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Ten Clinical Pearls in Microbiology: How Effective Collaboration Optimizes Patient Care

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ABSTRACT

Medical microbiology laboratories play an essential role in patient care—appertaining to infectious diseases diagnostics and treatment, infection prevention, and antimicrobial stewardship. Collaboration between clinicians and the microbiology laboratory can promote and enhance the safety, quality, and efficiency of patient care. We review practical, evidence-informed core concepts to explicate how effective partnership between clinicians and the microbiology laboratory improves patient outcomes.

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INTRODUCTION

Optimizing infectious diseases clinical care requires applying detailed knowledge from both clinical and laboratory sciences, alongside epidemiological principles and understanding of host-pathogen interactions. The microbiology laboratory plays a pivotal role by providing accurate and timely diagnostic and therapeutic data, which are essential for preventing, diagnosing, and treating infectious diseases. We review key concepts within the sphere of the microbiology laboratory that have immediate implications for clinicians who provide direct patient care.

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CLINICIANS HAVE A KEY ROLE IN PREVENTING PREANALYTICAL LABORATORY ERROR

The growing dependence on accurate laboratory data in clinical decision-making processes has magnified the entity of laboratory errors. Laboratory errors are categorized into preanalytical, analytical, and postanalytical domains, with pre- and postanalytic errors contributing to nearly three-quarters of errors (Table 1).[1-3] Preanalytical errors can occur prior to specimen collection (eg, patient misidentification), during specimen collection (eg, inadequate specimen volume collection or use of an inappropriate collection container), or after specimen collection (eg, specimen mislabeling).

The preanalytic phase occurs outside the laboratory and is usually performed by individuals with varying levels of quality-control training. Specimens of poor quality, including those that do not meet the requirements within the laboratory procedure manual, are rejected. Improper specimen collection, such as collection of tissue for anaerobic cultures in a nonanaerobic sterile container or a delay in specimen transport time to the laboratory, will decrease yield of meaningful pathogen recovery. For example, specimens collected to investigate for tuberculosis should not be placed in formalin containers as this can eliminate the organism and limit the yield of pathogen recovery.

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Preanalytical errors that occur after specimen collection, such as specimen or patient mislabeling, have a wide impact on patients—ranging from economic costs in repeating a test to diagnostic error and potential harmful therapies.[4] Mislabeling of specimens was noted to be as high as 5%.[5] Clinicians, particularly proceduralists, have a role to play in reducing such errors, as they are costly to the patient and the health care system. Similar to laboratorians, it may be beneficial for clinicians, particularly those who perform procedures, to have teaching and access to written standard operating procedures for specimen collection and handling to prevent preanalytical error.

CLINICAL SIGNIFICANCE

- Medical microbiology laboratories are key stakeholders in advancing infectious diseases diagnostics and treatment, informing infection prevention policies, and guiding antimicrobial stewardship efforts.
- Collaboration between clinicians and the microbiology laboratory improves the safety and quality of patient care.
- Clinicians play a critical role in preventing laboratory errors.
- Multiple factors contribute to microbiological detection of infectious pathogens.
- Clinical context is paramount when interpreting microbiological results.

MULTIPLE FACTORS IMPACT PATHOGEN RECOVERY IN THE LABORATORY

It is valuable for clinicians to understand the limitations associated with microbiological studies and utilize clinical examination in guiding antimicrobial use, as microbiological cultures by themselves are not sufficient to rule out infection.[6] Bacteremia is detected in upward of only 70% of patients with sepsis, and even lower detection rates are observed for candidemia. Detection of pathogens in the bloodstream by culture depends on the clinical context—as the yield of pathogen recovery approximates 2% in cellulitis, 20% in neutropenic fever, and 50% in disseminated fungemia. Negative blood cultures can result from preanalytical laboratory errors, exposure to antimicrobials prior to collection, or infection from pathogens that do not easily grow in routine blood culture media.[7]

Fastidious organisms such as *Neisseria gonorrhea, Legionella* spp., and Rickettsia will grow only in blood cultures with enriched media. Urine *Legionella* antigen is a useful test for diagnosing *Legionella pneumophila* serogroup 1 infection if found to be positive, but it will not detect presence of other *Legionella* serogroups that could be causing infection. Without enriched media, fastidious organisms may not grow nor be detected due to overgrowth of surrounding contaminants. For this reason, if clinicians are concerned about an infection from fastidious organisms, other molecular diagnostic methods are preferred.

Lastly, suboptimal collection and transport can also erroneously render microbiological cultures negative. Low organism load (from inadequate sampling) or use of improper transport media can lead to falsely negative microbiological results that delay optimization of therapy for patients.[8]

Table 1 Classes and Examples of Laboratory Error[3]

Preanalytical error
• Inappropriate test ordered
• Patient misidentification
• Insufficient clinical information on requisition accompanying sample
• Mislabeling or absence of labeling of specimen container
• Inappropriate container for specimen collection
• Insufficient volume of specimen
• Inappropriate storage, handling, or transport of specimen to laboratory
• Loss of specimen
Analytical error
• Equipment failure including calibration defects
• Full identification and susceptibility testing of commensal organisms
• Undetected quality control failure
• Interference with assay
• Deviation from procedure manual
Postanalytical error
• Incorrect clinical interpretation or response to laboratory result
• Excessive turn-around time or failure in reporting
• Data entry error

A POSITIVE MICROBIOLOGICAL CULTURE RESULT DOES NOT NECESSARILY DIAGNOSE INFECTION

Much like specimen collection, specimen selection has a tremendous impact on clinical decision-making and patient outcomes. Microbiological results must be taken in the context in which they were collected. The specimen collected should represent the site of infection, which is typically diagnosed clinically. Specimens taken from nonsterile sites, including skin, stool, and mucous membranes are colonized with bacteria. For example, superficial swabs from decubitus ulcers and diabetes-related foot ulcers, or nasal swabs from patients suspected to have sinusitis, are not helpful for guiding antimicrobial therapies.[9]

Similarly, specimens from catheter bags, tracheostomies or drains also contain flora that may not be representative of a particular infectious syndrome. A patient with a pyogenic liver abscess and *Streptococcus anginosus* bacteremia that is improving on ceftriaxone and metronidazole may be found to have *Pseudomonas aeruginosa* and coagulase-negative staphylococci in samples collected from the percutaneous abdominal catheter. However, presence of such organisms in an immunocompetent host typically represents pathogen colonization of the catheter device and need not be treated with culture-directed antimicrobials.[10]

Tissue and aseptically collected fluid (in select circumstances) are superior to swabs for microbiological diagnoses in cases of suspected clinical infection. While swabs are convenient to obtain, they are easily contaminated and hold only a small volume of samples that do not uniformly transfer to different media for microbiological testing. Reliance on swab specimens, while convenient, can inadvertently hinder patient outcomes by impeding receipt of useful information for clinical decision-making.

CLINICAL CONTEXT IS REQUIRED TO PROPERLY INTERPRET BLOOD CULTURE RESULTS

Laboratory detection of bloodstream infections through blood cultures is a common diagnostic procedure ordered by clinicians. If performed and interpreted properly, blood cultures can confirm infectious etiologies of disease, identify causative pathogens, and direct antibacterial therapy in a safe and efficacious manner. Selection of appropriate antimicrobials is paramount for treatment of sepsis and prevention of antimicrobial resistance.

One set of blood cultures consists of an aerobic and anaerobic bottle collected from a single venipuncture. While aerobic and facultative anaerobic organisms grow in both bottles, strict anaerobic pathogens grow only in the anaerobic bottle. Because bacteria and fungi may not be constantly present in the bloodstream, the sensitivity of a single blood culture set is limited. The yield of 1 and 2 sets of blood cultures is 73% and 90%, respectively.[11]

Each bottle should be inoculated with approximately 10 mL of blood in adults. This volume is recommended to optimize pathogen recovery, as bacterial and fungal burden is commonly <1 colony-forming unit per mL of blood. Each 1 mL of blood augments yield of bacteremia by up to 4%.[12,13]

Fever itself is not an independent predictor of bacteremia and should be used as part of a global assessment of a patient for features of bacteremia (eg, rigors, vitals, leukocytosis) to prompt blood culture collection.[14] Blood culture results require interpretation in the context of the patient's clinical syndrome. Pathogens that almost always represent true infection when isolated from blood cultures include *Staphylococcus aureus*, beta-hemolytic streptococci, gram-negative bacilli, anaerobes, and fungi. Conversely, coagulase-negative staphylococci, viridans/alpha hemolytic streptococci, *Corynebacterium* species, and *Cutibacterium acnes* often, but not always represent contamination.

MICROBIOLOGICAL RESULTS ARE HELPFUL FOR BOTH NARROWING AND STOPPING ANTIMICROBIAL THERAPY

It is well understood that microbiological sampling prior to initiation of antimicrobials enhances the yield of a microbiological diagnosis, providing clinicians confidence in narrowing antimicrobial therapy, which can prevent antimicrobial resistance. However, the benefits of securing a microbiological diagnosis go beyond reducing antibiotic resistance within a community.

Targeted antimicrobials are associated with improved mortality rates compared with their broader counterparts in select circumstances. For example, it is recognized that *S. aureus* bacteremia is associated with fatality rates approximating 25%.[15] While piperacillin-tazobactam and non-first-generation cephalosporins have activity against methicillin-susceptible *S. aureus* and are broader than anti-staphylococcal penicillins or cefazolin, use of broader agents is associated with higher mortality and worse outcomes.[16] Analogously, use of unnecessarily broad antibacterials in cases of non-drug-resistant infections is associated with higher mortality rates, even when adjusting for confounders.[17-19]

Lastly, securing a microbiological diagnosis can lead to cessation of unnecessary and potentially harmful antimicrobial therapy. For example, in a patient with acute hypoxia, fever, and pulmonary infiltrates, who was appropriately started on empiric antibacterials, a respiratory specimen resulting positive for influenza A can lead to discontinuation of antibacterials and optimization of infection prevention procedures within the hospital. Similarly, in a patient with meningoencephalitis who is started on antibacterials, identification of herpes simplex in cerebrospinal fluid can prompt cessation of antibacterials.

IN VITRO ANTIBIOTIC SUSCEPTIBILITY TESTING DOES NOT ALWAYS CORRELATE CLINICALLY

Accurate and timely detection of antimicrobial resistance is crucial for clinicians managing infections. Clinical microbiology laboratories employ a variety of manual and instrument-based methods to determine the antimicrobial activity of antibiotics against pathogens. Depending on the technique utilized, antimicrobial susceptibility testing is reported as categorical variables (susceptible, intermediate, resistant) or quantitatively as minimum inhibitory concentrations. Minimum inhibitory concentrations represent the lowest concentration of an antibiotic in mg/L (μg/mL) required to inhibit microbiological growth under controlled conditions. Laboratory committees, including the European Committee on Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute (CLSI), have established breakpoints (also known as interpretive criteria) for minimum inhibitory concentrations based on data from clinical, pharmacodynamic, and pharmacokinetic studies—and subsequently infer in vitro susceptibility.[20,21]

While interpretative criteria guide clinicians in choosing antimicrobials most likely to lead to therapeutic success, it is noteworthy that reliance on in vitro susceptibilities are not impervious to clinical failure. Use of antimicrobials deemed to be more active in the laboratory (in vitro) is an independent predictor of favorable clinical response compared with less active antimicrobials, but using "resistant" and "susceptible" anti-infectives does not always predict clinical failure and success, respectively.[22] Indeed, the 90-60 rule was established, which outlines that antibiotic

susceptibility testing is 90% accurate in predicting positive outcomes with susceptible results, but only 40% accurate in predicting negative outcomes with resistance.[23] Specifically, 10% of infections due to susceptible isolates do not clinically respond, while 60% of infections from resistant isolates demonstrate favorable clinical trajectory.

In cases of increased biological variability (eg, immunocompromised host) and situations where antibiotic combinations are used (eg, in undifferentiated sepsis), there was even less correlation between in vitro antibiotic susceptibility testing results and clinical outcomes.[24] Therefore, serial clinical evaluations used in conjunction with antibiotic susceptibility testing data are more valuable than relying on only the latter.

REPORTING OF ANTIMICROBIAL SUSCEPTIBILITY TESTING IS PURPOSEFUL AND GUIDED BY LABORATORY PRACTICE STANDARDS

Intrinsic resistance is a pattern of susceptibility shared among a pathogen species, independent of antimicrobial exposure and unrelated to lateral gene transfer. Understanding specific examples of intrinsic resistance can be helpful for clinicians in optimizing empiric antimicrobial therapy (Table 2). Clinicians can also anticipate the next organism a patient may be infected with based on the antimicrobial therapy they are exposed to. For example, in a patient on carbapenem therapy who develops a new gram-negative bacteremia, a clinician may be able to deduce *Stenotrophomonas maltophilia* as the cause of infection given the intrinsic resistance of this organism to carbapenems. For pathogen-drug combinations where inherent antimicrobial resistance is known, susceptibility testing is not required and may not be reported. Therefore, it is important that clinicians are cautious about inferring efficacy of antimicrobials that are not listed on susceptibility reports.

Selective or cascade reporting of antibiotic susceptibility testing is commonly used by institutions. Guided by the CLSI, cascade reporting involves selectively displaying secondary antimicrobials (eg, broader spectrum, more expensive) only if there is resistance to primary agents within an antibiotic class. An example of this is releasing cefepime or carbapenem susceptibilities to Enterobacterales isolates only if they are resistant to ceftriaxone.[25] By using the antibiotic susceptibility report to refine antibacterial usage, clinicians are actively engaging in antibiotic stewardship.[26]

Table 2 Pathogens with Intrinsic Resistance

Pathogen	Intrinsic Resistance
Gram-positive organisms	Aztreonam
Anaerobes	Aminoglycosides
Enterococci	Cephalosporins, Trimethoprim-sulfamethoxazole
Stenotrophomonas maltophilia	Carbapenems
Klebsiella spp.	Ampicillin
Candida krusei	Fluconazole

ANTIBIOGRAMS ARE HELPFUL IN SELECTING EMPIRIC THERAPIES AND MONITORING FOR TRENDS IN ANTIMICROBIAL RESISTANCE

An antibiogram is a facility-level summary of antimicrobial susceptibility data of various organisms isolated from patients used to monitor epidemiological trends pertaining to antimicrobial resistance. Updated antibiograms can be useful when selecting empiric antimicrobial therapy, and more specific than using UptoDate or the Sanford guide. Institutions have integrated antibiogram data in local clinical support applications such as FirstLine. Despite this, evidence suggests that some clinicians remain unfamiliar with incorporating antibiograms to inform empiric antimicrobial prescribing.[27]

Creation of an antibiogram is a yearly laboratory responsibility informed by CLSI guidelines. Only diagnostic (not surveillance) cultures with >30 isolates are included in an antibiogram—with only routinely used antimicrobial agents tested for susceptibility. Antibiograms are reflective of only the particular institution in which cultures from patients were obtained. There can be significant differences in antibiograms between institutions—and it is relevant for clinicians who utilize antibiograms to use ones that are updated and specific to their clinical setting.[28]

It is important for clinicians to recognize limitations of antibiograms. They provide a binary measure of susceptibility and do not provide additional quantitative information. Antibiograms also do not factor in considerations of antibiotic penetration. For example, a patient with methicillin-resistant *S. aureus* pneumonia complicated by bacteremia can have isolates of daptomycin be reported as microbiologically susceptible, although use of daptomycin is not reliable for pulmonary penetration. Being well versed in accessing and leveraging antibiograms not only instills confidence with prescribing, but also improves antimicrobial prescribing practices among clinicians.

CHARACTERISTICS OF PATHOGENS CAN GUIDE INVESTIGATIONS INTO THE CAUSE AND COMPLICATIONS OF INFECTIOUS SYNDROMES

Understanding the causes and complications of infectious syndromes is important in successfully treating infection and preventing relapse (Table 3). Investigations into the contributors and complications of infections are guided by the identity of the causative pathogen.

The human body is host to trillions of bacteria and protected from infection by defense mechanisms. Infections occur resultant to compromised defenses, including trauma or underlying diseases. The pathogenicity of an organism to cause symptomatic disease is determined by its virulence factors and ability to escape defense mechanisms. For example, gram-negative bacteria are constituents of gastrointestinal flora, and in the context of intact host defenses, do not migrate to sterile sites and cause infection. Thus, when encountered with cases of gram-negative bacteremia,

Table 3 Associations with Pathogens Identified in the Bloodstream

Pathogen	Associations
Staphylococcus aureus	Infective endocarditis
Group B Streptococcus	Diabetes, HIV, cirrhosis
Streptococcus pneumoniae	HIV, immunoglobulin deficiency
Streptococcus mutans	Dental caries
Streptococcus bovis, Clostridium septicum	Gastrointestinal mass
Non-tuberculous Mycobacteria	Cell-mediated immunodeficiency
Pseudomonas spp., *Staphylococcus aureus, Candida* spp.	Remove central lines
Gram-negative organisms	Source likely gastrointestinal, urinary, or biliary tract

HIV = human immunodeficiency virus.

not only are antibacterials necessary, investigations of the biliary tract, intraluminal gut, and urinary system should also be undertaken to assess for breaches in defense barriers that led to the infection. Similarly, identification of other pathogens in sterile sites, such as invasive pneumococcal disease (eg, primary *S. pneumoniae* bacteremia), should incite testing for diseases that reduce host susceptibility (eg, human immunodeficiency virus).[29]

Being familiar with the characteristics of an organism is also helpful in screening for infectious complications. Bacteremia from *S. aureus* (colonizer of the skin and mucous membranes) is common and associated with a 20% to 30% mortality rate. As infective endocarditis is identified in up to 25% of patients with *S. aureus* bacteremia, echocardiogram is recommended in all patients with *S. aureus* bacteremia.[30]

In addition to empiric antibacterials, microbiology also informs adjunctive treatment decisions. For example, decisions to remove central lines versus line salvage in cases of bloodstream infections are guided in part by the detected pathogen. *S. aureus, Pseudomonas aeruginosa*, and *Candida* spp. have biofilm-forming properties—and central access removal is suggested when such pathogens are implicated in the bloodstream.[31]

MOLECULAR MICROBIOLOGY CAN BE LEVERAGED FOR ITS INCREASED SENSITIVITY AND SPECIFICITY IN THE APPROPRIATE CLINICAL CONTEXT

The advent of molecular biology has substantially improved the sensitivity, specificity, and turnaround time associated with pathogen recovery and identification.[32] Nucleic acid tests, which detect specific sequences of DNA or RNA of a bacteria or virus, were previously limited to specialized laboratories, but are now commonplace and no longer considered high complexity.

Polymerase chain reaction (PCR) and loop mediated isothermal amplification (LAMP) are examples of nucleic acid amplification tests (NAAT), in which enzymes are used to exponentially amplify a sequence of nucleic acid rapidly for detection in vitro. The impressive turnaround time of

Table 4 Ten clinical pearls in microbiology

1	Clinicians have a key role in preventing pre-analytical laboratory error
2	Multiple factors impact pathogen recovery in the laboratory
3	A positive microbiological culture result does not necessarily diagnose infection
4	Clinical context is required to properly interpret blood culture results
5	Microbiological results are helpful for both narrowing and stopping antimicrobial therapy
6	*In vitro* antibiotic susceptibility testing does not always correlate clinically
7	Reporting of antimicrobial susceptibility testing is purposeful and guided by laboratory practice standards
8	Antibiograms are helpful in selecting empiric therapies and monitoring for trends in antimicrobial resistance
9	Characteristics of pathogens can guide investigations into the cause and complications of infectious syndromes
10	Molecular microbiology can be leveraged for its increased sensitivity and specificity in the appropriate clinical context

NAAT has led to its adoption as primary screening tests for infections such as *Chlamydia trachomatis* and *Neisseria gonorrhea*.[33] The exquisite sensitivity of NAAT is also illustrated in its ability to exclude infections with high confidence. For example, contemporary evidence has suggested that a single LAMP result for malaria outperforms thick and thin smears when trying to rule out malaria in a patient.[34]

While nucleic acid tests can be used to secure a diagnosis, their use as a test of cure is dubious and requires careful clinical correlation, as detection of molecular targets can be secondary to acute infection, pathogen colonization, or residual shedding from a previous infection. For example, detection of *Mycobacterium tuberculosis* in sputum via PCR can persist for years in patients after appropriate antituberculous therapy, and does not denote ongoing infection.[35] Similarly, patients treated for *Clostridioides difficile* diarrhea with clinical resolution can have persistently positive PCR toxin assays.[36] Stool PCR will detect *C. difficile* in healthy adults who are asymptomatically colonized—a rate that approximates upwards of 15%.[37] Therefore, it behooves clinicians to interpret the results of nucleic acid tests specific to a patient's clinical context.

CONCLUSION

The microbiology laboratory plays a vital role in surveillance, treatment, and prevention of infections. We identify and elaborate on 10 key concepts within the field of microbiology that hold relevance for clinicians (Table 4). In doing so, we highlight how collaboration with the microbiology laboratory significantly enhances patient care in the clinical arena.

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