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The Impact of Rapid Species Identification on Management of Bloodstream Infections: What's in a Name?

Running title: Management of Bloodstream Infections

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Article Highlights

1. Concise review of pathogen-specific management of patients with bloodstream infection intended for hospitalists and other frontline physicians
2. Readable summaries of initial pathogen-specific management of bloodstream infection prior to complete phenotypic antimicrobial susceptibility test results
3. Guidance on de-escalation of therapy in patients with bloodstream infection whose initial therapy is overly broad
4. Antimicrobial selection algorithm (FIG. 3) based on complex *Enterobacterales* antimicrobial resistance gene target identification
5. Pediatric perspectives for those bloodstream pathogens for which management differs from that in adults

Abstract

Bloodstream infections are a leading cause of morbidity and mortality. Molecular rapid diagnostic tests (mRDTs) are transforming care for patients with bloodstream infection by providing the opportunity to dramatically shorten times to effective therapy and speeding de-escalation of overly-broad empiric therapy. However, because of the novelty of these tests which provide information regarding microbial identification and whether specific antibiotic-resistance mutations were detected, many frontline providers still delay final decisions until complete phenotypic susceptibility results are available several days later. Thus the benefits of mRDTs have been largely limited to circumstances where antimicrobial stewardship programs closely monitor these tests and intervene as soon as the results are available. We searched PubMed and Google Scholar for articles published from 1980-2019 using the terms antibiotic, antifungal, bacteremia, bloodstream infection, candidemia, candidiasis, children, coagulase negative staphylococcus, consultation, contamination, costs, echocardiogram, endocarditis, enterobacteriaceae, enterococcus, gram-negative, guidelines, IDSA, immunocompromised, infectious disease or ID, lumbar puncture, meningitis, mortality, MRSA, MSSA, neonatal, outcomes, pediatric, pneumococcal, polymicrobial, pseudomonas, rapid diagnostic testing, resistance, risk factors, sepsis, staphylococcus aureus, stewardship, streptococcus, treatment. With the data from this search, we aim to provide guidance to frontline providers regarding the interpretation and immediate actions to be taken in response to the identification of common bloodstream pathogens by mRDTs. In addition to antimicrobial therapy, additional diagnostic or therapeutic interventions are recommended for particular organisms and clinical settings to either determine the extent of infection or control its source. Pediatric perspectives are offered for those bloodstream pathogens for which management differs from that in adults.

Abbreviations and Acronyms:

CDC = Centers for Disease Control and Prevention

CoNS = coagulase-negative staphylococci

CRE = Carbapenem-Resistant Enterobacteriaceae

CTX-M = CefoTaXime active β-lactamases, first isolated in Munich

CVC = central venous catheter

ESBL = Extended spectrum beta-lactamase

GAS = group A streptococcus

Hib = *Haemophilus influenzae* type b

IDSA = Infectious Diseases Society of America

IMP = Imipenem-resistant *Pseudomonas* (IMP)-type carbapenemases

IVIG = intravenous immunoglobulin

KPC = *Klebsiella pneumoniae* carbapenemase

MALDI-TOF = matrix-assisted laser desorption/ionization time-of-flight

MRSA = methicillin-resistant *Staphylococcus aureus*

MSSA = methicillin-susceptible *Staphylococcus aureus*

N.A. = not applicable

NDM = New Delhi Metallo-beta-lactamase

OXA = Oxacillin-hydrolysing (OXA) carbapenemases

SAB = *Staphylococcus aureus* bacteremia

STSS = streptococcal toxic shock syndrome

TEE = transesophageal echocardiogram

TTE = transtracheal echocardiogram

TMP-SMX = trimethoprim sulfamethoxazole

VIM = Verona Integron-Mediated Metallo-β-lactamase

Introduction

Each year ≥1.7 million adults in the United States develop sepsis, accounting for 270,000 deaths or 1 in 3 patients who die in a hospital.[1] Septicemia is the most expensive condition treated in U.S. hospitals, accounting for $24B in healthcare costs annually.[2] Delays in initiation of effective antimicrobial therapy increase the risk of mortality, particularly for patients with septic shock.[3, 4] Yet, in a meta-analysis of 70 individual studies, 46% of sepsis patients were found to have been given inappropriate empiric therapy.[5] When combined with an antimicrobial stewardship program, mRDTs for identification of the causative agent of bloodstream infection and the detection of salient resistance mutations result in more rapid implementation of pathogen-directed antimicrobial therapy, shorter length of stay, and reduced mortality.[6] For these reasons, the 2016 Infectious Diseases Society of America Antimicrobial Stewardship Program guidelines recommend the use of rapid diagnostic testing as a key to improving outcomes from bloodstream infections.[7]

A number of mRDTs have been developed both for whole blood and positive blood cultures that dramatically decrease the time to pathogen identification compared to conventional methods (Figure 1). As a general rule, microbiology laboratories will initially provide clinicians with the results of a Gram-stain of organisms found in positive blood cultures, then either simultaneously or within a few hours (depending on laboratory workflow at the same time), the laboratory will also provide the mRDT results for both the identity of the infecting organism and the presence of resistance genes.

In settings where mRDTs have been adopted by clinical microbiology laboratories, the identity of a bloodstream pathogen enables assessment of diagnostic and therapeutic management prior to complete phenotypic antimicrobial susceptibility results. When integrated with an antimicrobial

stewardship program, knowing the pathogen and whether important mutations that mediate antimicrobial resistance are present enables the provider to take immediate actions to optimize care.[8] Pathogen-directed therapy shortens time to effective therapy (by indicating when therapy needs to be escalated), allows for discontinuation of unnecessarily broad or toxic therapy (de-escalation) and provides insight into the source of infection, with significant impacts on clinical outcomes and the cost of care for patients with sepsis and bloodstream infections.[6, 9-11]

We searched PubMed and Google Scholar for articles published from 1980-2019 using the terms antibiotic, antifungal, bacteremia, bloodstream infection, candidemia, candidiasis, children, coagulase negative staphylococcus, consultation, contamination, costs, echocardiogram, endocarditis, enterobacteriaceae, enterococcus, gram-negative, guidelines, IDSA, immunocompromised, infectious disease or ID, lumbar puncture, meningitis, mortality, MRSA, MSSA, neonatal, outcomes, pediatric, pneumococcal, polymicrobial, *Pseudomonas*, rapid diagnostic testing, resistance, risk factors, sepsis, staphylococcus aureus, stewardship, streptococcus, treatment. With the data from this search, we aim to provide guidance for how mRDT results may be applied to modify antimicrobial therapy and expedite other aspects of management for patients with bloodstream infection. It is important to keep in mind that such general guidance cannot account for an individual patient's particular clinical circumstances and should never replace physician judgement. Nevertheless, identification of a specific bloodstream pathogen presents an opportunity to focus and/or de-escalate therapy, because initial empiric antimicrobial therapy is often overly broad and de-escalation provides important clinical and healthcare economic benefits.[12] Pediatric perspectives are included such as the need for examination of cerebrospinal fluid in children under 1 month of age for most bloodstream infections.

Staphylococci

Staphylococci are Gram-positive bacteria which appear in clusters on Gram stain. This genus includes highly pathogenic *S. aureus*, as well as coagulase-negative staphylococci (CoNS), which are common skin flora and blood culture contaminants.

Staphylococcus aureus. *S. aureus* most commonly causes skin and soft tissue infections, but can also cause pneumonia, bone and joint infections, bacteremia, and endocarditis. *S. aureus* bacteremia (SAB) is frequent, ranging from 18% for community-acquired to 30% for hospital-acquired bacteremia.[13] *S. aureus* found in the blood should always be treated as being a true bacteremia and it is associated with significant mortality (between 20 to 40% depending on methicillin resistance and comorbidities).[14]

Once *S. aureus* has been confirmed via conventional methods or by mRDT (i.e., when both "Staphylococcus" and "*S. aureus*" probes turn positive), treatment will depend on whether the *mec*A gene (the major determinant of methicillin-resistance) is detected (Figure 2). With infections due to methicillin-resistant *S. aureus* (MRSA) or when methicillin susceptibility is unknown, either vancomycin or daptomycin is generally recommended. Daptomycin may be preferable to vancomycin in patients receiving outpatient parenteral antimicrobial therapy and/or on hemodialysis, due to ease of use and dosing. Because of the risk of rhabdomyolysis, creatine kinase levels should be checked for patients on daptomycin and it is prudent to temporarily interrupt co-administration of statins. Daptomycin is not indicated in cases where SAB is associated with pneumonia; in such cases linezolid may be considered as an appropriate alternative to vancomycin. Many institutions require contact isolation for patients with MRSA infections.

If *mec*A is not detected, the isolate is almost certain to be methicillin-susceptible (i.e., MSSA). Clinicians however should be aware that although quite uncommon at present, other genes (e.g., *mec*C) that are not detected by all rapid diagnostic platforms (Table 1) can confer methicillin-resistance. Therapy for MSSA should be narrowed to anti-staphylococcal beta-lactam agents (e.g., oxacillin). These agents are superior to vancomycin for clearance of MSSA bacteremia and prevention of recurrence.[15] Cefazolin is an alternative choice for patients with non-anaphylactic penicillin allergies.

Next, clinicians should focus on source identification and control. The most common sources of SAB are complicated skin and soft tissue infections, intravenous catheters (both peripheral and central), implanted devices including prosthetic valves, or cerebrospinal fluid shunts.[16] Any potentially localizing symptoms such as back pain may indicate metastatic infection and can guide further imaging.

Depending on the clinical scenario, source control can include abscess drainage, osteomyelitis debridement, and CVC removal (when possible). Repeat blood cultures should be confirmed as being negative prior to placement of a new CVC.[17] In all cases of SAB, transthoracic echocardiography (TTE) should be performed to rule out endocarditis.[18, 19] Whether or not a transesophageal echocardiogram (TEE) is necessary for this evaluation requires careful consideration of the risk factors and overall pre-test probability for infective endocarditis.[20] Because the management of SAB often involves such nuanced decision-making, infectious disease consultation is *highly* recommended. Across multiple studies, it has been associated with improved outcomes, including decreased mortality.[21]

Pediatric Perspective: *In healthy children, SAB is often associated with skin or soft tissue infections or osteomyelitis.[22] Similar to adults, clinicians should conduct a thorough workup to*

identify a source in children with SAB, including TTE and musculoskeletal imaging.[18] Lumbar puncture should always be considered in neonates less than 30 days of age with SAB, sepsis, and without a focal source of infection.[23] Occasionally, no source of SAB is identified, particularly in children with co-morbidities that may increase their risk of bacteremia.[24]

Coagulase-negative Staphylococci (CoNS). CoNS, such as *S. epidermidis*, are common skin flora and frequently isolated from blood cultures.[25] CoNS often represent contamination rather than true bacteremia,[26] especially in the absence of CVCs or other foreign materials. An important exception is *S. lugdunensis*, which tends to behave more like *S. aureus* and can cause significant morbidity.[27] Features of CoNS associated with true bacteremia include ≥2 concomitant bottles with growth,[25] short time-to-culture positivity (i.e., ≤ 24 hours),[28] and presence of multiple SIRS criteria.[29] CoNS is identified based on a positive mRDT for the "Staphylococcus" genus but a negative result for "*S. aureus*". Clinicians utilizing mRDT in their practice should be careful to distinguish results indicating *S. aureus* vs. CoNS.

In cases of suspected blood sample contamination with CoNS in an asymptomatic patient who lacks relevant risk factors for true infection, it may be prudent to stop/withhold antibiotics while under close observation. For true bacteremia caused by CoNS, antibiotic selection can be guided by *mecA* results with either vancomycin or anti-staphylococcal beta-lactams being typical agents. Recommended durations of antibiotics vary, depending on the number of positive blood culture bottles, presence of any foreign material, and whether there are other metastatic foci of infection.[17, 30] In cases of catheter-related CoNS bacteremia, it may be reasonable in selected circumstances to defer catheter removal while treating with intravenous antibiotics and/or antibiotic lock therapy. However, if relapsing bacteremia or clinical deterioration occur, catheter removal is almost always required.[17] In cases of CVC infection with CoNS, infectious disease consultation is recommended.

Pediatric Perspective: *Although CoNS is frequently considered a contaminant, it can commonly cause symptomatic infections in the neonatal intensive care unit, particularly in extremely premature infants with a very low birthweight.*[31, 32] *In this population it can lead to late and late, late-onset sepsis. Because single blood cultures are frequently obtained in pediatric patients, if can be difficult to differentiate CoNS bacteremia from contamination. CoNS can be associated with device or surgical site infections patients with risk factors, including immunocompromised children. Associated mortality secondary to CoNS bacteremia was only 5% in one NICU study.*[31]

Streptococci

Streptococci are Gram-positive cocci that form pairs or chains. mRDTs are typically able to specifically identify Groups A (*S. pyogenes*), B (*S. agalactiae*) and *S. pneumoniae*; other species are identified only to the genus level as Streptococcus, which may represent beta-hemolytic Streptococci (e.g., Group C and G) or alpha-hemolytic (viridans) Streptococci. The clinical manifestations of disease due to beta-hemolytic Streptococci mimic those of Group A Streptococci while alpha-hemolytic Streptococci are often associated with endocarditis, dental or deep infections (e.g., intra-abdominal, liver or lung abscess and/or empyema) as well as sepsis, especially in immunocompromised patients with hematologic malignancies. Penicillin G, ampicillin, cefuroxime, ceftriaxone or cefotaxime are appropriate empiric therapy for non-speciated streptococcal infections with vancomycin held in reserve for penicillin-allergic patients, as adjunctive therapy with ceftriaxone for patients with meningitis or for treatment of severely ill neutropenic patients at risk for infection by penicillin-resistant viridans streptococci.[33] Because of variation in susceptibility, empiric therapy with clindamycin, fluoroquinolones and tetracyclines should be avoided.

S. agalactiae (Group B)

S. agalactiae is a common cause of neonatal sepsis and pneumonia. In adults, bacteremia is most often due to skin and soft tissue infections, but also accompanies septic arthritis, acute bacterial meningitis and endocarditis. Diabetes, alcohol abuse, recurrent urinary tract infections and hepatic cirrhosis are risk factors for invasive disease.[34] Group B streptococci are susceptible to penicillin G, ampicillin, and many cephalosporins. Resistance to clindamycin and erythromycin is found in up to 40-50% of isolates.[35]

Pediatric Perspective: *Group B streptococcal (GBS) bacteremia in infants is typically thought of as occurring early (within the first 6 days of life), late (7 to 89 days after birth) and late, late (after 90 days of birth).[36] Children with early onset and late onset GBS bacteremia should be evaluated for meningitis.[37] Because GBS bacteremia can be associated with musculoskeletal infections, clinicians should conduct a thorough physical examination and consider imaging of joints with MRI or x-ray if infection is suspected.[37] Treatment of GBS bacteremia should be with ampicillin and an aminoglycoside.[37] Aminoglycosides can be discontinued when clinical and microbiologic improvement is noted.[36]*

S. pneumoniae

Bacteremia due to *S. pneumoniae* most often accompanies pneumonia, but also prompts concern for meningitis, septic arthritis and endocarditis. Risk factors for bacteremia include impairment of humoral immunity (e.g., multiple myeloma, complement or immunoglobulin deficiencies), functional or anatomic asplenia, chronic liver or kidney disease, congestive heart failure, malnutrition, chronic obstructive airways disease, and HIV infection.

Except for cases of suspected meningitis, where high dose ceftriaxone and vancomycin should be given to overcome low-level resistance and poor drug penetration into the cerebrospinal fluid, monotherapy with penicillin, ampicillin, ceftriaxone, cefotaxime, or, for beta-lactam intolerant patients, vancomycin are the preferred therapies. Adults with *S. pneumoniae* meningitis also benefit from adjunctive corticosteroids if administered before or with the first dose of antibiotics.

Pediatric Perspective: *Children with S. pneumoniae bacteremia who are either less than 2 months of age or with altered mental status should undergo lumbar puncture as the risk of concurrent meningitis is high.[36] Since the introduction of pneumococcal conjugate vaccines, the rate of invasive pneumococcal disease has declined significantly,[38] therefore clinicians should consider evaluating immunized children over 2 with severe invasive pneumococcal disease for immunodeficiency, especially in children with invasive disease caused by a vaccine serotype.[39]*

S. pyogenes **(group A ß-hemolytic streptococcus)**

S. pyogenes bacteremia most often accompanies skin or soft tissue infection, particularly necrotizing fasciitis, but pneumonia, empyema, septic arthritis and, among those < 10 years of age, meningitis are also common sources and/or complications.[40] The most common underlying conditions include recent surgery, other skin/skin structure injury as well the risk factors listed above for *S. pneumoniae*.

Because of the universal susceptibility of S. pyogenes to penicillin, targeted therapy with penicillin can be quickly implemented based on mRDT detection alone, without waiting for phenotypic susceptibility results. Other appropriate therapies for Group A streptococcal (GAS) bacteremia include penicillin G and cefazolin. Vancomycin should be reserved for penicillin-allergic patients who cannot tolerate a cephalosporin; ciprofloxacin should not be used.

Although clindamycin resistance can occur,[41] it nonetheless has an important adjunctive role in persons with streptococcal toxic shock syndrome (STSS). Urgent surgical debridement is crucial in persons with necrotizing fasciitis; the role of adjunctive IVIG is less certain. To prevent person-to-person transmission, patients with cutaneous or draining *S. pyogenes* infections should be placed on contact isolation and, in the case of pneumonia or GAS pharyngitis, droplet isolation for at least the first 24 hours of antimicrobial therapy.[36]

Pediatric perspective. *Children with invasive GAS infections can present with localized infection, such as an abscess, or more systemic disease including STSS.[36] In STSS, streptococcal strains produce toxins that can lead to fever, erythroderma, hypotension, and multiorgan failure.[36] Children with GAS bacteremia should be monitored for the development of STSS and should receive supportive care as well as treatment with a bacterial protein synthesis inhibitor, such as clindamycin, in addition to penicillin.[36]*

Enterococci

Portals of entry for enterococcal bacteremia include the gastrointestinal tract, the urinary tract, intravascular catheters, and wounds. When found in only a single blood culture, a significant percentage of isolates are contaminants or of uncertain significance.[42] Severe sepsis in the setting of enterococcal bacteremia is uncommon and should raise suspicion for polymicrobial infection with Gram-negative bacteria. Persistent bacteremia should prompt concern for an infected vascular catheter or endocarditis. Higher risk of endocarditis is also associated with monomicrobial cultures with *E. faecalis*, prosthetic heart valve, male sex and community acquisition.[43]

Enterococci in the bloodstream are usually either *E. faecalis* or *E. faecium*, organisms that differ significantly in terms of antibiotic resistance and management. *E. faecalis* is typically treated with ampicillin (or vancomycin for penicillin-allergic patients); if endocarditis is a concern high-dose ceftriaxone or synergistic doses of gentamicin should be added. Beta-lactam and vancomycin resistance is common among *E. faecium* isolates, which should be treated with high-dose daptomycin (8-10mg/kg/day).[44] Vancomycin is appropriate therapy for *E. faecium* isolates that are *vanA/vanB* negative.

Central venous catheters should be removed in patients with repeatedly positive blood cultures or clinical deterioration. Echocardiography should be performed in patients with suspected endocarditis, in which case infectious diseases consultation is also recommended. For patients in whom endocarditis is not a concern, true bacteremia should be treated with systemic antibiotics for 7-14 days.[17] An attempt to sterilize short- and long-term catheters can be made by providing concurrent antibiotic lock therapy.

Enterobacterales

The bacterial order *Enterobacterales* consists of several species of Gram-negative rods that are often members of the human gut microbiota. The appropriate response to their identification by mRDT platforms can be challenging to interpret owing to the diversity of their clinical disease manifestations and capacity for antimicrobial resistance. Rapid identification platforms report different combinations of *Enterobacterales* and resistance genes that can be associated with them (Table 1).

The finding of *Enterobacterales* in blood often suggests an abdominal or urinary source. Pneumonia may also be a consideration, especially for patients at risk for hospital-acquired or

ventilator-associated pneumonia. *Klebsiella pneumoniae* can occasionally cause severe community acquired pneumonia. *Enterobacterales* are sometimes responsible for catheter-associated and skin and soft tissue infections in the nosocomial setting.

An important distinction must be made here between genotypic and phenotypic resistance detection. There are many resistance mechanisms in Gram-negative bacteria, particularly *Enterobacterales*, and multiple mechanisms may be simultaneously present with additive, synergistic, or antagonistic effect. Furthermore, all resistance mechanisms are not captured by mRDT, thus genotypic resistance detection may not be sufficient to rule out resistance and de-escalate antibiotics. However, mRDTs are sufficient to rule in resistance and escalate antibiotics if a specific marker is identified. Thus, the choice of empiric antimicrobial therapy for *Enterobacterales* bacteremia depends on the following factors: 1) species identification; 2) detection of resistance genes by the rapid diagnostic platform; and 3) patient's epidemiologic risk for infection with an antimicrobial-resistant organism. When no resistance mechanisms are detected, the clinician must still assess the risk that infection is caused by an antibiotic resistant organism. Factors that influence this likelihood include recent colonization or infection with a resistant organism, recent antibiotic use, residence in a long-term care facility, and hospital onset of infection. In *E. coli* and related organisms (see Figure 3), if no such factors are present, ceftriaxone is reasonable empiric therapy. Otherwise, ertapenem is likely a better choice, with the optional addition of amikacin if the patient is critically ill or has a history of infection with carbapenem-resistant organisms. Fluoroquinolones may also be options depending on local antibiograms.

On the other hand, some enteric organisms are capable of inducible *ampC* β-lactamase production. These organisms may initially show phenotypic susceptibility to ceftriaxone but may develop resistance with treatment. Among *Enterobacterales, ampC* induction is most

commonly present in *Enterobacter*, but can also be present in (among rapid pathogen identification targets) *Klebsiella aerogenes, Serratia marcescens, Citrobacter,* and *Morganella morganii.*[45, 46] Identification of any of these species from blood (especially *Enterobacter* and *K. aerogenes*) should prompt consideration of empiric therapy with cefepime or a carbapenem even when no resistance genes are detected, though ceftriaxone may still be a reasonable choice in non-critically ill patients in which source control has been achieved. Ertapenem is a particularly attractive option when carbapenemases are not present and co-infection with *Pseudomonas* is not present. General *Enterobacterales* probe positivity without species-specific probes turning positive indicates bacteremia with a less common member of the *Enterobacterales* order; consultation with Infectious Diseases is suggested when this occurs, though ertapenem (with optional addition of amikacin if critically ill) should be adequate therapy.

The resistance genes detected by rapid diagnostic platforms that can be found in *Enterobacterales* include CTX-M, the most common extended spectrum β-lactamase (ESBL) in the United States, carbapenemases (KPC, NDM, VIM, IMP), and extended-spectrum β-lactamases (OXA, OXA-48-like) that can have carbapenemase activity when combined with efflux pumps and other resistance mechanisms that impair membrane permeability.[47] If CTX-M alone is detected in an *Enterobacterales* isolate, ertapenem is generally the best choice for empiric therapy, with the optional addition of amikacin if the patient is critically ill or has a history of infection with carbapenem-resistant organisms. KPC is presently the most common carbapenemase in the United States; if no other carbapenemases are found organisms that harbor KPCs can be treated with ceftazidime-avibactam, meropenem-vaborbactam or imipenem cilastatin-relebactam. If OXA, or OXA-48-like genes are detected, ceftazidime-avibactam (alone or in combination with another agent) is likely the best choice.[48] Carbapenemases of the metallo-β-lactamase family (NDM, VIM, IMP) pose the greatest challenge for treatment, as

aside from cefiderocol,[49] most new agents that have activity against non-metallo-β-lactamase carbapenemases (e.g., ceftazidime-avibactam, meropenem-vaborbactam, imipenem cilastatin-relebactam) are not active against them. Identification of any of the carbapenemases should prompt immediate implementation of contact isolation, notification of infection control and infectious diseases consultation for management of these complex cases. Many facilities also isolate persons with ESBL or CRE.

Pediatric Perspective: *The isolation of a gram-negative rod has specific implications for pediatric patients. While widespread antimicrobial prophylaxis for Group B Streptococcus carriage has led to a decline early onset GBS infection, rates of neonatal E. coli infections remain unchanged.[50] Neonatal E. coli infection should raise the concern for galactosemia in a newborn. All infants with bacteremia due to Citrobacter (and other Enterobacterales such as Proteus and Cronobacter sakazakii), should be evaluated for meningitis and brain abscess, as these organisms have a propensity to invade the central nervous system, and approximately 10% of infants with neonatal meningitis will develop brain abscess.[51] Isolation of Serratia marcescens in an otherwise healthy child should prompt evaluation for chronic granulomatous disease.*

Pseudomonas aeruginosa

P. aeruginosa is a gram-negative rod that causes bacteremia principally in persons with severe neutropenia, extensive prior antibiotic exposure or burn injuries or in infants with hypogammaglobulinemia.

To assure effective treatment against potential multi-drug resistant isolates empiric therapy for critically ill patients should include two antimicrobial agents with differing mechanisms of action, e.g., an aminoglycoside and an antipseudomonal ß-lactam antibiotic; monotherapy with a

reliably active antipseudomonal ß-lactam antibiotic is an alternative for less ill patients. For ß-lactam allergic patients, use of aztreonam is preferred over anti-pseudomonal fluoroquinolones (ciprofloxacin or levofloxacin) due to the higher rates of fluoroquinolone resistance. Amikacin is the most reliably active aminoglycoside. ß-lactam antibiotics with activity against *P. aeruginosa* include piperacillin/tazobactam, ceftazidime, cefepime, imipenem and meropenem; the choice depends on local antibiotic resistance patterns. Note that ertapenem does not have activity vs. *Pseudomonas.*

Neisseria meningitis

N. meningitidis is a gram-negative diplococcus. The most feared complication is meningitis and overwhelming meningococcemia/sepsis; patients with hereditary or acquired (e.g., due to receipt of eculizumab) complement-deficiency are at increased risk of infection. Additionally, bacteremia can occur without an apparent primary source of infection or may be associated with isolated pneumonia or septic arthritis. High-dose cefotaxime or ceftriaxone is preferred until meningitis has been ruled out. For other infections high dose penicillin G or cefuroxime can be used. Options are not well studied for penicillin-allergic patients who cannot tolerate a cephalosporin. Chloramphenicol is no longer readily available. Moxifloxacin and aztreonam show promise and occasional allergic patients tolerate meropenem. Because of the risk of outbreaks, patients should be placed in droplet isolation and public health should be notified. Chemoprophylaxis with rifampin, ciprofloxacin or ceftriaxone is advised for household and other intimate contacts of the patient.

***Candida* species**

Identification of a Candida species in a blood sample should trigger a rapid change in therapeutic management as these organisms can cause life-threatening infections and it is unusual for patients to have been placed on empiric antifungal therapy. Intensive care patients are at increased risk of candidemia, particularly those with long-term stays in intensive care, central venous catheters, broad spectrum antibiotics or a history of abdominal surgery.[52] Another candidemia risk group is immunocompromised patients including solid organ transplant recipients and patients with hematologic or solid-organ malignancies status post chemotherapy.[52]

C. albicans, *C. tropicalis*, *C. dublienensis*, and *C. parapsilosis* are typically azole susceptible. In contrast, all azoles have less activity against *C. glabrata* strains and *C. krusei* is intrinsically resistant to some azoles. With the exception of *C. auris* (see below), most *Candida* species retain susceptibility to amphotericin B and the echinocandins. As a general rule, infectious diseases should be consulted for all cases of candidemia to assure appropriate management including consideration for indwelling catheter removal.[53]

Regardless of species, the 2016 IDSA guidelines recommend initial therapy with echinocandins, e.g., caspofungin, micafungin or anidulafungin, for most cases of candidemia.[54] Echinocandins have an excellent safety profile, with mild fever, thrombophlebitis, headache, and liver aminotransferase elevations as the primary side effects. Depending on the likely susceptibility, patients on intravenous echinocandin therapy who are stable can usually be stepped down to oral azole therapy after five days, resulting in considerable cost savings.[55, 56]

Echinocandins also generally have activity against *C. auris*, an emerging cause of invasive candida infections that is usually resistant to azoles and sometimes resistant to amphotericin B. Originally isolated from the ear of a patient in Japan in 2009, *C. auris* has rapidly spread internationally. The CDC has now reported hundreds of cases in the US, primarily in medically

complex patients from nursing facilities New York, New Jersey, Chicago, and Orange County, California.[57, 58] The organism persists on hard surfaces for weeks, can grow at temperatures up to 42°C, and is resistant to killing by certain disinfectants. Infectious diseases consultation is highly recommended for all patients with *C. auris* infections, who should be promptly placed in contact isolation and infection control should be notified; because of the hardiness of the organism facilities should use isolation similar to that used for *C. difficile*. Of note, some labs may not be able to detect or may misindentify *C. auris* by mRDT or MALDI-TOF, so if *C. auris* infection is suspected, the laboratory should be notified to ensure their ability to detect *C. auris*.

Pediatric Perspective: *A common cause of diaper dermatitis and oral thrush in infants and young children, candida can also cause systemic infections, primarily in immunocompromised patients. Risk factors are similar to those seen in adults, including broad spectrum antibiotics, neutropenia and indwelling central line catheters.[59] Removal of the central line is critical to eradicating candida from the bloodstream and preventing spread to liver, spleen, bones, joints and the central nervous system. Preterm infants are particularly susceptible to invasive candida infections, including meningitis, and the isolation of fungus from the bloodstream necessitates investigation of the central nervous system. Neonatal candidiasis is associated with 20% mortality, and 50% of survivors have severe neurodevelopmental impairment.[60, 61] Amphotericin B deoxycholate is well tolerated in infants; lipid formulations can also be used, but are not preferred.[62]*

Polymicrobial bacteremia

One disadvantage of mRDT is reduced sensitivity in detection of all bacteria from polymicrobial cultures.[63] It is also important to remember that a single species may be detected by multiple

positive organism probes on mRDT platforms. For example, bacteremia with *E. coli* will lead to positivity of the general *Enterobacteriaceae* probe as well as the *E. coli* probe on the BioFire BCID panel. Similarly, *S. aureus* will cause a general *Staphylococcus* probe to turn positive in addition to a *S. aureus* probe. Isolation of two separate species, however, implies a breach of mucosal or skin integrity that allows organisms access from a typically non-sterile site into the bloodstream as can be seen in intra-abdominal infections, necrotizing infections of the perineum, infection of decubitus ulcers, catheter-associated urinary tract infections, severe burns, and injection of stool or other foreign materials into an intravenous line in the setting of a factitious disorder.[64, 65] Antimicrobial therapy depends on the organisms involved, but for polymicrobial bacteremia from infections involving the abdomen or pelvis, anaerobic coverage is likely warranted even if a specific anaerobe is not identified from blood.

Bacteremia without mRDT positivity

Rarely, a blood culture may have positive gram stain results without any of the mRDT probes becoming positive. This suggests bacteremia with an uncommon organism. In general, Infectious Diseases should be consulted when this occurs. For Gram-positive organisms without mRDT identification, vancomycin is likely appropriate empiric therapy, unless the vanA/B gene is positive, in which case daptomycin is likely most appropriate. For Gram-negative organisms without mRDT identification, choice of antibiotic therapy is less clear and Infectious Diseases consultation should be obtained urgently.

Discussion

Inappropriate antimicrobial prescribing, which accounts for 30-50% of all use, is a major driver of increased antimicrobial resistance, *Clostridioides difficile* infection, and other adverse events and unnecessary health care costs.[66, 67] To avoid undertreatment of seriously ill, septic patients, guidelines emphasize early administration of broad, empiric therapy. Consequently, broad-spectrum therapy is given far more often than can be justified by culture results.[66, 68] Although societal and CDC recommendations emphasize de-escalating therapy as soon as culture results are available,[69, 70] de-escalation being safe,[6, 71-73] and every day of additional therapy increasing harm,[74] many de-escalation opportunities are still missed.[45, 75]

New diagnostic tests that rapidly identify common pathogens and detect important mechanisms of resistance provide new opportunities to more quickly administer targeted and highly effective antibiotic therapy. However, the results of these tests are not often acted upon by front line providers in a timely manner.[6]

We have reviewed how providers can use the information provided by mRDTs to administer appropriate, streamlined antibiotic therapy to bacteremic and candidemic patients. In addition, we have emphasized what sources of infection should be considered when the pathogen is identified (and how that might affect patient management), and whether specific infection control measures should be put in place to prevent person-to-person transmission.

Therapeutic changes can be made with confidence when mRDT detect organisms with reliable patterns of antimicrobial susceptibility and for which complex mechanisms of resistance are rare, e.g., Streptococci, *H. influenza, N. meningitidis* and *Candida spp.* For *S. aureus,* the presence or absence of *mecA* (see Figure 2) and for Enterococci, the presence or absence of *vanA* and *vanB* (see Table 2) are sufficient to confidently select targeted therapy.

With other organisms, decision-making is somewhat more complicated. Nevertheless, for the most common causes of Gram-negative bacteremia, i.e., *E. coli* and *K. pneumonia*, the absence of resistance genes or risk factors for infection with a resistant organism (see Figure 3), allows for the confident use of ceftriaxone (rather than a carbapenem or anti-pseudomonal beta-lactam) in many patients. Conversely, when resistance genes are detected, broad-spectrum therapy and consultation by an infectious diseases expert is needed.

Finally, when bacteremia is found to be due to a Gram-negative (or Gram-positive) pathogen, therapy directed against Gram-positive (or Gram-negative) pathogens can be confidently stopped unless there are serious concerns about polymicrobial bacteremia (e.g., in patients with necrotizing fasciitis or complex intra-abdominal infections). Similarly, *B fragilis* infection is nearly always polymicrobial in nature.

Conclusion

The use of mRDTs is an evolving field with frequent introduction of new technologies and assays. However, while the information provided by new tests will change, the principles of patient management remain the same. Timely alteration in treatment to ensure appropriately targeted and effective antibiotic therapy and optimization is every provider's responsibility. Every day of unnecessary therapy matters.

Supplementary Materials: Management of bloodstream infection due to *Haemophilus influenzae, Listeria monocytogenes, Bacteroides fragilis*, *Stenotrophomonas*, and *Acinetobacter*.

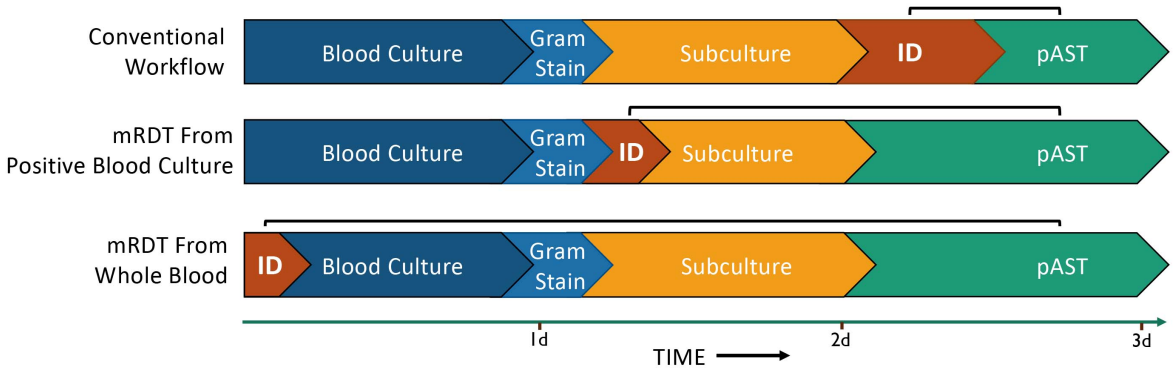

Figure 1. Impact of mRDTs on microbiologic diagnosis of bloodstream infections. In conventional workflow, identification (ID) and phenotypic antimicrobial susceptibility test (pAST) results are typically reported 2-3 days after blood culture samples are drawn. Molecular rapid diagnostic tests (mRDTs) for positive blood culture or whole blood shorten the time to identification of bloodstream pathogens and increase the time gap between ID and pAST results.

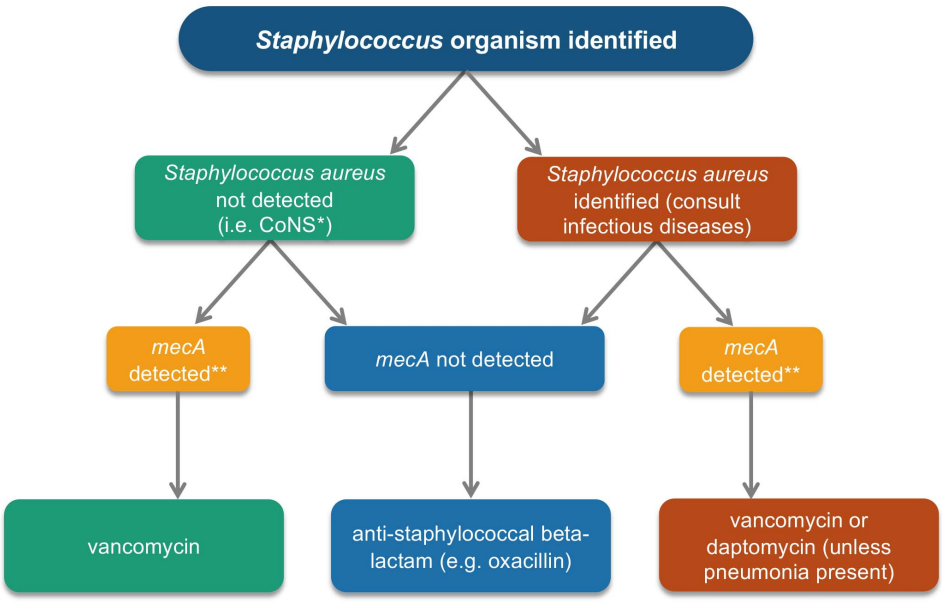

Figure 2: General approach to empiric treatment for staphylococcal bacteremia based on rapid diagnostic testing. *CoNS = Coagulase-negative Staphylococcus. **Or when methicillin-resistance status (i.e., *mec*A) is unknown.

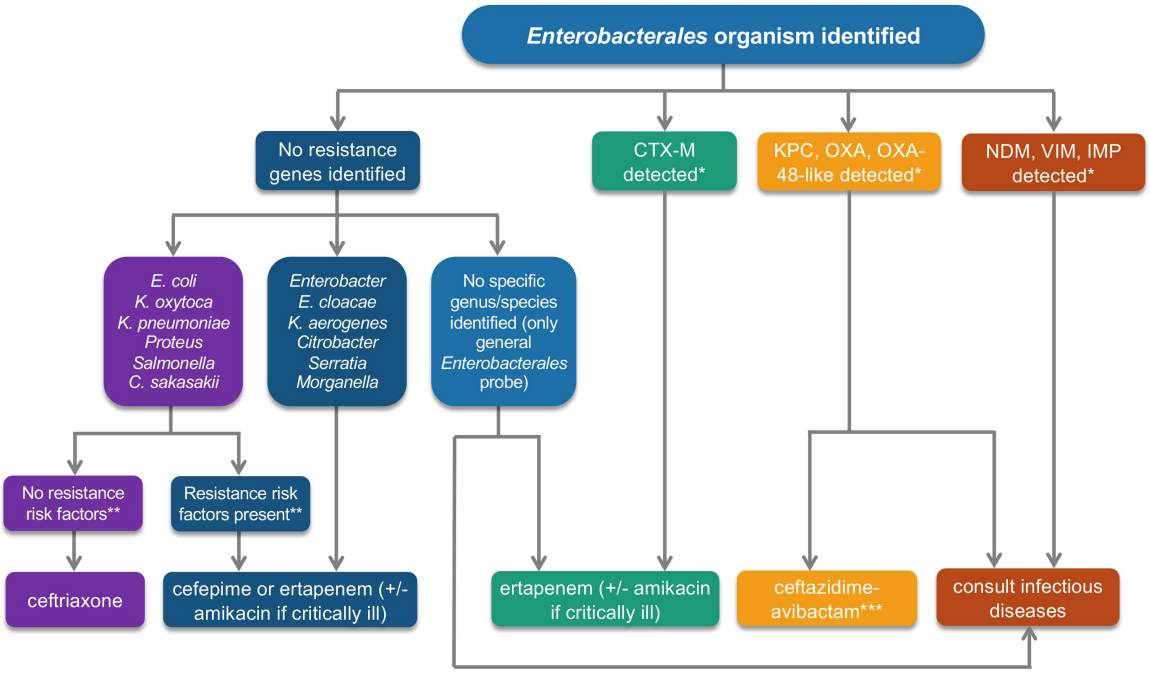

Figure 3: Antibiotic selection for *Enterobacterales* bacteremia identified by rapid diagnostic testing. *If multiple resistance genes are detected, use the option furthest to the right on the chart**.*** Risk factors include colonization or infection with a resistant organism, antibiotic use, residence in a long-term care facility, and hospital onset of infection within the prior three months. ***If only KPC is identified, meropenem-vaborbactam and imipenem cilastatin-relebactam can be considered as alternatives to ceftazidime-avibactam. CTX-M = CefoTaXime active β-lactamases, first isolated in Munich. IMP = Imipenem-resistant *Pseudomonas* (IMP)-type carbapenemases. KPC = *Klebsiella pneumoniae* carbapenemase. NDM = New Delhi Metallo-beta-lactamase. OXA = Oxacillin-hydrolysing (OXA) carbapenemases. VIM = Verona Integron-Mediated Metallo-β-lactamase.

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Table 1: Coverage of bloodstream pathogen identification by mRDTs

Gram-Negative Pathogens	BioFire BCID	Verigene BC-GN	GenMark BCID-GN	Gram-Positive Pathogens	BioFire BCID	Verigene BC-GP	GenMark BCID-GP
Acinetobacter baumanii	x		x	*Bacillus cereus group*			x
Bacteroides fragilis	x*		x	*Bacillus subtilis group*			x
Enterobacterales (general)	x			*Corynebacterium*			x
Citrobacter		x	x	*Cutibacterium acnes*			x
Cronobacter sakazakii			x	*Enterococcus*			x
Enterobacter		x		*Enterococcus faecalis*	x*	x	x
Enterobacter cloacae complex	x		x	*Enterococcus faecium*	x*	x	x
Enterobacter (non-cloacae)			x	*Lactobacillus*			x
Escherichia coli	x	x	x	*Listeria*		x	x
Klebsiella aerogenes	x*			*Listeria monocytogenes*	x		x
Klebsiella oxytoca	x	x	x	*Micrococcus*		x	x
Klebsiella pneumoniae	x	x	x	*Staphylococcus*	x	x	x
Morganella morganii			x	*Staphylococcus aureus*	x	x	x
Proteus	x	x	x	*Staphylococcus epidermidis*	x*	x	x
Proteus mirabilis			x	*Staphylococcus lugdunensis*	x*	x	x
Salmonella	x*		x	*Streptococcus*	x	x	x
Serratia			x	*Streptococcus agalactiae*	x	x	x
Serratia marcescens	x	x	x	*Streptococcus anginosus*		x	x
Fusobacterium nucleatum			x	*Streptococcus pneumoniae*	x	x	x
Fusobacterium necrophorum			x	*Streptococcus pyogenes*	x	x	x
Haemophilus influenzae	x		x	**Gram-Positive Resistance Genes**			
Neisseria meningitidis	x		x	*mecA*	x	x	x
Pseudomonas aeruginosa	x	x	x	*mecC*	x		x
Stenotrophomonas maltophilia	x*		x	*vanA/B*	x	x	x
Gram-Negative Resistance Genes				**Fungal Pathogens**[#]			
CTX-M	x*	x	x	*Candida albicans*	x		x
IMP	x*	x	x	*Candida auris*	x*		x
KPC	x	x	x	*Candida glabrata*	x		x
OXA		x	x	*Candida krusei*	x		x
OXA-48-like	x*			*Candida parapsilosis*	x		x
NDM	x*	x	x	*Candida tropicalis*	x		x
VIM	x*	x	x	*Cryptococcus neoformans/gatti*	x*		x
Mcr-1	x*						

BioFire and GenMark BCID panels are multiplex PCR, Verigene's assay is microarray based. *Indicates new target on the BioFire BCID2 Panel [#]GenMark's BCID-FP panel is used to identify the fungal pathogens shown as well as *C. dublienensis, C. famata*, *C. guilliermondii, C. kefyr, C. lusitaniae, Fusarium and Rhodotorula*

Table 2: Suggested initial antimicrobial therapy pending susceptibility results

Organism Identification	Primary Therapy	Adjunctive / Alternative Therapy	Beta-Lactam Allergy
Acinetobacter	meropenem plus amikacin	meropenem alone if not critically ill and antibiogram ≤10% R	
Bacteroides fragilis	cefazolin plus metronidazole, ceftriaxone* plus metronidazole;	consider carbapenem if concern for antimicrobial resistance in a potentially polymicrobial infection	carbapenem; fluoroquinolone plus metronidazole
Candida albicans	echinocandin (eg micafungin) pediatrics: amphotericin B	not critically ill: fluconazole	N.A.
Candida glabrata, Candida krusei	echinocandin (eg micafungin) pediatrics: amphotericin B	fluconazole not indicated	N.A.
Enterococcus faecalis	ampicillin	if endocarditis is a concern add high-dose ceftriaxone or synergistic doses of gentamicin	vancomycin
Enterococcus faecium	high-dose daptomycin (8-10 mg/kg/day) (if vanA or vanB detected)	vancomycin (if vanA and vanB absent) is an alternative 1st line choice	N.A.
Enterobacterales	see Figure 3		
Haemophilus influenzae	ceftriaxone		aztreonam; fluoroquinolone
Listeria monocytogenes	ampicillin plus gentamicin		trimethoprim - sulfamethoxazole
Neisseria meningitidis	ceftriaxone	high-dose penicillin G or ampicillin	moxifloxacin; aztreonam
Pseudomonas aeruginosa	cefepime, piperacillin-tazobactam, anti-pseudomonal carbapenem – selection based on local resistance patterns	if septic: add amikacin or a fluoroquinolone	aztreonam
Staphylococcus	see Figure 2		
Stenotrophomonas maltophilia	trimethoprim - sulfamethoxazole	levofloxacin	N.A.
Streptococcus agalactiae	ampicillin	ceftriaxone; pediatric: ampicillin + gentamicin	vancomycin
Streptococcus pneumoniae	ceftriaxone	add vancomycin for patients with meningitis	vancomycin
Streptococcus pyogenes	ampicillin or penicillin G	consider adding clindamycin	vancomycin or daptomycin
other Streptococcus spp.	ceftriaxone	add vancomycin for patients with neutropenia and risk of infection by penicillin-resistant viridans streptococci	vancomycin

* throughout this table, cefotaxime can be used in place of ceftriaxone