpoint ratio as a clinical tool possesses significant disadvantages, limitations, and challenges that must be carefully considered.

Risk of oversimplification of intricate host-pathogen-drug interactions

Clinical outcome in infectious diseases is a complex interplay of numerous factors, including the patient's immune status, the site and severity of infection, the bacterial inoculum size, the presence of specific virulence factors, and the actual drug concentrations achieved at the infection site—which can be influenced by patient-specific pharmacokinetics.[14] Also, evidence is strongest only for select drug–bug pairs (e.g., cefepime–*Pseudomonas aeruginosa*; vancomycin–MRSA), and remains early or mixed elsewhere. [6,12] A single, numerically derived ratio based on an *in vitro* MIC and a population-derived breakpoint cannot encapsulate this multifaceted biological complexity. There is a substantial risk that such a ratio, if not interpreted with extreme caution and within the broader clinical context, could lead to misleading confidence (e.g., with a "low" ratio) or undue concern (e.g., with a "high" ratio). The MIC itself is an *in vitro* measurement performed under standardized laboratory conditions and has inherent limitations in its ability to predict *in vivo* efficacy perfectly; it is a summary measure of events in a test tube and does not account for drug degradation or the development of resistance during therapy within the patient.[13,14]

Impact of Inherent Mic Variability And Testing Precision On Quotient Reliability

Antimicrobial susceptibility testing, including the reference broth microdilution (BMD) method, is subject

to inherent variability. It is generally accepted that an MIC determination can vary by ±1 $\log_2$ dilution (i.e., one twofold dilution up or down) upon repeat testing of the same isolate.[20] This means a reported MIC of 4 mg/L could, on retesting, yield a result of 2 mg/L, 4 mg/L, or 8 mg/L. Such variability can profoundly impact any calculated MIC-to-breakpoint ratio, especially when the MIC is close to the clinical breakpoint. An isolate might appear to have a "favorable" ratio in one test run and an "unfavorable" one in another, merely due to the inherent imprecision of the MIC test method itself. For *Pseudomonas aeruginosa* tested against piperacillin-tazobactam, absolute agreement (exact MIC match) in one study was as low as 74%, although essential agreement (within ±1 $\log_2$ dilution) was higher at 94%.[20]

Several factors contribute to this MIC variability, including minor differences in inoculum concentration, specific operator techniques, variations in media composition, inherent properties of the bacterial strain, and the materials or processes used in testing.[20] The selection and magnitude of PK/PD indices have also been shown to be sensitive to uncertainties in MIC values,[13] a concern that would directly extend to any MIC-to-breakpoint ratio.

Dependence on the Accuracy and Clinical Relevance of Established Breakpoints

The utility of an MIC-to-breakpoint ratio is intrinsically linked to the accuracy and clinical relevance of the breakpoint value used as the denominator. Clinical breakpoints are not static; they are periodically reviewed and revised by authoritative bodies like CLSI and EUCAST as new data on MIC distributions, PK/PD relationships, resistance mechanisms, and clinical outcomes become available.[4] If a clinical breakpoint is not optimally set—meaning it does not accurately reflect clinically achievable PK/PD targets or reliably predict clinical outcomes for the intended patient population and dosing regimens—then any quotient derived from it will inherit these flaws.

Moreover, discrepancies can exist between the breakpoints set by different international or national agencies (e.g., CLSI versus EUCAST versus FDA) for the same drug-organism combination.[4] Such differences would inevitably lead to different MIC-to-breakpoint ratio values and potentially conflicting interpretations for an identical MIC result. An MIC-to-breakpoint ratio is, therefore, only as reliable as the breakpoint it references. For instance, if CLSI sets a susceptible breakpoint at ≤8 mg/L and EUCAST sets it at ≤4 mg/L for the same drug-organism pair, an MIC of 4 mg/L would yield a ratio of 0.5 according to CLSI criteria (appearing favorable) but 1.0 according to EUCAST criteria (appearing borderline). This lack of universal breakpoint harmonization complicates any attempt to implement a standardized MIC-to-breakpoint ratio.

Potential for Misinterpretation Without Adequate Clinical Context and PK/PD Understanding

A significant concern is the potential for misinterpretation of an MIC-to-breakpoint ratio if clinicians lack a thorough understanding of the underlying PK/PD principles, the inherent limitations of MIC testing, and the importance of overall clinical context. There is a risk of over-reliance on this single numerical value, potentially leading to inappropriate therapeutic decisions. A clinician might be falsely reassured by a "low" ratio in a complex patient with multiple risk factors for treatment failure, or conversely, might inappropriately withhold an otherwise effective therapy due to a "high" ratio despite other favorable clinical indicators. The recognized need for more sophisticated approaches like TDM or individualized dosing in many complex clinical situations, such as in critically ill patients or those with altered pharmacokinetics,[19,22] suggests that a simple ratio may often be insufficient.

APPLICABILITY ACROSS ORGANISMS AND ANTIMICROBIALS

The relevance and potential utility of an MIC-to-breakpoint ratio are likely to vary depending on the specific pathogen-drug combination and the characteristics of the organism.

Considerations for organisms with unique susceptibility profiles or testing challenges

The applicability of an MIC-to-breakpoint ratio is not universal and must consider the specific characteristics of the organism and the infection:

- **Intrinsic resistance**: For organisms that possess high levels of intrinsic resistance to a particular antimicrobial agent, their MICs will typically be well above any clinically relevant breakpoint. In such cases, the drug would not be considered a therapeutic option, rendering an MIC-to-breakpoint ratio irrelevant.

- **Slow-growing or fastidious organisms**: The determination of MICs for slow-growing or fastidious bacteria can be more technically challenging and may exhibit greater inter-laboratory

Submit a Manuscript: https://jaspi.saspi.in/ ISSN: 3048-4510 (Online)
SASPI: https://saspi.in/ DOI: 10.62541/jaspi089

variability.[20] This increased variability in the primary MIC measurement would amplify the uncertainty and reduce the reliability of any derived MIC-to-breakpoint ratio.

- **Biofilm-associated infections**: Standard MIC testing is performed on planktonic (free-floating) bacteria. However, many chronic infections involve bacteria growing within biofilms, where they can exhibit significantly increased tolerance to antimicrobial agents (phenotypic resistance) not reflected by standard MICs. An MIC-to-breakpoint ratio based on planktonic MICs would likely have limited predictive value for the efficacy of treatment against biofilm-associated infections.

- **Heteroresistance**: Some bacterial populations may exhibit heteroresistance, where a small subpopulation of cells possesses significantly higher MICs than the majority of the population. Standard MIC testing methods may not reliably detect these resistant subpopulations. Consequently, treatment failure can occur even if the bulk population MIC suggests a favorable MIC-to-breakpoint ratio. The issue of heteroresistant vancomycin-intermediate *S. aureus* (hVISA) is an example of this challenge.[12]

CONCLUSION

The concept of using an MIC-to-breakpoint ratio, while theoretically appealing for refining antimicrobial therapy, faces substantial hurdles regarding its current status, practical implementation, and the need for further scientific validation. A suggested roadmap is standardization of definition and formula, interpretive thresholds and reporting formats, framing clinical use guardrails and establishing validation and implementation protocols. Additionally, they need to be integrated into existing Laboratory Information Systems (LIS) and clinical workflows.

Also, the current body of evidence regarding the clinical significance of MIC values relative to breakpoints is largely derived from retrospective observational studies or analyses of existing datasets. While these studies are valuable for generating hypotheses and identifying associations, they do not definitively prove the clinical utility of prospectively calculating and acting upon a formal MIC-to-breakpoint ratio. There is a pressing need for rigorous validation studies, including: well-designed prospective clinical trials, effectiveness research comparing therapeutic decisions and patient outcomes and Head-to-Head comparisons of utility, practicality, and cost-effectiveness of using an MIC-to-breakpoint ratio against other established or emerging methods for therapy optimization, such as TDM or PTA calculations.

Despite the challenges, this holds significant promise for refining clinical decisions by offering a simplified indicator of the likelihood of achieving PK/PD targets, thereby helping to stratify patient risk and guide dosing optimization, especially in cases where an organism's MIC is high yet still within the susceptible range.

Authors' Contributions:

ED: Conceptualization; Data curation; Literature review, Analysis; Writing the draft

JR: Data curation; Literature review, Analysis; Writing the draft

MV: Supervision, Validation, Review & editing.

ACKNOWLEDGEMENT

Nil

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

SOURCE OF FUNDING

None

DECLARATION FOR THE USE OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) IN SCIENTIFIC WRITING

Grammarly was used for refining the sentences (language and grammar correction) in certain sections.

REFERENCES

1. Paula C Mister, Donald C Lehman. Antimicrobial susceptibility testing. In: Mahon CR, Lehman DC, editors. Textbook of diagnostic microbiology. St. Louis, MO: Elsevier; 2023. page 271–307.
2. Barbara L. Zimmer, Darcie E. Carpenter, German Esparza, Kevin Alby, Amelia Bhatnagar, Andrea L. Ferrell, et al. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 12th edition. Wayne, Pennsylvania: Clinical Laboratory Standards Institute; 2024.
3. EUCAST. Clinical breakpoints - breakpoints and guidance [Internet]. EUCAST: Clinical breakpoints and dosing of antibiotics [cited 2025 Jun 6];Available from: https://www.eucast.org/clinical_breakpoints

ISSN: 3048-4510 (Online)
DOI: 10.62541/jaspi089

4. Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev 2007;20(3):391–408, table of contents.
5. Kahlmeter G, Turnidge J. How to: ECOFFs—the why, the how, and the don'ts of EUCAST epidemiological cutoff values. Clin Microbiol Infect 2022;28(7):952–4.
6. Su TY, Ye JJ, Yang CC, Huang CT, Chia JH, Lee MH. Influence of borderline cefepime MIC on the outcome of cefepime-susceptible Pseudomonas aeruginosa bacteremia treated with a maximal cefepime dose: a hospital-based retrospective study. Ann Clin Microbiol Antimicrob 2017;16:52.
7. Sabu P, Elangovan D, Pragasam AK, Bakthavatchalam YD, Rodrigues C, Chitnis DS, et al. Efficacy ratio: A tool to enhance optimal antimicrobial use for intra-abdominal infections. Indian J Pharmacol 2018;50(6):332–5.
8. Grillon A, Chabaud A, Zambardi G, Caniaux I, Jehl F. Breakpoint to MIC quotient: A parameter to rapidly evaluate the in vitro bactericidal activity of β-lactams on Enterobacteriaceae. Int J Antimicrob Agents. 2019;53(5):674–7.
9. Dhandapani S, Priyadarshi K, Rajshekar D, Sivaradjy M, Madigubba H, Sastry AS. The role of cascade reporting integrated with breakpoint to minimum inhibitory concentration quotient (minimum inhibitory concentration therapeutic index) and minimum inhibitory concentration guiding table on clinical microbiology reporting of culture-proven bloodstream infections. J of Curr Res in Sci Med 2023;9(2):104.
10. Evans RN, Harris J, Rogers CA, MacGowan AP. The relationship between minimum inhibitory concentration and 28 day mortality in patients with a Gram-negative bloodstream infection: an analysis of data from a cohort study (BSI-FOO). JAC Antimicrob Resist 2022;5(1):dlad009.
11. Arshad F, Saleem S, Jahan S, Tahir R. Assessment of Vancomycin MIC Creep Phenomenon in Methicillin-Resistant Staphylococcus aureus isolates in a Tertiary Care Hospital of Lahore. Pak J Med Sci 2020;36(7):1505–10.
12. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant Staphylococcus aureus Bacteremia: Support for Consensus Guidelines Suggested Targets. Clin Infect Dis 2011;52(8):975–81.
13. Nielsen EI, Cars O, Friberg LE. Pharmacokinetic/Pharmacodynamic (PK/PD) Indices of Antibiotics Predicted by a Semimechanistic PKPD Model: a Step toward Model-Based Dose Optimization. Antimicrob Agents Chemother 2011;55(10):4619–30.
14. Rodríguez-Gascón A, Solinís MÁ, Isla A. The Role of PK/PD Analysis in the Development and Evaluation of Antimicrobials. Pharmaceutics 2021;13(6):833.
15. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant Staphylococcus aureus bacteremia. J Clin Microbiol 2004;42(6):2398–402.
16. Research C for DE and. FDA Rationale for Piperacillin Tazobactam Breakpoints for Pseudomonas aeruginosa. FDA [Internet] 2024 [cited 2025 Jun 6];Available from: https://www.fda.gov/drugs/development-resources/fda-rationale-piperacillin-tazobactam-breakpoints-pseudomonas-aeruginosa
17. Zelenitsky SA, Ariano RE. Support for higher ciprofloxacin AUC24/MIC targets in treating Enterobacteriaceae bloodstream infection. J Antimicrob Chemother. 2010;65(8):1725–32.
18. Helen Christina Hill. Ciprofloxacin Therapy for Neonates and Young Infants: A Clinical Pharmacological Perspective including Pharmacokinetics (PK) and Pharmacodynamics (PD) [Internet]. 2016 [cited 2025 Jun 6];Available from: https://livrepository.liverpool.ac.uk/3001728/1/200119314_April2016.pdf
19. Abdul-Aziz MH, Alffenaar JWC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med 2020;46(6):1127–53.
20. Bhalodi AA, Oppermann N, Campeau SA, Humphries RM. Variability of Beta-Lactam Broth Microdilution for Pseudomonas aeruginosa. Antimicrob Agents Chemother 65(10):e00640-21.
21. Cunney R. Interpretative reporting and selective antimicrobial susceptibility release in non-critical microbiology results. J Antimicrob Chemother. 2000;45(5):705–8.
22. Pais GM, Chang J, Barreto EF, Stitt G, Downes KJ, Alshaer MH, et al. Clinical Pharmacokinetics and Pharmacodynamics of Cefepime. Clin Pharmacokinet 2022;61(7):929–53.