Diagnostic stewardship in infectious diseases

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Diagnostic stewardship in infectious diseases: a continuum of antimicrobial stewardship in the fight against antimicrobial resistance

Johnny Zakhour[a], Sara F Haddad[b], Anthony Kerbage[c], Heiman Wertheim[d], Pierre Tattevin[e], Andreas Voss[f], Serhat Ünal[g], Abdoul Salam Ouedraogo[h], Souha S Kanj[a,*], on behalf of the International Society of Antimicrobial Chemotherapy (ISAC) and the Alliance for the Prudent Use of Antibiotics (APUA)

[a] Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[b] Division of Infectious Diseases, Department of Medicine, College of Medicine, Mayo Clinic, Rochester, MN, USA
[c] Division of Gastroenterology, Department of Medicine, Mayo Clinic, Rochester, MN, USA
[d] Department of Medical Microbiology and Radboudumc Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands
[e] Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France
[f] Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, Groningen, The Netherlands
[g] Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[h] Bacteriology and virology department, Sourou Sanou University Hospital, Burkina Faso

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ABSTRACT

Antimicrobial resistance (AMR) has been exacerbated by the inappropriate use of diagnostics, leading to excessive prescription of antimicrobials, and is an imminent threat to global health. Diagnostic stewardship (DS) is an auxiliary to antimicrobial stewardship (AMS) and comprises ordering the right tests, for the right patient, at the right time. It also promotes the judicious use of rapid and novel molecular diagnostic tools to enable the initiation of proper antibiotic therapy, while avoiding excessive use of broad-spectrum antibiotics. Proper interpretation of test results is crucial to avoid overdiagnosis and excessive healthcare costs. Although many rapid diagnostic tools have been developed with a high diagnostic yield, they are often limited by accessibility, cost, and lack of knowledge regarding their use. Careful consideration of clinical signs and symptoms with knowledge of the local epidemiology are essential for DS. This enables appropriate interpretation of microbiological results. Multidisciplinary teams that include well trained professionals should cooperate to promote DS. Challenges and barriers to the implementation of DS are mostly caused by scarcity of resources and lack of trained personnel and, most importantly, lack of knowledge. The lack of resources is often due to absence of awareness of the impact that good medical microbiology diagnostic facilities and expertise can have on the proper use of antibiotics.

1. Introduction

Antimicrobial stewardship (AMS) programs have been developed worldwide to help curtail the pandemic of antimicrobial resistance (AMR). The goal of these programs is to ensure that patients receive timely and appropriate therapy, while reducing overuse of unnecessary drugs, costs, and medication-related adverse events [1]. Diagnostic stewardship (DS) promotes the

Abbreviations: AAT, Appropriate antimicrobial therapy; AMR, Antimicrobial resistance; AMS, Antimicrobial stewardship; BAL, Bronchoalveolar lavage; BC, Blood culture; BCID, BC Identification; BSI, Blood stream infection; CDI, *Clostridioides difficile*infection; CRP, C-reactive protein; DS, Diagnostic stewardship; ESBL, Extended spectrum beta-lactamase; ID, Infectious diseases; IP-10, Interferon-inducible protein 10; LMIC, Low- and middle-income country; LOS, Length of hospital stay; MALDI-TOF MS, Matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MIC, Minimal inhibitory concentrations; mNGS, Metagenomic next generation sequencing; MRSE, Methicillin-resistant *Staphylococcus epidermidis*; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; NAAT, Nucleic acid amplification testing; POC, Point-of-care; PCR, Polymerase chain reaction.

* Corresponding author at: Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, PO Box 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon.
E-mail address: sk11@aub.edu.lb (S.S. Kanj).

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appropriate use of the right diagnostic tools for every patient, to limit overuse and guide timely patient management. This strategy also enables early discontinuation of antimicrobial therapy, thereby limiting the risk of AMR and improving clinical outcomes [2]. DS is highly relevant in settings that involve immunocompromised and critically ill patients, where there is often a tendency for excessive use of microbiologic testing. It is also important in non-severe infections that do not always require testing, and where cultures of colonizers or contaminated samples might lead to unnecessary prescription of antimicrobial agents, such as sputum cultures in evident viral respiratory infections or blood cultures (BCs) in simple cellulitis [3,4]. Effective DS requires multidisciplinary collaboration between clinicians (including infectious diseases [ID] specialists and intensivists in critically ill patients) and clinical microbiologists, to ensure that diagnostic testing is timely and appropriate to optimize patient care and outcomes. Although the role of most members of the stewardship team is fairly consistent across different healthcare systems, the role of the medical microbiologist is variable. Microbiological expertise is crucial for AMS. The microbiology laboratory serves as a service department in many settings, particularly in most low- and middle-income countries (LMICs), whereas the medical microbiologist can be heavily involved in direct patient care and stewardship efforts in other healthcare models, particularly in Europe. Many factors contribute to the lower rates of AMR and antibiotic use that are observed in high-income countries. For instance, the availability of laboratory infrastructure and trained personnel, rigorous infection prevention and control, availability of novel diagnostics and the involvement of medical microbiologists in direct patient care all contribute to improved stewardship. Furthermore, diagnostic tests are more readily available in high-income countries, whereas LMICs are more likely to resort to appropriate diagnostics after treatment failure, thus creating reporting bias of AMR [5].

Many diagnostic tools have been developed in recent years to support the implementation of DS, including point-of-care (POC) tests and advanced molecular tools; however, the concept of DS is yet to be widely recognized and incorporated into regular clinical practice. This may be due to the lack of awareness regarding its potential to reduce inappropriate antimicrobial prescription and healthcare-related costs. DS prioritizes simple and basic diagnostics, and regulates the use of novel diagnostics that may not be available in low-resource settings or might impose excessive costs compared with conventional tests [6].

This review provides an insight into areas of the diagnostic pathway where DS may be of great importance, and highlights the role of novel tools in DS. Also covered is the importance of DS in five commonly encountered infectious syndromes, as well as the challenges of the implementation of effective and durable DS. Herein are described the microbiological aspects of DS further topics relevant to DS, such as chemistry (biomarkers) and imaging studies, are beyond the scope of this paper.

2. Diagnostic stewardship across the diagnostic pathway

The diagnostic pathway can be divided into three main phases: the pre-analytical, analytical, and post-analytical phases. DS is important across all three phases to ensure judicious use of diagnostic tools.

In the first step of the pre-analytical phase, the appropriate test is chosen after careful consideration of the clinical signs and symptoms. In addition to rational considerations whether or not to test, healthcare professionals should use clinical practice guidelines to optimize the use of diagnostic tools [7]. Accuracy, availability, cost-effectiveness, turnaround time and clinical impact are ideal characteristics that affect the choice of testing [8]. However, the diagnostic performance of a test also depends on the type of specimen used and the time of collection. It is important to avoid tests that are either low-yield or carry a high risk of false positivity [9,10]. Similarly, diagnostics that are unlikely to affect patient management should be avoided [11]. Hence, the chosen diagnostics should be tailored to the pre-test probability of the disease, so that treatment choice can be supported by accurate and clinically relevant results [12]. This is important when dealing with acute pharyngitis, for example, where requesting streptococcal antigen or throat culture should be guided by the pre-test probability of the likelihood of bacterial pharyngitis.

Once appropriate testing is decided, proper sampling is crucial to maximize yield [2]. Guidance is widely available for common specimens (urine, blood, stool, respiratory samples, wound and genital swabs) as summarized in Table 1. During the analytical phase, the microbiology lab plays an important role in reducing unnecessary testing. Sample rejection is an intervention that has consistently shown great potential to reduce unnecessary testing and treatment. For instance, laboratories may not perform urine culture in the absence of significant pyuria, except in neutropenic patients, or refuse *Clostridioides difficile* infection (CDI) testing for non-loose stools. Specific institutional criteria should be established by ID specialists and microbiologists to avoid testing inappropriate samples. Also, microbiologists should quickly report inappropriately sampled, damaged or unsealed samples.

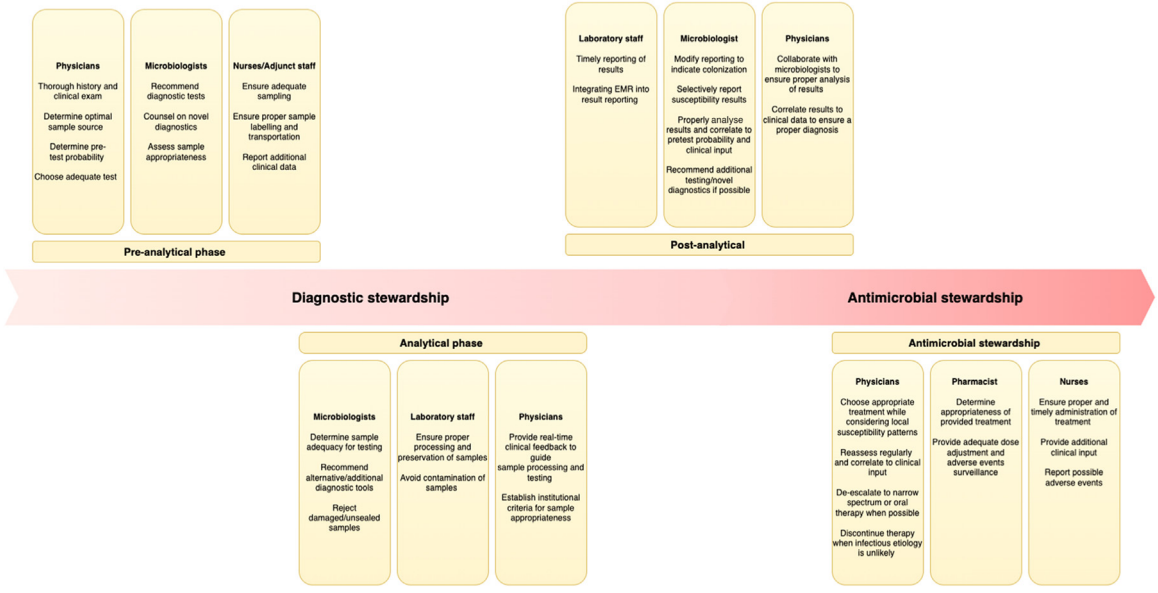
During the post-analytical phase, multidisciplinary interventions are necessary to enable correct interpretation of results. The integration of these interventions in the electronic medical record (EMR), whenever available, can improve communication and enable timely decision-making [7]. It is important that results are reported quickly to reduce time to optimal antimicrobial therapy. Furthermore, selective susceptibility reporting, where broad-spectrum antimicrobial susceptibility is not reported if the isolate is susceptible to narrow-spectrum agents, has been attempted and has shown promising results [13]. Modified reporting of culture results can also reduce unnecessary treatment by indicating probable colonization rather than infection [14]. Medical microbiologists are responsible for reporting results in a way that guides clinicians, and they play a key role in the multidisciplinary team to improve interpretation of results and encourage clinicians to discontinue treatment when deemed unnecessary (Scheme 1) [15].

3. Integrating novel diagnostic tools in the diagnostic pathway

Delay of appropriate antimicrobial therapy (AAT) has been associated with increased mortality in many instances [16]. Clinicians are often torn between giving broad-spectrum empirical therapy to cover a broad range of pathogens, including resistant organisms, and narrowing the spectrum to avoid the future emergence of resistance. For example, outcomes of patients with blood stream infection (BSI) due to *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA) may be heavily compromised if empirical therapy does not cover such resistant organisms. Hence, rapid pathogen identification and susceptibility testing may improve time to AAT and reduce mortality [17,18]. In addition, timely identification may also reduce the length of hospital stay (LOS) and healthcare costs [19,20]. In general, rapid initiation of AAT is mainly hindered by the long turnaround time of standard culturing techniques, identification, and susceptibility testing. POC tests and new techniques, such as molecular tests, reduce time to identification and may even detect markers of resistance to commonly used antimicrobials (Table 2). Implementing POC tests in routine practice requires careful consideration of the impact on patient care. Ideally, diagnostic tests should be accurate, rapid, sensitive, and specific. Portable tests that do not require technical skills for operation and that use heat-stable reagents provide on-demand POC testing, are cost-effective for patient care, accommodate a broad

Table 1
Best practices for sample collection, preparation and transportation during the pre-analytical phase [2].

General considerations	- Sampling by well trained professionals - Sampling prior to antimicrobial initiation - Proper labeling with a unique patient identifier, name, date of birth, specimen type, date of collection, hospital, or community origin - Transportation with clinical information - Encourage judicious use of novel diagnostics
Urine cultures	- Patient education on reducing contamination (clean catch) - Prompt transportation or refrigeration to reduce proliferation of contaminants
Blood cultures	- Encourage peripheral venipuncture sampling over central line sampling - Attempt to obtain two samples with adequate blood volume
Respiratory cultures	- Swab both nostrils and pharynx to increase the yield of nasopharyngeal sampling - Provide patients with proper instructions on providing expectoration for sputum culture - Consider distal sampling (like bronchoalveolar lavage [BAL], mini-BAL, bronchial washing), if possible, to increase diagnostic yield
Throat cultures	- Avoid throat cultures when clinical history is inconsistent with bacterial infection (acute viral infection)
Stool culture and *Clostridioides difficile* toxin and polymerase chain reaction	- Collect in a clean container - Keep at room temperature and transport within 2 hours of sampling
Genital swabs for sexually transmitted diseases culture and polymerase chain reaction	- For cultures, inoculate into growth medium on the bedside to improve the detection of *Neisseria gonorrhea* - Transport quickly
Wound swab	- Ensure deep wound culturing whenever possible - Favor needle aspiration from wound borders or tissue cultures from surgical debridement to avoid contamination and improve diagnostic yield



Scheme 1. Diagnostic stewardship involving multidisciplinary teams across the diagnostic pathway.

range of clinical samples, and are highly desirable [7]. In addition, novel diagnostic tools can identify a small microbial load on uncultured samples.

POC testing is affordable, sensitive, specific, user-friendly, and rapidly accessible in most settings. It has a great advantage, particularly in LMICs, where resources to advance DS and AMS are lacking. POC testing has often been shown to optimize management, including avoiding neonatal complications through POC testing for group B streptococcal carriage [21]. By rapidly identifying the responsible pathogen, POC testing enables more targeted antimicrobial treatment.

i. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS)

MALDI-TOF MS is a novel, rapid and reliable diagnostic tool that enables rapid turnaround time and minimal cost of consumables. The technique relies on the determination of the time-of-flight of ionized particles of microbial organisms to identify the isolated pathogen (including mycobacteria and fungi) and even detects resistance markers [22–24]. The turnaround time of less than 1 h is far shorter than conventional methods and has reduced time to identification by up to 48 h [25]. However, it is limited by the need

Table 2
Novel diagnostic tools for the identification of organisms causing bloodstream infection.

Assay	Detected pathogens	Resistance markers	Turnaround time*
PNA-FISH	**Gram positive** *Staphylococcus aureus* and coagulase-negative staphylococci *Enterococcus faecalis* and other enterococci **Gram negative** *Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	No	1.5-3 h
QuickFISH	**Gram positive** *Staphylococcus aureus* and coagulase-negative staphylococci *Enterococcus faecalis* and other enterococci **Gram negative** *Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	No	<30 min
Gene Xpert MRSA	*Staphylococcus aureus*	*mecA*	< 1 h
Verigene Gram-positive	*Staphylococcus aureus* and coagulase-negative staphylococci *Streptococcus* spp. *E. faecalis and E. faecium* *Listeria* spp.	*mecA, vanA, vanB*	2.5 h
Verigene Gram-negative	*E. coli* *Shigella* spp. *K. pneumoniae and K. oxytoca* *P. aeruginosa* *Serratia marcescens* *Acinetobacter* spp. *Proteus* spp. *Citrobacter* spp. *Enterobacter* spp.	KPC, NDM, CTX-M, VIM, IMP, OXA	2 h
MALDI-TOF	Gram-positive and Gram-negative bacteria, mycobacteria	Multiple	10–30 min
FilmArray (BCID)	**Gram positive** *S. aureus* and other staphylococci *Streptococcus* spp. *Enterococcus* spp. *Listeria monocytogenes* **Gram negative** *Hemophilus influenza* *Neisseria meningitides* *Enterobacter cloacae complex* *E. coli* *K. pneumoniae* and *K. oxytoca* *P. aeruginosa* *Serratia marcescens* *Acinetobacter baumanii* *Proteus* spp.	*mecA, vanA, vanB* IMP, KPC, NDM, VIM, OXA-48-like, *mcr-1*, CTX-M,	1 h

* Once BCs are positive

to perform conventional cultures first. In addition, its performance is suboptimal in polymicrobial samples and is rarely accessible in LMICs. For instance, an evidence-based intervention that integrated MALDI-TOF, rapid antimicrobial susceptibility testing, and near–real-time AMS reported a significant difference in median time to identification (36.6 h vs 11 h, $P<0.001$), median time to obtain susceptibility (47.1 h vs 24.4 h, $P<0.001$) and median time to adjust therapy (75 h vs 29 h, $P=0.004$). These findings prove that combining MALDI-TOF and AMS decreases LOS and costs and, most importantly, time to initiation of optimal therapy [26]. In addition, a randomized controlled trial (RCT) including 1005 patients that compared MALDI-TOF to conventional microbiological methods (Gram stain, standard cultures) showed that there were no significant differences between the two groups regarding the proportion of patients receiving optimal antimicrobial therapy in the absence of an AMS program [27]. Despite the benefits of MALDI-TOF, it does not spare the time for culturing, which can take more than 24 hours.

ii. Polymerase chain reaction (PCR)

On the other hand, molecular diagnostics detect small microbial loads with high sensitivity and specificity. For example, a PCR-based detection system designed to identify MRSA or methicillin-susceptible *S. aureus* (MSSA) on positive BC or wound specimens has been shown to have 98.3–100% sensitivity and 98.6–99.4% specificity [28]. The Gene Xpert MRSA can detect MRSA by reverse transcriptase (RT)-PCR in around 1 h, including the *mec*A gene mutation with a sensitivity of 98.1% and a specificity of 99.6% [29].

Detection of multiple pathogens and some resistance genes is also possible with highly sensitive and specific microarray-based techniques with a turnaround time of 1–2.5 h [30–32]. In fact, the use of PCR assays to rapidly identify MRSA/MSSA has been associated with a reduced time to AAT, LOS, and healthcare costs when paired with AMS [33,34]. Using rapid multiplex PCR for BSI has been shown to decrease the use of broad-spectrum antibiotics in an RCT. The addition of AMS increased the opportunity for de-escalation of therapy [15].

Multiplex PCR methods like the Verigene, can detect many Gram-positive and Gram-negative organisms, and many genes associated with AMR (Carbapenemases, mecA, VanA, VanB) in 2–2.5 h. The Verigene has been reported to have 96.4% concordance to the species level for BC during a 5-year retrospective analysis. In addition, it had a positive percent agreement (PPA) for MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE)

of 100% compared with conventional antimicrobial susceptibility testing. However, a high false positive rate of 43% was observed for *Streptococcus pneumoniae* and has been reported in other studies. Hence, adjunct testing methods, such as bile solubility testing or antigen testing, may be necessary for *S. pneumoniae* [32,35]. The Verigene has also shown a high concordance for the identification of Gram-negative organisms (99% for monomicrobial BC and 83.3% for polymicrobial BC) and for resistance markers (92.3%), with a median time to bacterial identification of 21 h and to susceptibility results of 43 h. The Verigene assay could enable earlier evidence-based management for bacteremic patients, but it cannot replace phenotypic methods as solid medium isolation is essential for polymicrobial cultures to identify undetected organisms and to obtain minimal inhibitory concentrations (MIC) [36].

Another molecular tool, the Biofire FilmArray BC identification assay, is a multiplex PCR assay that identifies many Gram-positive and Gram-negative organisms with a turnaround time of 1 h, and detects the mecA, Van A, and Van B resistance genes of Gram-positive bacteria as well as carbapenemase, extended spectrum beta-lactamase (ESBL), and colistin resistance genes for Gram-negative organisms [22]. The use of the FilmArray BC Identification (BCID) panel was compared to standard culture and antimicrobial susceptibility testing in a single-center RCT. A third arm was included in the study where BCID was used alongside real-time AMS. In the BCID arm, pathogen identification was 21 h faster and broad-spectrum antibiotic use was reduced. However, significantly quicker de-escalation was only reported in the group using BCID plus AMS [37].

Respiratory infections are an important cause of overuse and inappropriate use of antimicrobials. Many multiplex PCR panels, including the BioFire FilmArray RP, Nanosphere Verigene RV+ test, and Hologic Gen-Probe Prodesse, are available for these infections. These assays can provide valuable information for decision-making regarding initiation and choice of antimicrobial therapy in patients with positive results. However, the possibility of contamination must always be considered, particularly if the pre-test probability is low [38].

iii. Metagenomic next generation sequencing (mNGS)

Compared to conventional methods, mNGS can accurately identify multiple pathogens and their resistance genes in a short period of time without the need for culture [39]. A meta-analysis evaluating the clinical use of mNGS revealed that it had an excellent performance and high diagnostic efficacy for ID. However, it may not perform as well with RNA viruses, fungi, and intracellular bacteria [40]. Conventional culture diagnostic yield is severely affected after administration of antimicrobials, whereas mNGS can still detect the causative organism, even after initiation of antimicrobials, which can help improve the appropriateness of antimicrobial agents [41]. In addition, mNGS can be affected by contaminating DNA and cannot differentiate colonization from infection [42]. Hence, DS is crucial when using mNGS in the clinical setting to avoid the risk of false positives and unnecessary antimicrobial therapy. Further clinical studies are needed to assess its utility for DS.

iv. Host response-based diagnostics

Host response-based diagnostics offer a new perspective to ID diagnoses, particularly gene expression signatures. Interestingly, methods that rely on identifying the human body's reaction to a particular disease may be able to differentiate between noninfectious and infectious etiologies of illness, notably viral or bacterial [43]. For instance, an assay including a 3-peptide panel of interferon-inducible protein 10 (IP-10), TNF-related apoptosis-inducing ligand (TRAIL), and C-reactive protein (CRP) has been used to differentiate viral from bacterial acute respiratory illness, alone or combined with other biomarkers [44–46]. In a retrospective analysis comparing gene expression to clinical judgment, gene expression correctly differentiated bacterial, viral, or noninfectious illness in 74.1% of subjects and avoided overdiagnosis and inappropriate treatment, which was seen in 33.3% of cases in the control arm. Gene expression was also found to have a significantly higher weighted accuracy (79.9%) compared with procalcitonin (71.5%) and clinical judgment (76.3%) [47]. However, more trials are needed to decide whether these findings translate into improved patient outcomes.

In light of the accumulating evidence regarding the accuracy of novel diagnostic techniques, the need to develop and optimize new microbiological diagnostics is greater than ever, particularly for DS. The availability of novel diagnostics should not replace basic diagnostics, which are less costly and have been repeatedly proven to reduce inappropriate antimicrobial use [48,49]. To expedite approvals of diagnostic tests, the Master Protocol for Evaluating Multiple Infection Diagnostics (MASTERMIND study) has been conceived. In this study, the same sample is used to evaluate the effectiveness of many experimental diagnostics to maximize the generation of valuable data on their efficacy, with the goal of improving the accessibility to novel diagnostics. Initially, the MASTERMIND study evaluated nucleic acid amplification testing (NAAT) for oropharyngeal and rectal gonorrhea and chlamydia. Results showed that the use of NAAT in the emergency department setting led to a significant reduction of excessive and inappropriate antimicrobial treatment for women compared with standard of care [50]. The Platforms for Rapid Identification of MDR-Gram Negative Bacteria and Evaluation of Resistance (PRIMER) studies have been conducted with the primary goal of improving the interpretation of the results of rapid molecular diagnostic (RMD) platforms. The findings showed that RMD platforms can provide valuable information to guide empirical antimicrobial therapy [51–53].

There is a consistently increasing variety of available diagnostic tests, and their abundance may lead to overuse and increased healthcare costs [54,55]. Research and development in the diagnostics field is continuously generating new tools. Ultrasensitive quantitative toxin assays [56], NAAT PCR cycle threshold analysis [57], PCR-electrospray identification [58], targeted metagenomics [59], and many other tools are being developed with the primary focus of advancing DS. Many studies have shown that rapid diagnostics are optimized by the presence of a multidisciplinary AMS that oversees the interpretation of the results [26,60–62].

4. Rationale behind diagnostic stewardship in common infectious syndromes

There are many reasons why healthcare providers disregard DS principles in daily practice, including absence of good clinical microbiological diagnostics, lack of knowledge of guidelines, misleading reporting of results, disease severity, or lack of personnel training. In the setting of critical illness, physicians are at risk of overprescribing antimicrobials to reduce mortality. For instance, up to 50% of patients treated with antibiotics for suspected ventilator-acquired pneumonia (VAP) in the ICU may not actually have VAP [63]. This is likely driven by the significant increased mortality when appropriate antimicrobial therapy is delayed in such patients [64]. Additionally, the availability of obtaining respiratory samples in these patients may increase the risk of treating colonizers in the absence of infection [64,65]. Clinicians should consider pre-test probability, microbiology, clinical score, and biomarkers (e.g., CRP, procalcitonin) when making treatment decisions.

Regarding bloodstream infections (BSI), the absence of clear-cut indications for ordering BCs may lead to unnecessary treatment, increased LOS, and costs [11,66]. In fact, only 5-15% of BCs yield positive results, with up to 56% being contaminations [67]. De-

spite being weakly correlated with BSI, fever or leukocytosis are the most common drivers for ordering BCs [68,69]. Pre-test probability and the effect on management should be considered prior to ordering BCs. In low-risk patients, BCs are unlikely to affect the management of the patient and should not be ordered if there is no concern for sepsis or septic shock [11]. BCs prior to initiation of antimicrobials may be warranted if primary infection site sampling is not possible, regardless of the probability of sepsis. Most importantly, critically ill infected patients should have BCs drawn promptly to initiate empirical antimicrobial therapy [11]. Individual centers should also be periodically monitoring their positivity rates and contamination rates to inform the end users and plan the needed educational activities to achieve the DS goals.

Asymptomatic bacteriuria is one of the most common causes of unnecessary antimicrobial use [70]. The decision to obtain urine cultures should be based on high clinical suspicion of urinary tract infection (UTI) to avoid unnecessary testing, excessive use of antimicrobials, emergence of resistance, and complications, such as CDI and drug-related toxicity [71–73]. However, in a subset of patients, such as pediatric, pregnant, neutropenic, or renal transplant patients, or those requiring urological procedures, clinicians should have a lower threshold for ordering urine cultures [73]. The absence of pyuria and bacteriuria on microscopy has a negative predictive value of 97-100% for UTI [9,74]. On the other hand, the signs and symptoms of UTI in critically ill patients may be atypical and misleading, particularly in the presence of an indwelling urinary catheter. Catheter-associated bacteriuria (CAB) is very common, with an acquisition rate of 3-5% per catheter-day [73]. In that case, it is often indicative of colonization rather than true infection and might be delayed but not prevented by antimicrobials. In critically ill patients with a high index of suspicion of an infectious process, in the absence of pyuria, urine cultures should only be performed after other infectious syndromes are ruled out.

Rapid and accurate diagnostic tools are crucial to reduce morbidity and mortality associated with central nervous system (CNS) infections like meningitis and encephalitis. With 90% accuracy and a turnaround time of 1 h, microarray PCR can rapidly identify causative agents in cerebrospinal fluid (CSF) [75]. Also, it can detect smaller quantities of pathogens and may be useful in patients who received antimicrobials prior to lumbar puncture [76]. In the pediatric population, microarray can increase pathogen identification, but requires further confirmation [77]. However, false positives and overdiagnosis are pertinent issues with such highly sensitive tests, particularly in patients with a low pre-test probability [75,78]. In the absence of evidence-based guidance, DS efforts are crucial to decrease excessive use of microarray testing and subsequent unnecessary antimicrobial prescription [65,79–82].

CDI is a common complication of antimicrobial treatment among hospitalized patients [83]. Unlike toxin or antigen-based tests (toxin A, toxin B, glutamate dehydrogenase [GDH]), new molecular diagnostics have a sensitivity that approaches 100% [84]. However, it is estimated that over half of patients with positive NAAT results are colonized, rather than infected, by *C. difficile* [85,86]. The contrast between high-income countries and LMICs is significant. On one hand, colonization rates are increasing with the adoption of NAAT instead of antigen- or toxin-based testing by most hospitals in high-income countries [87]. On the other hand, NAAT is not as widely available in LMICs, and the diagnosis of CDI is suboptimal [88]. Thus, there is a need for DS for CDI that takes into account the availability of diagnostic tests. The absence of approved biological markers with a high specificity for CDI further complicates the diagnosis when clinical signs and *C. difficile* testing are inconclusive [87]. Avoiding unnecessary treatment is essential in this population, given that antimicrobials may aggravate the underlying dysbiosis in patients with CDI [89,90]. With the wide availability of highly sensitive diagnostics and the lack of prospectively validated criteria to diagnose CDI [91–93], inappropriate testing may be common in the absence of DS guidance [94–96]. Test results should be interpreted with consideration of clinical suspicion of CDI. If clinicians opt for toxin-based testing, they should consider that the negative predictive value of toxin assays may not be enough to rule out CDI [97,98]. Although patients with negative toxin findings may have a lower risk of severe disease and complications, the absence of toxins does not rule out CDI [85,99].

According to the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), NAAT can be used alone or in combination with GDH or toxin testing as part of a diagnostic algorithm [95]. Although NAAT has a high sensitivity, it may lead to a high rate of false positives and increased costs [85]. In LMICs, the high cost and unavailability of NAAT have led many centers to only use toxin immunoassays, despite their low sensitivity. Using toxin assays alone can lead to a high rate of false negatives and has serious implications for patient outcomes and infection prevention and control [100]. A cost analysis study comparing multiple algorithms for the diagnosis of CDI showed that rapid toxin immunoassay and GDH followed by arbitrary NAAT is the best approach for the diagnosis of CDI and had the lowest cost, whereas NAAT alone had the highest cost of illness management [88].

Ultimately, a multidisciplinary team approach involving infection control and prevention, and auditing and quality control, are essential practices that can reduce CDI rates, unnecessary CDI antimicrobial treatment duration, and mortality [101,102].

Table 3 highlights studies that have reported the impact of DS interventions on patient outcomes, hospitalization costs, appropriateness of therapy, and healthcare provider knowledge. The IDSA has published guidelines addressing the diagnosis of VAP [103], CDI [95], and asymptomatic bacteriuria [73]. These guidelines reiterate the need for clinicians to consider both clinical and microbiological criteria, routinely reevaluate for the possibility of a non-infectious process, judiciously use novel diagnostics, and discontinue antimicrobial therapy when deemed unnecessary.

5. Challenges of implementing diagnostic stewardship

There are important barriers to implementing successful DS principles in different settings. In the ICU, clinicians are often faced with particularly challenging scenarios, where severe presentations and overlapping organ dysfunctions lead to hesitancy in delaying the initiation or de-escalation of antimicrobial therapy, even when an infectious etiology is not proven. Although reducing unnecessary testing decreases the occurrence of unnecessary treatment, it might increase the risk of delaying diagnosis and appropriate treatment of infections. This may correlate with worse outcome, particularly in high-risk patients, such as neutropenic or bone marrow transplant recipients. DS guidelines must identify the optimal strategy for testing that minimizes overdiagnosis and unnecessary treatment without putting critical patients at risk.

Furthermore, in LMICs, DS implementation is hindered by inadequate medical microbiological knowledge and governance, limited diagnostic tools and funding support [118]. The scarcity of DS and AMS specialists and required (old and new) antimicrobials in these countries, in addition to the lack of physicians' education and training, often means physicians are reluctant to modify current practices of antimicrobial prescribing, particularly when pressured by patients demanding antibiotic prescriptions [119]. For this reason, effective collaboration among ID experts, critical care physicians, and medical microbiologists is required to optimize patient care and offer evidence-based DS recommendations to hospitals in such settings. Research on the implementation of AMS programs in LMICs is crucial, as interventions that are effective in low-resource

Table 3
Interventions that have shown effectiveness at promoting DS.

Author	Intervention	Outcome	Recommendation
VAP			
Hellyer et al. [104]	Using levels of IL-1β and IL-8 to discontinue therapy	No effect on AMS due to the reluctance of physicians to discontinue therapy	Conventional and novel biomarkers can be helpful when deciding on the duration of treatment Risks vs. benefits should be weighed in deciding which sampling technique to use as non-invasive sampling may be sufficient in most cases Modified reporting is essential for AMS efforts and unnecessary treatment reduction Gram-stain on respiratory cultures may substantially reduce unnecessary therapy, and is a widely available and inexpensive means to promote DS, particularly in LMICs
Berton et al. [105]	Invasive sampling (BAL, mini-BAL, bronchial washing) vs. non-invasive sampling (ETA)	No difference in mortality, ICU LOS, days on MV, or changes of antimicrobials	
Musgrove et al. [106]	Reporting sputum cultures as "no MRSA and no *Pseudomonas* spp." vs. "polymicrobial respiratory flora"	De-escalation increased from 39% to 73% ($P<0.001$) Median duration of anti-pseudomonal antimicrobials decreased from 7 to 5 days ($P<0.001$) Significant decrease of MDR isolation from respiratory cultures from 8% to 1%	
Yoshimura et al. [107]	Gram-stain guided vs. standard empirical therapy (covering MRSA and *Pseudomonas* spp.)	Decreased use of anti-pseudomonal and anti-MRSA drugs No significant difference in coverage rates (92% in interventional arm vs. 95% in control)	
BSI			
Copeland-Harpelin et al. [108]	Using a clinical decision tool using 3 criteria Post-operative BCs for post-operative BSIs (hypotension, fever, >2 days post-operatively)	85% reduction of BC orders while maintaining the same diagnostic yield	In the absence of hypotension and fever before 2 post-operative days, BCs are likely unnecessary Institutional guidance and training should be provided to HCWs to reduce excessive testing that may lead to unnecessary treatment Follow-up BCs may not be useful in patients who are responding well to treatment, except in cases of *S. aureus*, endovascular infection, *S. lugdunensis*, and persistence of signs of infection after 72 h of therapy
Fabre et al. [109]	Quality intervention study providing education and algorithms that help guide ordering new or repeat BCs	Significant reduction in BC orders BC positivity rate increased from 8.1% to 11.5% ($P<0.001$) in the ICU No effect on mortality and readmission rates	
Scheer et al. [110]	BCs after initiation of antimicrobials	BC positivity rate was reduced by 20% when obtained during antimicrobial therapy	
UTI			
Lee et al. [111]	Two-step algorithm sending urine samples to culture only if urinalysis shows pyuria	Significant reduction of antimicrobial use without affecting mortality Improved clinicians' confidence when withholding antimicrobials	Urine samples from asymptomatic patients with no pyuria on urinalysis should not be cultured to reduce the risk of treating asymptomatic bacteriuria Modified reporting of urine samples suggestive of ASB improves the appropriateness of antimicrobial therapy Two-step algorithm may also be used for CAUTI in critically ill patients where MDR burden is higher
Daley et al. [13]	Reporting urine samples as "possibility of being asymptomatic bacteriuria" vs. standard reporting Clinicians needed to call the microbiology lab to obtain identification and AST results	Higher rates of appropriate antimicrobial therapy were achieved in the intervention arm (80% vs. 52.7%, $P=0.002$)	

(*continued on next page*)

Table 3 (*continued*)

Author	Intervention	Outcome	Recommendation
Epstein et al. [112]	Reflex urine protocol in patients suspected to have CAUTI	Reduced the rates of culturing and CAUTIs without affecting patient outcomes in critically ill patients	
CNS infections			
Broadhurst et al. [113]	Restricting CSF microarray testing to samples showing pleocytosis in immunocompetent adults	Significant increase of microarray testing yield from 11.5% to 18.6% 75% of false-positive results were avoided without any additional false-negative results Excluding immunocompromised patients, normal CSF WBC count was found to have a very high overall negative predictive value of 98-100% for nonviral agents	Restricting microarray testing to immunocompetent adult patients with CSF anomalies reduces unnecessary testing and improves diagnostic yield
CDI			
White et al. [10]	Reminder to check for laxative use when ordering stool testing	Reduction of inappropriate testing	Avoid testing for CDI in patients who are on laxatives or patients with low clinical suspicion of CDI Use the EMR to implement soft (review prior to ordering) or hard (block ordering) stops that promote DS The microbiology lab should not test non-loose stools or samples obtained from patients with low-pretest probability of CDI
Quan et al. [114]	Real-time checking of clinical criteria suggestive of CDI when ordering stool testing	Improved testing appropriateness Reduced hospital-onset CDI	
Quan et al. [114]	Blocking stool test order when clinical criteria are absent	56% reduction was observed for CDI testing and 54% reduction for HO-CDI laboratory-identified events	
Christensen et al. [115]	Implementation of a clinical review and pre-authorization protocol for CDI testing	Reductions in HO-CDI and oral vancomycin prescription	
Brecher et al. [116]	Allowing labs to refuse non-loose stools for stool testing	43% decrease in CDI testing was noted along with a 60% decrease in CDI events	
Truong et al. [117]	Microbiology labs were allowed to cancel CDI testing orders in the absence of clinical criteria (such as ≥3 loose stools in the past 24 h in the absence of laxative use in the past 48 h)	32% decrease in CDI testing and did not have any significant increases in ICU admission or 30-day all-cause mortality	

VAP, ventilator-acquired pneumonia; BAL, bronchoalveolar lavage; ICU, intensive care unit; LOS, length of stay; ETA, endotracheal aspirate; MV, mechanical ventilation; MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*; EAT, empiric antimicrobial therapy; BSI, bloodstream infection; BC, blood culture; HCW, healthcare workers; UTI, urinary tract infection; CAUTI, catheter-associated urinary tract infection; LMICs, low- and middle-income countries; ASB, asymptomatic bacteriuria; CNS, central nervous system; CSF, cerebrospinal fluid; WBC, white blood cells; CDI, *Clostridioides difficile* infection; HO-CDI, hospital-occurring CDI; EMR, electronic medical record.

settings may differ from those that have been successful in larger hospitals in high-income countries.

Although novel diagnostic tools have been shown to contribute to the appropriate use of antimicrobials in various clinical syndromes, the use of these tools is still significantly limited by their high cost and unavailability, particularly in LMICs. These techniques add to the healthcare financial burden, are time-consuming, and many require equipment and tools that are only available in well-resourced facilities [120]. However, some of these techniques may reduce antimicrobial use, LOS, and healthcare costs, and can be cost-effective when used judiciously. AMS teams should provide guidance on the proper use of these techniques within an institution. Global collaboration between all stakeholders, including industry corporations and governments, is essential to increase access to novel diagnostic tools across the world.

6. Conclusion

DS in ID management requires ordering the right test, for the right patient, at the right time to positively impact patients' outcomes without overusing (or underusing) the available tests. DS is an important concept that has been applied in settings where the clinical microbiology laboratory played a role beyond a service laboratory, but it is still lacking in many countries, and requires further development and elaboration. Healthcare facilities need to engage in DS by investing in hiring qualified clinical microbiologists, who can help establish clear criteria for ordering various tests and acquiring the appropriate technology for patients. Highly sensitive novel diagnostics should not replace clinical input and basic tests. Large-scale research is needed to provide further evidence of the benefits of DS on patient outcomes and healthcare costs. Moreover, studies from low-resource settings are needed to better understand how to implement DS in such contexts. As healthcare facilities become motivated to implement DS, providers and clinicians must be trained in effective principles of DS. Diagnostic tools and laboratory resources must be refined and made widely accessible across all settings to effectively inform clinical decisions and improve patient care. The impact of proper diagnostics and expertise is considerable and much needed. Good clinical microbiology should embrace DS as a core activity to enable successful AMS and infection prevention. Finally, the potential of DS cannot be fully reached unless paired with proper AMS.

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