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REVIEW

Non-culture based diagnostics for intravascular catheter related bloodstream infections

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ABSTRACT

Introduction: intravascular catheter related bloodstream infection (IVC-BSI) is a leading cause of nosocomial infections and associated with significant morbidity and mortality. Early detection and adequate treatment of causative pathogens is critical for a favourable outcome. However, it takes significant time to receive microbiological results due to the current reference diagnostic method's reliance on microbial growth.

Areas covered: This review discusses culture and non-culture based techniques for the diagnosis of non IVC-BSI and IVC-BSI, including molecular methods and biomarkers. Different diagnostic strategies are evaluated and the potential of new generation of diagnostic assays highlighted.

Expert commentary: The development of additional diagnostic methods has potential to beneficially supplement conventional culture diagnosis, and molecular techniques have particular potential to fulfil this need. They would also contribute significant new knowledge on the bacterial species present on catheters that are generally missed by diagnosis using traditionally culture-dependent methods. Advances in molecular strategies, together with new biomarkers, might lead to the development of faster, more sensitive and cheaper technologies and instruments. This review aims to provide a platform for the further development of IVCBSI diagnostic techniques.

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Intravascular catheter; catheter related bloodstream infection; blood culture; molecular methods; diagnosis

1. Introduction

Catheterization of large central veins and arteries is often necessary in the effective management of hospitalized patients. Central venous catheters of all types, peripheral venous catheters and peripheral arterial catheters are collectively referred to as intravascular catheters (IVCs). IVCs, in essence, are small bore plastic tubes inserted into the veins and arteries to deliver medication, fluids, and nutrition directly to the bloodstream, and also for blood tests and invasive blood pressure measurement. IVCs occupy a very important place in the day-to-day provision of healthcare in hospitals and in the community. Over 300 million IVCs are used each year in North America alone, and approximately 10 million in Australia [1]. Along with their undoubted advantages, however, the application of IVCs is also associated with life-threatening infections [2]. IVC-related infections are the leading cause of nosocomial bloodstream infections and associated with significant morbidity [3]. Every year, approximately 5,000 Australians are diagnosed with catheter-related bloodstream infections (CRBSIs) [4], and up to 250,000 cases occur annually in the USA [5,6]. These infections are associated with a fatality rate of up to 35% [7,8]. In addition, significant increases in hospital stays are incurred, with increased treatment costs of US$33,000–$75,000 per episode estimated [9–12]. CRBSIs also contribute to the inappropriate and excessive use of antimicrobial agents and may lead to the selection of antibiotic-resistant organisms.

The clinical suspicion of catheter-related infection is initially based on signs of local or general infection but its confirmation requires microbiological methods. The key reference diagnostic methods for CRBSI are culture-dependent methods principally used by hospital laboratories worldwide for blood, and potentially also catheter tip cultures [8,13]. The most frequently isolated bacteria from IVCs are coagulase-negative staphylococci and *Staphylococcus aureus* [8,14,15]. Other major bacterial species include *Enterobacter spp., Stenotrophomonas maltophilia, Pseudomonas aeruginosa*, and *Citrobacter freundii* [16]. For many patients with suspected CRBSI, microbiological cultures are negative, making the optimal antimicrobial therapy empiric [17]. It has been reported that fastidious pathogens and patients' antibiotic treatment greatly contribute to false-negative blood culture results, even when a BSI is strongly suspected clinically. Early detection and adequate treatment of causative pathogens, however, is critical for a favorable outcome in patients with CRBSIs [18].

This review discusses culture and nonculture-based techniques for the diagnosis of CRBSI including molecular methods. Different diagnostic strategies are evaluated and the potential benefit of new generation of diagnostic assays is highlighted. Molecular methods discussed may also be applied on the diagnosis of any bloodstream infections. It is hoped that this review will provide a platform for the further development of CRBSI diagnostic techniques.

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2. Definitions

Localized catheter colonization are defined as significant growth of a microorganism (>15 CFU) from the catheter tip, subcutaneous segment of the catheter, or catheter hub [19]. IVC-related localized infections are defined according to one of the following criteria: (i) erythema or induration within 2 cm of the catheter exit site, in the absence of concomitant bloodstream infection and without concomitant purulence or (ii) tenderness, erythema, or site induration >2 cm from the catheter site along the subcutaneous tract of a tunneled (e.g. Hickman or Broviac) catheter, in the absence of concomitant bloodstream infection or (iii) purulent fluid in the subcutaneous pocket of a totally implanted IVC that might or might not be associated with spontaneous rupture and drainage or necrosis of the overlaying skin, in the absence of concomitant bloodstream infection or (iv) concordant growth of the same organism from the infusate and blood cultures (preferably percutaneously drawn) with no other identifiable source of infection [19].

CRBSI is defined as occurring in a patient with an IVC with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (i.e. fever, chills, and/or hypotension), and no apparent source for the bloodstream infections except the catheter. One of the following should be present: a positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10^3 CFU/catheter segment catheter) culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood; alternatively, simultaneous quantitative blood cultures with a ≥3:1 ratio CVC versus peripheral; differential period of CVC culture versus peripheral blood culture positivity of >2 h [8]. The differential time to positivity is based on the relative microorganism load and the time required, of the two positive blood cultures. If the catheter is the source of infection, the blood from the hub will have a higher microbe load and therefore the time to culture positivity will be shorter compared to that of the peripheral blood culture [19].

Central line-associated bloodstream infection (CLABSI) (that is *not* secondary to an infection at another body site), (excludes mucosal barrier injury laboratory-confirmed bloodstream infection), is where the IVC was in place for >2 calendar days when all elements of the CLABSI criterion were first present together, with the day of device placement being day 1, and the IVC was in place on the date of the event or the day before. If the IVC was in place for >2 calendar days and then removed, the CLABSI criteria must be fully met on the day of CVC discontinuation or the next day [20]. This will be a blinded diagnosis by an infectious disease physician.

Culturing the catheter tip or matched blood cultures is not a criterion for CLABSI. In contrast, CRBSI is more rigorous clinical definition and requires specific laboratory testing to identify the IVC as the source of the BSI through either tip culture or a matched blood culture [19].

3. Blood culture sampling

Blood culture from an IVC requires that skin is decontaminated and allowed to dry then 20–30 mL extracted and 10–15 mL (evenly distributed) inoculated into both aerobic and anaerobic blood culture bottles [21]. If peripheral access is poor, blood may be taken through the new IVC immediately after insertion. The standard incubation time is 5 days for the majority of microorganisms to be recovered including the HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella*) group of fastidious bacteria and *Brucella spp.*[22]. If standard incubation times were increased, many other slow-growing microorganisms might be recovered such as *Candida* spp., *Mycobacterium spp.,* and *Propionibacterium spp*. Modern automated incubators including continuous monitoring for positive blood culture detection have significantly reduced the workload and contamination rates. Ideally, blood cultures should be loaded into the automated incubators immediately to reduce the chance of false-negative samples. It has been shown that blood samples held at room temperature for more than 12 h have significantly reduced microbial recovery [23]. After positive blood culture bottle detection, more time is needed for the gram stain, subculture onto agar plates, biochemical and phenotypic tests, and antimicrobial susceptibility testing [24].

4. Pathogen detection and identification using blood culture and molecular techniques

Speed is critically important for the diagnosis of CRBSI. A variety of techniques have been developed for the detection of pathogens as summarized in Figure 1. Table 1 provides an overview a few selected commercial systems for diagnosing BSI. However, the limitation of techniques listed in this section is that they require already confirmed positive blood culture bottle fluid and cannot be used initially and directly for blood samples.

4.1. Blood culture and FISH: PNA-FISH

PNA-FISH is one of the most studied commercial techniques for microbial detection in positive blood cultures [25–27]. The fluorescent-labeled peptide nucleic acid probes target the rRNA genes of a limited number of bacterial species, and target the rDNA of *Candida* species. Different commercial assays target different microbial species with the most common microbes included being *Staphylococcus aureus* or coagulase-negative staphylococci, *Enterococcus faecalis* or other selected enterococci, *Escherichia coli*, or *Pseudomonas aeruginosa* and *Candida albicans/C. parapsilosis, C. tropicalis*, or *C. glabrata/C. krusei*. Slides of positive blood culture need to be prepared, hybridized with fluorochrome-labeled oligonucleotide probes targeted to rRNA, and visualized microscopically. The test takes approximately 2.5–3 h. The sensitivities and specificities for the different kits are reported to be high, with the mean being very close to 99% and 100%, respectively [25,26]. However, these vary between different kits, with some having high specificity for the detection of *S. aureus* (99%), but low sensitivity (72%) [37]. This method can only detect a limited number of pathogens.

4.2. Blood culture and multiple PCR, hybridization: HYPLEX

Hyplex BloodScreen (BAG, Germany), a multiple PCR with subsequent bacterial identification such as methicillin-sensitive *S. aureus*, methicillin-resistant *Staphylococcus aureus,*

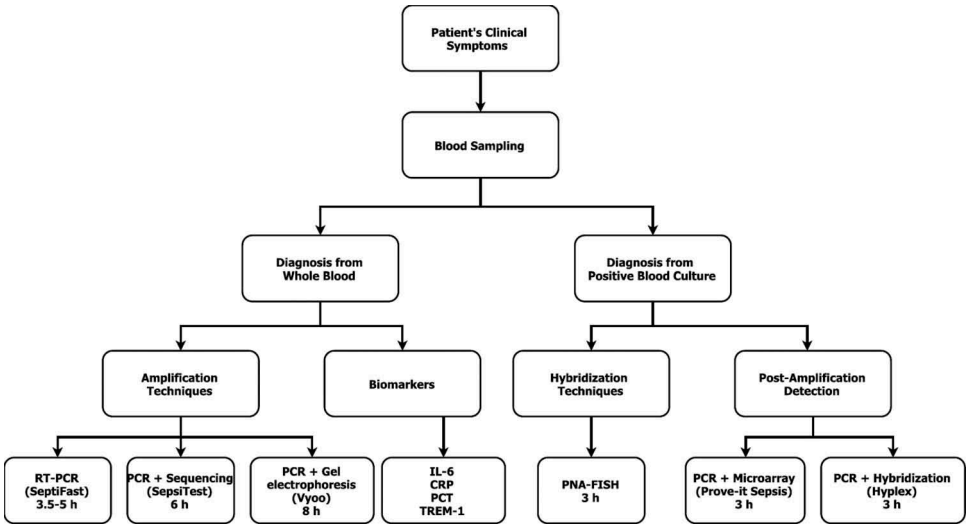

Figure 1. Diagram of diagnostic techniques for CRBSI.

Table 1. Commercially available molecular systems for diagnosis of BSI.

Systems	Method	Number of pathogens detected	Resistance and virulence marker	Turnaround time (hours)	Sensitivity and Specificity (%)	Reference
Positive bloods culture						
PNA-FISH	Fluorescence-based hybridization	10	0	3	94–99, 99–100	[25–27]
HYPLEX	Multiplex PCR with hybridization	10	mecA	3	96–100, 92.5–100	[28]
Prove-it sepsis	Mutiplex PCR with microarray	50	mecA	3	92–96, n.a.	[29,30]
Whole blood						
SepsiTest	Broad-range PCR with sequencing	>300 pathogens	0	6	61–88.5, 83.5–85.8	[31,32]
VYOO	Multiplex PCR with gel electrophoresis	34	mecA, vanA, vanB, vanC, and bla_{SHV} genes	8	30–51, n.a.	[33]
SeptiFast	Multiplex real-time PCR	25	mecA	3.5–5	60–90, 74–99	[34–36]

n.a.: not available; BSI: bloodstream infection.

Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus pneumoniae, Enterococcus faecalis, and *Enterococcus faecium, Escherichia coli, Enterobacter aerogenes, Pseudomonas aeruginosa*, and *Klebsiella* spp. Hybridization in an ELISA-like format is used in positive cultures. Antibiotic resistance biomarkers such as *van* genes and several β-lactamase genes can also be detected in this assay. The turnaround time is 4 h, and it is reported that this assay presents relatively high sensitivity (96.6–100%) and specificity (92.5–100%) [28].

4.3. Blood culture and microarray: prove-it sepsis

Prove-it sepsis (Mobidiag, Helsinki, Finland) is the microarray-based assay designed specifically for diagnosis of sepsis using positive blood culture. This assay is a microarray format that is based on amplification and detection of *gyrB, pareE,* and *mecA* genes of 50 bacterial species including pathogens commonly involved in etiology of sepsis, such as *Listeria monocytogenes, Streptococcus agalactiae*, and *Clostridium perfringens*, whereas adjunctive gram-negative species that are detectable are *Acinetobacter baumannii, Stenotrophomonas maltophilia, Haemophilus influenzae, Neisseria meningitidis, Campylobacter jejuni, Campylobacter coli, Bacteroides fragilis, Bacteroides vulgatus*, and a wider group of *Enterobacteriaceae* [29]. The turnaround time is 3 h. The company claims 94% sensitivity and 96% specificity. Unfortunately, microbiological results have not been compared to clinical information thus far. Bacterial detection limits have been reported between 11 and 600 colony forming unit/mL (CFU/mL) [30]. The clinical application of this assay is still limited since it is only used for positive blood cultures and not directly for blood samples. This assay has great future potential to apply directly to blood samples through improvements in the amplification step.

5. Pathogen detection and identification directly independent of blood culture

The prerequisite of molecular methods for diagnosing BSI is achieving highly purified genomic DNA from blood samples. The main challenges include the presence of PCR inhibitors in the blood samples and the interference of high levels of human DNA. Many commercial kits are available which can be easily used in a routine laboratory with standard equipment and provide high-quality DNA. Their main advantages

include increased sensitivity and substantially reduced the turnaround time.

5.1. PCR and electrophoresis: VYOO

VYOO (SIRSLab, Germany) is a multiplex PCR-based assay. It can detect 35 bacterial species (*S. aureus, S. pyogenes, S. pneumoniae, S. agalactiae, E. faecalis, E. faecium, C. perfringens, Bacillus cereus, E. coli, E. aerogenes, E. cloacae, K. oxytoca, K. pneumoniae, Proteus mirabilis, Serratia marcescens, Morganella morganii, P. aeruginosa, S. maltophilia, A. baumannii, Burkholderia cepacia, H. influenzae, N. meningitidis, B. fragilis, Prevotella buccae, Prevotella melaninogenica*, and *Prevotella intermedia*) and 6 fungal species (*C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei*, and *Aspergillus fumigatus*) [33]. It can also detect five common antibiotic resistance markers (*blaSHV, blaCTX-M, mecA, vanA,* and *vanB*). Vyoo has modified microbial DNA extraction methodology which can remove over 90% human DNA and it therefore significantly improves the sensitivity for pathogen detection (3–10 CFU/mL, claimed by the company). The overall turnaround time is 8 h.

5.2. PCR and sequencing: SepsiTest

SepsiTest (Molzym Germany) is a brand-range PCR targeting 16S rRNA genes of bacteria and 18S rRNA genes of fungi. The presence of bacteremia or fungemia can be detected within 4 h through broad-range amplification of 16S and 18S rRNA genes. The sequence analysis of the positive amplicon is performed for identification of 300 pathogens within 8–12 h. The diagnostic sensitivity and specificity are 88.5% and 83.5%, respectively [31]. This method is sensitive but has a high risk of false positives through DNA contamination. In addition, the relative long turnaround time might affect its clinical application for rapid BSI diagnosis.

5.3. Real-time PCR: SeptiFast

The LightCycler SeptiFast Test (Roche Molecular Systems, Branchburg, NJ) is multiplex real-time PCR assay that can detect 25 bacterial and fungal pathogens, including *S. aureus*, several coagulase-negative staphylococci, *S. pneumoniae*, several other streptococcal species, *E. faecalis, E. faecium, E. coli, E. aerogenes, E. cloacae, K. oxytoca, K. pneumoniae, P. mirabilis, S. marcescens, P. aeruginosa, S. maltophilia, A. baumannii, C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei*, and *A. fumigatus*. The assay uses dual fluorescent resonance energy transfer (FRET) probes targeting the species-specific internal transcribed spacer regions.

DNA is extracted by mechanical lysis with ceramic beads in a Magnalyzer instrument (Roche Molecular Systems), and after purification, it is processed in three parallel multiplex real-time PCRs, i.e. gram-positive bacteria, gram-negative bacteria, and fungi. The melting profile of amplified products is calculated, and pathogens could be identified at the genus or species level [34]. The presence of the resistance gene mecA may be detected with a separate test. The initial volume of blood required is small at 1.5–3 mL. The turnaround time is approximately 4.5–6 h [34]. The main technical advantage of this assay is its real-time format that markedly reduces the risk of contamination. However, the assay may not be sufficient to detect low-grade bacteremia, and its attractiveness is reduced by current very high cost and the lack of provided information on antimicrobial susceptibility [35,36].

5.4. High-throughput sequencing

Metagenomics is a relatively new scientific discipline that utilizes high-throughput DNA sequencing technologies and associated computational and statistical methods for data analysis [38]. It refers to culture-independent studies of the collective set of genomes of mixed microbial communities and applies to explorations of all microbial genomes in consortia that reside in all types of environmental niches, including those that coexist with plants or animal hosts. Importantly, metagenomic approaches can reveal and capture the genetic identities of complex microbial communities without having to first isolate and culture the microorganisms. The cultivation-independent approaches inherent to metagenomics are now being used to reveal 'new' pathogens, that previously went undetected by culture-based methods as well as identifying the polymicrobial nature of some infections [39]. To date, there has been only one published investigation worldwide into the bloodstream using metagenomic techniques. In 2015, Faria et al. compared the microbial communities from healthy volunteers to patients with sepsis using culture and high throughput sequencing (illumine 16S rRNA gene V3 region) [40]. Diverse microbial groups were identified and the dominant bacterial groups included *Streptococcus, Staphylococcus*, and *Enterobacter*. This method requires knowledge of bioinformatics analysis and is currently only used in research laboratories.

6. Nonmolecular biomarkers

6.1. Interleukin-6 (IL-6)

IL-6 is secreted by T cells and macrophages, as inflammatory cytokine, in response to infectious pathogens and host injury [41]. IL-6 has a long half-life and can be measured reliably in blood. IL-6 is an important mediator in BSI and has been used to predict severity and clinical outcome in BSI [42,43]. However, IL-6 is an unspecific biomarker in BSI since its level is found to be elevated under other conditions including in the acute-phase response to injury, in acute pancreatitis, and in renal transplant patients with an increased risk of acute rejection [44].

6.2. C-reactive protein (CRP)

CRP is an acute-phase protein of hepatic origin that increases following IL-6 secretion. The synthesis of CRP in response to inflammation starts very rapidly, and serum concentration rises after 6 h and peaks at 48 h and a short half-life (approximately 19 h) [45]. CRP can modulate the complement cascade and

regulates bacterial opsonization and phagocytosis. However, studies have found CRP levels to be elevated in some noninfectious conditions including post myocardial infarction settings and rheumatologic diseases [46]. Other factors might also impact on the CRP level in pediatric patients. Lai et al., reported from 2004 to 2012, from a total of 986 BSI in 772 neonates in the NICU, that 25% (247) had a normal or low initial CRP level, which was more likely in low birth weight or preterm infants, and those with earlier onset of BSI [47]. It is currently indicated that CRP level alone should not be used to rule out BSI or to guide systemic antibiotic treatment.

6.3. Procalcitonin (PCT)

PCT is a 116 amino acid polypeptide of calcitonin that is produced in the parathyroids and is involved in calcium homeostasis [48]. PCT has effects on a variety of inflammatory conditions including cardiogenic shock, trauma, burns, surgery, and infection. PCT has recently been recognized as a biomarker for the diagnosis of various microbial infections [49]. PCT levels are lower in the serums of healthy humans and significantly increased in those suffering from BSI [50]. It is also reported that PCT might be used as a biomarker to distinguish BSI from systemic inflammatory response syndrome (SIRS) in pediatric patients [48]. However, it has been reported that PCT cannot consistently differentiate BSI from other noninfectious causes of SIRS in critically ill adults [51]. PCT levels are correlated with BSI-related organ failure scores, and high and persistent elevations in PCT might indicate worse outcomes for ICU patients. PCT is one of the most promising biomarkers for BSI [52] and more studies need to be done to prove its clinical usefulness to be used as rapid diagnostic biomarker. In a recent publication, PCT was successfully used as a rapid diagnostic marker in children with suspected CRBSI [48]. PCT levels were significantly higher in patients with confirmed CRBSI than those without CRBSI [52].

6.4. Triggering receptor expressed on myeloid cells 1 (TREM-1)

The triggering receptor expressed on myeloid cells 1 (TREM-1) is part of the immunoglobulin superfamily and is upregulated in response to bacterial or fungi infections. TREM-1 stimulates the level of cytokines when bound to ligand [53]. TREM-1 is not upregulated in noninfectious inflammatory disorders. A soluble form of TREM-1 is shed from the membranes of activated phagocytic cells and can be quantified in human body fluids. It has been suggested that TREM1 can be used as a diagnostic biomarker in BSI, and has been shown to be more sensitive and specific than CRP and PCT [54]. However, more studies need to confirm its specificity and sensitivity for diagnosis of BSI, and its possible value in guiding patients' antibiotic treatment.

7. Expert commentary

Microbiological diagnosis is heavily reliant on culture-dependent methods. Isolation of causal pathogens provides irrefutable evidence of infection and allows microbial identification and antibiotic resistance examination. Many unculturable microorganisms on IVCs have been reported [39,55,56]. For the majority of patients with suspected CRBSI, microbiological cultures are negative, restricting the administered antimicrobial therapy to an empiric approach [18].

Early detection and adequate treatment of causative pathogens within 24 h is critical for a favorable outcome in patients with CRBSI. However, reliance on paired blood cultures, or quantitative/semi-quantitative tip culture methods is far from accurate. A study of 631 arterial and central venous catheters reported 207 (33%) were removed due to clinical signs and symptoms suspicious of CRI, yet definitive diagnosis from matched catheter and blood cultures was only achieved in only 27 (13%) of suspected cases, and catheter tip colonization in 114 (55%) of suspected cases [57]. Additionally, it may take 2–4 days to obtain results from tip cultures using the roll-plate method, and the best treatment opportunity for patients with serious infections might be delayed or missed. Finally, the culture method is of limited value for slow-growing or fastidious bacteria, for nonculturable or intracellular pathogens, which are specific cause of endocarditis (e.g. some viridians Streptococci). Its sensitivity may also be reduced during antibiotic pretreatment. The development of additional diagnostic methods has potential to fulfill the important medical need to supplement conventional culture diagnosis and molecular techniques have the potential to fulfill this need. They would also contribute significant new knowledge of the bacterial species which are presenting on catheters that are generally missed by diagnosis using traditionally microbiological methods.

Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry has been used for identification of bacterial and fungi species from positive blood cultures [58]. Dubourg et al. recently reviewed the application of MALDI-TOF on pathogen identification from positive blood culture [59]. It can provide a short turnaround time, however, still requires initial culture of microorganisms and antimicrobial resistance to be determined by traditional methods. MALDI-TOF can only identify one organism per culture and is unable to identify mixed microbial populations due to dynamic range issues in the mass spectrometry [58]. The presence of human proteome, charcoal, and low organism numbers (slow growing or contamination microbe) could interfere with analysis [58].

The measurement of host responses to microbial infection has been used as an alternative method to detect pathogens. Biomarkers or biomarker plus pathogen identification might improve the detection and management of BSI. Although biomarkers are less expensive and have higher throughput, their roles in BSI diagnosis are still controversial due to their nonspecificity [44,47,51].

A few molecular strategies have been applied in CRBSI diagnosis with a number of methodological methods proposed [39,60] and many studies have been published such as RT-PCR was used to diagnose Staphylococcal CRBSI [61,62], and Guembe et al. used universal 16S rRNA PCR to diagnose venous access port-related BSI [63]. These methods provide fast and sensitive detection of a variety of microbial pathogens and can be used directly from blood specimens. However, molecular methods have drawbacks. Molecular detection of microbial genomic DNA does not necessarily indicate the presence of viable microorganisms responsible for the given

infection. The high sensitivity needed for the diagnosis of CRBSI may increase the risk of false-positive results due to contamination of blood samples. Furthermore, the available molecular assays for the diagnosis of CRBSI might not provide information on the antimicrobial susceptibility of the detected pathogen/s. More studies are needed to evaluate and establish detection thresholds for different categories of patients, and to confirm the clinical usefulness of this new laboratory parameter as an adjunct to blood culture.

8. Five-year view

The development of molecular methods for microbiological diagnosis of BSI has opened up a new era in the microbiological laboratory. Molecular methods can be used directly on blood specimens to avoid the steps involved in culture methods. High-throughput sequencing might facilitate diagnosing IVC-BSI and providing information on the antimicrobial susceptibility of the detect pathogens, which would have greater impact on patients' antimicrobial treatment and recovery. Applying molecular methods as a complement to conventional culture methods are likely to improve the diagnosis and management of patients; however, the limitations of molecular methods need to be considered when interpreting results. Advances in molecular strategies together with new biomarkers will lead to the development of faster, more sensitive and cheaper technologies and instruments. The ability of improved IVC-BSI detection assays will be routinely used in the clinical diagnostic laboratories.

Key issues

- IVC-related infections are the leading cause of nosocomial bloodstream infections and associated with significant morbidity.
- The key reference diagnostic methods for IVC-BSI are culture-dependent methods.
- Fastidious pathogens and patients' antibiotic treatment greatly contribute to false negative blood culture results, even when a BSI is strongly suspected clinically.
- A few molecular strategies including PCR, RT-PCR, microarray, hybridization have been applied in IVC-BSI diagnosis with a number of methodological methods proposed.
- Molecular methods used in independent of blood culture avoid the drawbacks of culture-dependent methods, and increase the sensitivity, and substantially reduced the turnaround time.
- High throughput sequencing platforms might facilitate diagnosing IVC-BSI and providing information on the antimicrobial susceptibility of the detect pathogens.
- Biomarkers might improve the detection and management of BSI based on detecting peptides and proteins or nucleic acids but they are limited in aiding the diagnosis of BSI.
- The development of molecular methods for microbiological diagnosis of BSI has opened up a new era in the microbiological laboratory.

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