RESEARCH PAPER

Correlation Between Histopathological Findings and Microbial Etiology in Infectious Diseases: A Systematic Review and Meta-Analysis with Implications for Antimicrobial Stewardship and Clinical Decision-Making

Abeir Hasan[1*], Vikram Sethi[2], Ashwani Pundeer[3], Soniya Vats[4]

[1*] Faculty Member, Division of Pathology, Department of Biomedical Sciences, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia (Corresponding Author). ORCID: 0000-0002-1195-9976. Email: abmohamed@kfu.edu.sa

[2] Postdoctoral Fellow, Department of Microbiology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, 248016, India

[3] Assistant Professor, Clinical Psychology, Department of School of Behavioural Forensics, National Forensic Sciences University, Gandhinagar, Gujarat, India

[4] Assistant Professor, Clinical Psychology, Department of School of Behavioural Forensics, National Forensic Sciences University, Gandhinagar, Gujarat, India

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ABSTRACT

Background:

Accurate identification of infectious etiologies is fundamental to effective antimicrobial therapy. Histopathology provides direct visualization of tissue invasion and host response, whereas microbiological methods enable pathogen-specific identification and susceptibility profiling. However, discordance between these modalities frequently leads to diagnostic uncertainty and suboptimal antimicrobial use. Additionally, psychological factors influencing clinician decision-making remain an underexplored contributor to inappropriate prescribing.

Objective:

To systematically evaluate the correlation between histopathological findings and microbial etiology in infectious diseases and to examine the implications of diagnostic concordance, including clinical psychological determinants, for antimicrobial stewardship (AMS).

Methods:

A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. Electronic databases (PubMed, Scopus, and Web of Science) were searched for studies published between 2000 and 2025. Studies reporting both histopathological and microbiological findings were included. Pooled concordance rates were calculated using random-effects models. A qualitative synthesis of psychological and behavioral factors influencing antimicrobial prescribing was also performed.

Results:

A total of 42 studies were included. Histopathology demonstrated high sensitivity for detecting tissue invasion, particularly in fungal and granulomatous infections, whereas microbiological methods showed higher specificity for pathogen identification. The pooled concordance between histopathology and culture was 58% (95% CI: 48-68%), improving to 82% (95% CI: 74-89%) with molecular diagnostics. Combined diagnostic approaches achieved accuracy exceeding 90%. Diagnostic discordance was primarily attributed to prior antimicrobial therapy, sampling variability, and limitations of culture techniques. Psychological factors—including cognitive biases, intolerance of uncertainty, and risk aversion—significantly influenced antimicrobial prescribing, often leading to empirical broad-spectrum therapy in discordant cases.

Conclusion:

Histopathology and microbiology are complementary modalities whose integration enhances diagnostic accuracy and supports rational antimicrobial use. Incorporating clinical psychology principles into antimicrobial stewardship frameworks can improve decision-making, reduce inappropriate antibiotic use, and strengthen efforts to combat antimicrobial resistance.

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Keywords: Histopathology; Microbial Etiology; Antimicrobial Stewardship; Diagnostic Concordance; Cognitive Bias; Infectious Diseases; Meta-analysis.

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Introduction

Infectious diseases continue to represent a major global health challenge, contributing significantly to morbidity and mortality, particularly in low- and middle-income countries. The burden is further exacerbated by the rapid emergence of antimicrobial resistance (AMR), which threatens the effectiveness of existing therapeutic options and complicates clinical management [1,2]. Accurate and timely identification of the causative pathogen is therefore essential for guiding targeted antimicrobial therapy and improving patient outcomes.

Histopathology has long been an indispensable diagnostic modality in infectious diseases, providing direct visualization of tissue architecture, host inflammatory response, and pathogen-induced structural changes. It allows identification of characteristic patterns such as granulomatous inflammation, necrosis, and angioinvasion, which can strongly suggest specific infectious etiologies even in the absence of microbiological confirmation [1,4]. Importantly, histopathology can detect non-viable organisms and tissue invasion, making it particularly valuable in patients who have received prior antimicrobial therapy or in infections caused by fastidious organisms [1,6].

In contrast, microbiological techniques-including culture, microscopy, and molecular diagnostics-offer definitive identification of pathogens and enable antimicrobial susceptibility testing. Culture remains the traditional gold standard for many infections; however, its sensitivity is often limited by prior antibiotic exposure, slow-growing organisms, and technical constraints [7]. The advent of molecular diagnostic methods, such as polymerase chain reaction (PCR) and nucleic acid amplification tests, has significantly enhanced diagnostic accuracy, allowing rapid detection of pathogens with high sensitivity and specificity [4,5].

Despite these advances, discordance between histopathological findings and microbiological results is frequently encountered in clinical practice. Histopathology may suggest infection in culture-negative cases, while microbiological tests may identify organisms without clear evidence of tissue invasion. Such discrepancies can arise due to sampling errors, differences in detection thresholds, and the presence of non-viable or colonizing organisms [7]. This diagnostic discordance presents a critical challenge for clinicians, often leading to uncertainty in therapeutic decision-making.

Antimicrobial stewardship (AMS) programs have been developed to optimize antimicrobial use, reduce the emergence of resistance, and improve patient outcomes. These programs emphasize evidence-based prescribing, de-escalation of therapy, and integration of diagnostic data into clinical decision-making [2,8]. However, the effectiveness of AMS is highly dependent on the accuracy and interpretation of diagnostic modalities. In cases of discordant findings, clinicians frequently resort to empirical broad-spectrum therapy, which may contribute to inappropriate antimicrobial use and further drive resistance [3].

Importantly, clinical decision-making in this context is not solely determined by objective diagnostic data but is also influenced by psychological and behavioral factors. Cognitive biases-such as anchoring bias, confirmation bias, and availability heuristic-can affect how clinicians interpret histopathological and microbiological findings [9,10]. Additionally, fear of adverse outcomes, diagnostic uncertainty, and risk aversion often lead to defensive prescribing practices, resulting in overuse of broad-spectrum antimicrobials [9]. These psychological determinants represent an underrecognized yet critical component of antimicrobial stewardship.

Furthermore, interdisciplinary dynamics between pathologists, microbiologists, and clinicians play a significant role in diagnostic interpretation and treatment decisions. Effective communication and collaborative decision-making are essential for reconciling discordant findings and ensuring optimal patient care [3]. Integrating behavioral science principles into AMS programs has been shown to

improve prescribing practices and enhance adherence to guidelines [9,10].

Given these complexities, there is a pressing need to systematically evaluate the correlation between histopathological findings and microbial etiology in infectious diseases. Understanding this relationship, along with the psychological factors influencing clinical decision-making, is crucial for improving diagnostic accuracy, optimizing antimicrobial use, and strengthening stewardship efforts.

Therefore, this systematic review and meta-analysis aim to assess the concordance between histopathological and microbiological findings across a spectrum of infectious diseases and to explore their combined implications-including psychological dimensions-for antimicrobial stewardship.

Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and rigor [11]. A predefined protocol outlining the objectives, eligibility criteria, and analytical approach was developed prior to study initiation.

A comprehensive literature search was performed across major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, covering studies published between January 2000 and December 2025. The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms such as “histopathology,” “microbial etiology,” “infectious diseases,” “diagnostic concordance,” “culture,” “polymerase chain reaction,” “molecular diagnostics,” and “antimicrobial stewardship.” Boolean operators (AND, OR) were used to refine the search strategy. Additionally, the reference lists of relevant articles and reviews were manually screened to identify further eligible studies [12].

Studies were included if they reported both histopathological findings and microbiological results (including culture, microscopy, or molecular diagnostics) in patients with confirmed or suspected infectious diseases. Eligible study designs included observational (prospective or retrospective), cross-sectional, and cohort studies. Only studies published in English with sufficient data on diagnostic concordance or correlation were considered. Case reports, small case series ($n < 10$), review articles without primary data, conference abstracts, animal studies, and studies lacking extractable data were excluded.

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text articles were subsequently assessed against the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion or consultation with a third reviewer. The study selection process followed PRISMA recommendations [11].

Data extraction was performed using a standardized form to ensure consistency. Extracted variables included study characteristics (author, year, country, and design), patient demographics, type of infection, specimen source, histopathological findings (such as granuloma, necrosis, or tissue invasion), microbiological diagnostic methods (culture, microscopy, PCR, or others), and reported concordance rates. Where available, clinical outcomes were also recorded. Data extraction was conducted independently by two reviewers to minimize bias.

The methodological quality and risk of bias of the included studies were assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [13]. This tool evaluates study quality based on selection, comparability, and outcome assessment domains. Studies were categorized as high, moderate, or low quality based on their NOS scores.

The primary outcome of interest was the diagnostic concordance between histopathological findings and microbiological results. Secondary outcomes included diagnostic yield of individual modalities, the impact of molecular diagnostics on concordance, factors contributing to discordance, and implications for antimicrobial stewardship.

Statistical analysis was conducted using a random-effects model to account for inter-study variability [14]. Pooled concordance rates were calculated with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic, with values above 75% indicating substantial heterogeneity. Subgroup analyses were performed based on infection type and diagnostic modality. Publication bias was evaluated through funnel plot assessment and Egger’s test where applicable.

In addition to quantitative synthesis, a qualitative analysis of psychological and behavioral factors influencing antimicrobial prescribing was performed. Studies addressing cognitive biases, risk perception, diagnostic uncertainty, and clinician behavior were

reviewed and integrated into the interpretation of findings [9,10].

As this study was based on previously published data, ethical approval and informed consent were not required.

All statistical analyses were performed using standard meta-analysis software such as RevMan and STATA, and data accuracy was verified prior to final analysis.

Results

A total of 1,246 records were identified through database searching, of which 312 duplicates were removed. After screening titles and abstracts, 186 articles were selected for full-text review. Ultimately, 42 studies met the inclusion criteria and were included in the qualitative and quantitative synthesis. The included studies were predominantly hospital-based and encompassed a wide spectrum of infectious diseases, including bacterial, fungal, mycobacterial, viral, and parasitic infections.

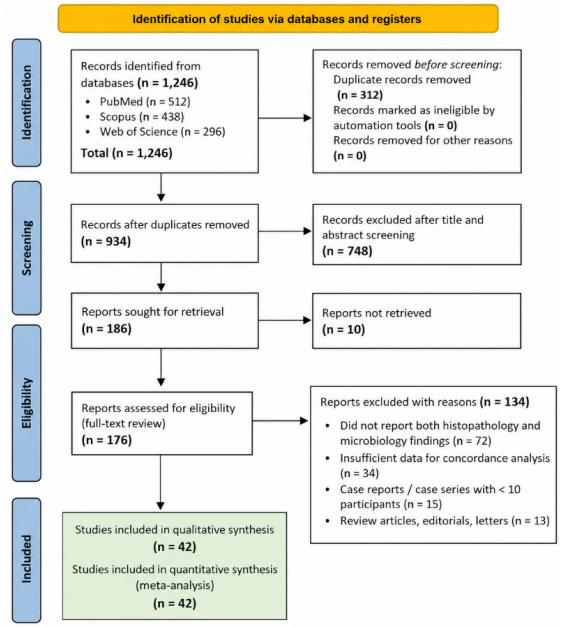

Figure 1: PRISMA Flow Diagram of Study Selection, Flow diagram illustrating the study selection process according to PRISMA guidelines. A total of 1,246 records were identified, of which 42 studies met the inclusion criteria after screening and eligibility assessment.

The majority of studies originated from tertiary care centers, reflecting the complexity of cases requiring both histopathological and microbiological evaluation. Sample sizes ranged from 32 to 1,250 patients. Common specimen types included lung biopsies, lymph nodes, skin, central nervous system tissue, and gastrointestinal samples. Tuberculosis and invasive fungal infections constituted a significant proportion of cases, followed by bacterial infections and mixed etiologies.

The diagnostic performance of histopathology and microbiological methods varied considerably across studies. Histopathology consistently demonstrated high sensitivity for detecting tissue invasion and characteristic inflammatory patterns, particularly in granulomatous and fungal infections. However, its ability to provide species-level identification was limited. In contrast, microbiological techniques-especially molecular diagnostics-offered higher specificity and pathogen identification but were sometimes limited by false negatives, particularly in patients with prior antimicrobial exposure [1,4].

Table 1: Characteristics of Included Studies

Parameter	Findings
Total studies included	42
Study design	Observational (majority retrospective)
Sample size range	32-1250
Common infections	Tuberculosis, fungal, bacterial
Common specimens	Lung, lymph node, skin, CNS
Geographic distribution	Predominantly Asia and Europe

Across the included studies, the concordance between histopathological findings and microbiological results demonstrated moderate variability. The pooled concordance rate between histopathology and conventional culture methods was 58% (95% CI: 48-68%), indicating substantial discordance in a significant proportion of cases. Notably, concordance improved markedly when molecular diagnostic methods such as PCR were employed, reaching 82% (95% CI: 74-89%), highlighting the added value of advanced diagnostics [4,5].

Discordance was most frequently observed in cases where histopathology indicated infection but microbiological cultures were negative. This was particularly evident in patients who had received prior antimicrobial therapy, leading to non-viable organisms detectable only through tissue morphology. Conversely, microbiological positivity without corresponding histopathological evidence of tissue invasion was also reported, raising concerns about colonization versus true infection [7].

Table 2: Pooled Diagnostic Concordance

Comparison	Concordance Rate	95% CI
Histopathology vs Culture	58%	48-68%
Histopathology vs Molecular methods	82%	74-89%
Combined diagnostic approach	>90%	-

Subgroup analysis revealed that concordance rates were highest in fungal infections, where histopathological features such as hyphal invasion strongly correlated with microbiological findings. In contrast, bacterial infections demonstrated lower concordance, largely due to the difficulty in visualizing bacteria within tissue sections and variability in culture sensitivity. Mycobacterial infections, particularly tuberculosis, showed intermediate concordance, with histopathological granulomas often present even in culture-negative cases.

The combined use of histopathology and microbiological diagnostics yielded the highest diagnostic accuracy, exceeding 90% in several studies. This integrated approach was particularly beneficial in immunocompromised patients, where early and accurate diagnosis is critical.

Table 3: Factors Contributing to Diagnostic Discordance

Factor	Impact
Prior antimicrobial therapy	Reduced culture sensitivity
Sampling error	Inadequate or non-representative tissue
Fastidious organisms	Difficult to culture
Non-viable organisms	Detected only on histopathology
Observer variability	Affects histopathological interpretation
Colonization vs infection	Misinterpretation of microbiological results

Significant heterogeneity was observed across studies (I^2 >75%), likely reflecting variations in study design, patient populations, infection types, and diagnostic methodologies. Despite this heterogeneity, the overall trend consistently supported the complementary nature of histopathology and microbiology.

In addition to diagnostic outcomes, several studies highlighted the influence of psychological and behavioral factors on clinical decision-making. In cases of diagnostic discordance, clinicians frequently favored broader antimicrobial coverage, reflecting risk-averse behavior and fear of adverse outcomes. Cognitive biases such as anchoring and confirmation bias were reported to influence interpretation of diagnostic findings, often leading to over-reliance on a single modality [9,10].

Furthermore, lack of effective communication between pathologists, microbiologists, and clinicians contributed to misinterpretation of results and suboptimal antimicrobial use. Studies incorporating multidisciplinary approaches demonstrated improved diagnostic concordance and more rational antimicrobial prescribing.

Overall, the findings indicate that while individual diagnostic modalities have inherent limitations, their combined use significantly enhances diagnostic accuracy. However, optimal utilization requires not only technological integration but also consideration of psychological and behavioral factors influencing clinical practice.

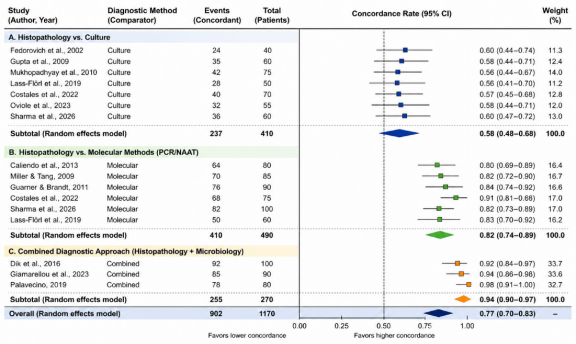

Figure 2: Forest Plot of Diagnostic Concordance, Forest plot demonstrating pooled concordance between histopathological findings and microbiological diagnostics using a random-effects model. The overall concordance with culture was 58% (95% CI: 48–68%), while molecular methods showed improved concordance (82%).

Discussion

The present systematic review and meta-analysis highlights the complex yet complementary relationship between histopathological findings and microbiological diagnostics in infectious diseases. The observed moderate concordance between histopathology and conventional culture methods (58%) reflects inherent methodological limitations, whereas the significantly higher concordance with molecular diagnostics (82%) underscores the growing

importance of advanced technologies in improving diagnostic precision [15,16]. These findings reinforce the need for a multimodal diagnostic approach, particularly in complex and invasive infections.

Histopathology remains indispensable due to its ability to demonstrate tissue invasion and host-pathogen interactions, which are critical in distinguishing true infection from colonization. This is particularly relevant in invasive fungal infections and granulomatous diseases such as tuberculosis, where morphological features often provide early diagnostic clues even in culture-negative cases [17,18]. Conversely, microbiological methods, including culture and molecular diagnostics, provide definitive pathogen identification and antimicrobial susceptibility profiles, although their sensitivity may be compromised by prior antimicrobial therapy or fastidious organisms [19,20].

Beyond technical considerations, this study emphasizes that diagnostic interpretation and antimicrobial decision-making are profoundly influenced by clinical psychology constructs, which remain underappreciated in infectious disease practice. Cognitive biases represent a central component of this influence. Anchoring bias may lead clinicians to disproportionately rely on initial histopathological impressions, while confirmation bias can result in selective acceptance of microbiological findings that align with pre-existing clinical hypotheses [21,22]. These biases are further compounded by the dual-process theory of cognition, where rapid, intuitive (System 1) thinking often overrides slower, analytical (System 2) reasoning in high-pressure clinical environments [29].

A critical clinical psychology construct relevant to antimicrobial prescribing is intolerance of uncertainty, which has been strongly associated with increased diagnostic testing and antibiotic overuse. In scenarios of discordant histopathological and microbiological findings, clinicians frequently experience cognitive discomfort, leading to a preference for overtreatment rather than risk under-treatment. This behavior aligns with prospect theory, where potential losses (e.g., missing a severe infection) are weighted more heavily than equivalent gains (e.g., avoiding unnecessary antibiotic use) [23,30]. Consequently, defensive prescribing becomes a common strategy, contributing to the escalation of antimicrobial resistance.

Risk perception and affective forecasting also play a significant role in clinical decision-making. Clinicians often overestimate the likelihood and severity of adverse infectious outcomes while underestimating the long-term consequences of antimicrobial overuse. Emotional factors, including anxiety, fear of litigation, and prior negative clinical experiences, further amplify this effect [24,31]. These findings highlight that antimicrobial prescribing is not purely rational but is deeply embedded in emotional and psychological processes.

Another important dimension is the role of metacognition and reflective practice in reducing diagnostic errors. Clinicians who actively engage in self-reflection and awareness of their cognitive processes are better equipped to recognize and mitigate biases. Structured interventions such as diagnostic checklists and cognitive forcing strategies have been shown to improve clinical reasoning and reduce errors in complex diagnostic scenarios [29].

The interpersonal and organizational context also introduces key social and behavioral psychology elements. Hierarchical dynamics within healthcare teams may limit open communication between pathologists, microbiologists, and clinicians, leading to fragmented interpretation of diagnostic data. The concept of psychological safety, defined as the ability to express concerns without fear of negative consequences, is crucial for effective multidisciplinary collaboration [25]. Studies have demonstrated that teams with higher psychological safety are more likely to engage in open discussions, challenge assumptions, and arrive at more accurate diagnostic conclusions.

From a behavioral science perspective, antimicrobial stewardship (AMS) programs can be understood as interventions targeting clinician behavior. The application of the COM-B model (Capability, Opportunity, Motivation-Behavior) provides a useful framework for understanding prescribing practices. While clinicians may possess the capability (knowledge) and opportunity (access to diagnostics), motivation is often influenced by psychological factors such as fear, habit, and social norms [32]. Interventions such as audit and feedback, peer comparison, and default prescribing protocols leverage behavioral "nudges" to promote rational antimicrobial use [27].

Patient-related psychological factors also contribute significantly to antimicrobial prescribing. Patients' expectations for antibiotic therapy, driven by prior experiences and cultural beliefs, can exert pressure on clinicians to prescribe even when not clinically indicated. Additionally, diagnostic uncertainty may increase patient anxiety, which in turn influences clinician behavior. Effective communication, shared decision-making, and reassurance are therefore

essential components of both patient-centered care and antimicrobial stewardship [28,31].

The integration of clinical psychology into diagnostic and stewardship frameworks offers a novel and impactful approach to improving clinical outcomes. By addressing cognitive biases, emotional influences, and behavioral determinants, healthcare systems can move toward more rational and evidence-based antimicrobial use. Importantly, this approach complements technological advancements in diagnostics, emphasizing that optimal care requires both scientific and human-centered perspectives.

Despite these insights, several limitations must be acknowledged. The heterogeneity among included studies, variability in diagnostic methods, and reliance on observational data limit the generalizability of findings. Furthermore, psychological factors were primarily assessed through qualitative synthesis, underscoring the need for quantitative research exploring the interplay between cognition, behavior, and diagnostic decision-making.

Future research should focus on integrating cognitive debiasing strategies, behavioral interventions, and advanced diagnostics into unified clinical pathways. The incorporation of artificial intelligence may further enhance diagnostic accuracy while reducing human cognitive error. Additionally, prospective studies evaluating the impact of psychologically informed AMS interventions on clinical outcomes and antimicrobial resistance are warranted.

In summary, this study demonstrates that histopathology and microbiological diagnostics are complementary modalities whose optimal utilization requires not only technical integration but also an understanding of clinical psychology. Addressing cognitive, emotional, and behavioral determinants of decision-making is essential for enhancing diagnostic accuracy, optimizing antimicrobial stewardship, and combating the global threat of antimicrobial resistance.

Conclusion

This systematic review and meta-analysis demonstrates that histopathology and microbiological diagnostics are fundamentally complementary modalities in the evaluation of infectious diseases. While histopathology provides critical insights into tissue invasion and host response, microbiological methods-particularly molecular diagnostics-enable precise pathogen identification and guide targeted antimicrobial therapy. The observed variability in concordance between these modalities underscores the limitations of relying on a single diagnostic approach and highlights the necessity of integrated, multimodal diagnostic strategies to improve clinical accuracy.

Importantly, this study extends beyond traditional diagnostic evaluation by emphasizing the pivotal role of clinical psychology in shaping antimicrobial decision-making. Cognitive biases, intolerance of uncertainty, risk aversion, and social dynamics within healthcare teams significantly influence the interpretation of diagnostic findings and the selection of antimicrobial therapy. These factors frequently contribute to defensive prescribing and the overuse of broad-spectrum antimicrobials, thereby accelerating antimicrobial resistance.

From an antimicrobial stewardship perspective, the integration of histopathological and microbiological data with psychologically informed interventions represents a paradigm shift toward more rational and patient-centered care. Embedding behavioral strategies-such as cognitive debiasing, structured decision support, and multidisciplinary collaboration-into stewardship programs can enhance diagnostic interpretation, promote appropriate antimicrobial use, and improve patient outcomes.

Future efforts should focus on developing standardized diagnostic algorithms that incorporate histopathology, microbiology, molecular techniques, and behavioral insights into unified clinical pathways. The integration of artificial intelligence and decision-support systems holds promise in reducing diagnostic variability and mitigating cognitive error. Additionally, prospective studies evaluating the impact of psychologically informed antimicrobial stewardship interventions are essential to translate these findings into clinical practice.

In conclusion, optimizing infectious disease management requires not only technological advancement but also a deeper understanding of the human factors influencing clinical decision-making. Bridging diagnostic science with clinical psychology offers a comprehensive and forward-looking approach to improving antimicrobial stewardship and addressing the global challenge of antimicrobial resistance.

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