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An Overview of Blood Stream Infection

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Abstract: Blood stream infections (BSI) are the major cause of morbidity & mortality among patients admitted in Intensive care units. . *Staphylococcus aureus*, Coagulase Negative *Staphylococcus* species, and *Enterococci* account for; approximately 30 to 50% of cases in most clinical settings. . Blood cultures being one of the most important laboratory tests performed in the diagnosis of serious infection and leads to a definitive diagnosis against the causative organisms.

Keywords: BSI- Blood stream infection, CRBSI- Catheter related blood stream infection, CFU- Colony forming unit

INTRODUCTION

Infections in the day today world, are one of the most important mortality and morbidity cause more so in low and lower-middle income countries [1,2]. Global Burden of Diseases Study have also reported that even though the mortality and morbidity due to infections has decreased in the last 30 years, they still remain as an important cause of death [2] and also persist as the most important cause of disability [1,3]. Multiple factors that are responsible for these complications are; rapid urbanization, ageing population, and recently emerging viral and bacterial infections combined with the age-old upstream predisposing factors such as poverty, inequality, and illiteracy [4,5,6]. In India also, infections remain an important cause of morbidity and mortality like the rest of the world [7,8]. In the last century, the causative agents for infectious diseases in India have been mainly due to parasitic (malaria, leishmaniasis), viral (measles, poliomyelitis, and others), or bacterial [7]. The incidence of fungal infections has risen substantially over the past several decades posing a serious threat [9].

Blood stream infections (BSI) are the major cause of morbidity & mortality among patients admitted in Intensive care unit thus, surveillance of etiological agents in these infections are important for their prevention & treatment. Blood stream infection refers to the infection that required one or more cultures positive for a bacteria or a fungus of blood samples obtained in the presence of fever (>38-degree C) not attributable to other causes (based on US centres of Disease control & prevention) [7]. Community acquired bacteraemia (CAB) is defined as; if the first positive blood culture was obtained before or within 48 hours of hospitalization. Blood stream infections are considered to be nosocomial (hospital acquired), if signs & symptoms of these infections became evident after 48 hours following hospital admission and/or if the patient had been hospitalized during the 2 weeks before the current admission.

The invasion of microorganisms in the circulating blood also poses a major threat to every organ in the body leading to serious consequences including shock, multiple Organ failure, DIC & Death. Blood stream infections with primary diseases admitted in ICU are Infective Endocarditis, CAP (community acquired pneumonia), Uro-sepsis & Meningitis [11]. BSI with

Secondary bacteraemia refers to the infections resulting from health care interventions such as vascular catheter insertion, infection following urinary catheter related sepsis, infection of surgical sites, and ventilator associated pneumonia [12].

The only way to avoid infections from this intervention is strict attention to asepsis during any insertion of vascular access devices and regular review of each vascular channel so that they are kept as long as essential. The use of antisepsis agents such as Chlorhexidine-based preparations & insertion of Central line through the Subclavian access reduces infection rate [13,14]. The patients with BSI manifest clinically with the systemic signs of infection such as Fever, Leucocytosis and raised inflammatory markers. Blood cultures obtained from both the peripheral & vascular access device should be taken within 15 minutes to detect CRBSI [15]. So, the patients in ICU with sepsis are empirically treated with Glycopeptide antibiotics like Vancomycin to cover Gram positive pathogens such as Methicillin sensitive and methicillin resistant *Staphylococcus aureus* and *S. epidermidis*. In many cases of CRBSI removal of the vascular access device is mainstay of treatment to prevent further complication [11,12].

According to one American study, the incidence of Bacteraemia in critical care settings was estimated to be 3 cases per 1000 population [16] with Mortality rate between 20 % to 50 % & Mean mortality rate of 28.6%. Similar study showed Mortality rate of 34% at 28 days & 45% at 5 months. Patients who developed Sepsis after the second day in the hospital had even higher mortality than those who were septic on admission [14] .

The most common bacteria isolated from patients in ICU are gram positive aerobic bacteria (*S. aureus, Enterococcus)* and; gram negative aerobic bacteria (Enterobacteriaceae, *Pseudomonas aeruginosa*) & the common fungi include *Candida albicans* in both immune competent & immune compromised patients [11]. CONS (Coagulase negative *Staphylococcus*) which were previously considered as contaminants have increased in the clinical importance & are now recognized as pathogens [13,17]. They are the etiologic agents of catheter associated bacteremia in patients with Vascular & other prosthesis. So judging its clinical significance is very challenging.

The most widely used set of definitions was developed by consensus committee of experts in 1992 [18,19]. The American College of chest physicians or society of critical care medicine (ACCP/ SCCM) consensus conference defined Sepsis as a systemic inflammatory response syndrome (SIRS) caused by infectious process [11].

SIRS (SYSTEMIC INFLAMMATORY RESPONSE SYNDROME) [18]: SIRS refers to abnormal generalized inflammatory reaction in organs remote from the initial insult. SIRS is defined as the systemic response to a wide range of stresses. Currently used Criteria include two or more of the following.

SIRS CRITERIA [12,16,18,19]:

- Temperature > 38ºC or < 36ºC
- Heart Rate > 90 beats / minute
- Respiratory rate > 20 breaths / min
- WBC > 12000 Cells / mm^3 or < 4000 Cells / mm^3 or > 10% immature neutrophils (band) forms.

SEPSIS: Sepsis is defined as the invasion of microorganisms or their toxins into the blood stream together with the host response to this invasion. If SIRS occurs in a patient with proven or suspected infection, it is known as sepsis. SIRS is called sepsis in the American consensus scheme [19].

BACTEREMIA: Presence of the bacteria in blood, as evidenced by positive blood cultures.

SEPTICAEMIA: Presence of microbes and, or their toxins in blood. Septicaemia is defined as clinical syndrome characterized by fever, chills, malaise, tachycardia, hyperventilation and toxicity (or) prostration [20].

SEVERE SEPSIS: Sepsis with one or more than one signs of organ dysfunction of the following [19,21]:

[1] CVS–SBP<90mmHg

[2] Renal system– Urine output < 0.5ml/kg/hr for 1 hr

[3] Respiratory – PO_2 / FIO_2 < 250

[4] Haematology – platelet count < 80,000/ml or 50% decrease in platelet count recorded for past 3 days

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SEPTIC SHOCK [19]: Sepsis with hypotension (SBP<90 mmHg, for at least one hour despite adequate fluid resuscitation.

RETRACTORY SEPTIC SHOCK [19,21]: Septic shock that lasts for > 1 hour & does not respond to fluid or vasopressor administration.

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS) [19]: Dysfunction of more than one organ thus, requiring intervention to maintain homeostasis.

EPIDEMIOLOGY:

Sepsis account for more than 2,00,000 deaths per year in US. Sepsis related incidence and mortality rates increases with age and pre-existing co morbidity. In a survey of hospital discharge records from Seven States in 1995, Angus and Colleagues [22] estimated the annual incidence of sepsis to be 300 cases per 1,00,000 population. The estimated crude mortality rate was 28%. The median age for patients with sepsis is approximately 60 years. The attack rate in very high in infants.

A survey conducted in the Intensive Care Units in the US [12] and Europe during the year 1990 and 2000 approximately 70 to 80% of cases of severe Sepsis in adults occurred in the individuals who were already hospitalized for other reasons. In 30 to 50% cases no definite etiology was found.

Sepsis caused by gram positive bacteria has steadily increased over the last two decades. *Staphylococcus aureus*, CONS and *Enterococci* account for; approximately 30 to 50% of cases in most clinical setting. Another recent trend is the emergence of fungi particularly *Candida* as etiological agents in blood stream infections. *Candida* spp. caused 5 to 20% of sepsis cases [11].

PATHOPHYSIOLOGY OF SEPSIS:

Infection is initiated when bacteria penetrate host barriers like skin and mucosa. Depending on the virulence of infecting agents, immune status of the patients, local host defense mechanism is overwhelmed, leading to microbial invasion of the bloodstream. Sepsis is characterized by the loss of haemostatic balance and endothelial dysfunction, which in turn severely compromise the cardio circulatory system as well as the intracellular haemostasis. Cellular hypoxia and apoptosis then eventually contribute to organ dysfunction and death.

PATHOPHYSIOLOGY OF SEPSIS IN SCHEMATIC ORDER [16,23]:

- Microbial stimulus
- Host immune response in sepsis
- Loss of haemostatic balance
- Endothelial dysfunction
- Cardiac and circulatory dysfunction (microcirculatory dysfunction)
- Endocrine dysfunction
- Tissue hypoxia
- Apoptosis

MICROBIOLOGICAL STIMULUS:

GRAM NEGATIVE SEPSIS:

In gram negative bacteremia; initiation of immune response is mediated by LPS (Lipopolysaccharide), a product of bacterial cell wall. In plasma, LPS is bound to the LPS binding protein (LBP). Bound LPS is then transported to opsonic receptor CD14, which is located on several cell membranes including on the monocytes [22]. A soluble form of the CD14 interacts with CD14 negative cells. (e.g. Dendritic cells). However, these CD14 alone cannot explain the action of LPS, because CD14 does not have an intercellular tail.

Another binding site of the LPS in transmembrane receptor TLR 4 (Toll Like Receptor), which exist in combination with the accessory protein MD2 [18]. In monocytes, LPS also induces cytokine transcription via the triggering receptors expressed on myeloid cells-1 and the myeloid DAP-12 associated lectin [24]. Intracellular pattern recognition protein in monocytes for LPS has recently been identified as an alternative pathway of cytokine expression and include nucleotide binding oligomerization domain 1 & 2 as LPS binding sites [23].

GRAM POSITIVE SEPSIS:

During the last decade, gram positive bacteria have gained a greater importance as causative organisms for sepsis [20]. They lack endotoxins and are recognized by the cell wall components such as peptidoglycans and released bacterial toxins (exotoxins). Recently, LTA

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(Lipotechoic acid), a component of the cell wall in all gram positive bacteria, has been recognized as on of the main pattern for recognition of gram positive bacteria. TLR2 has been identified as the only pattern recognition protein receptors for gram positive bacteria [22]. TLR 2 is not a specific receptor for LTA. Clinically gram positive sepsis and gram negative sepsis are not distinguished. Peptidoglycans and LTA stimulate the release of TNF α, IL 6 & IL 10.

FUNGAL SEPSIS:

Blood cultures remain an important diagnostic tool for disseminated fungal infections. Lysis centrifugation system is used now days to detect filamentous fungi causing sepsis. Among fungi, *Candida albicans* is most frequently isolated from the blood leading to 10% of all nosocomial infections [23]. *Candida* infection is usually associated with malignancy, neutropenia, HIV/AIDS and other immunosuppressive conditions.

BLOODSTREAM INFECTIONS:

Microorganisms that enter the blood stream by various mechanisms and lead to complications like shock, multiple organ failure, disseminated intravascular coagulation (DIC) and death. These microbial agents causing bacteremia are bacteria, fungi, viruses and parasites [11].

TYPES OF BLOOD STREAM INFECTIONS:

- Bacteremia can be transient, intermittent or continuous:

1. TRANSIENT BACTEREMIA: This occurs when organisms (alters members of normal flora) are introduced into the blood stream, by minimal trauma to membranes (e.g. brushing of teeth, straining during bowel movements, medical procedures) [25].

2. INTERMITTENT BACTEREMIA: This occurs when bacteria from any infected site are periodically released into the blood. (e.g. Abscess, colitis, infection of body cavities)

3. CONTINUOUS BACTEREMIA: This occurs when infection is intravascular like infected endothelial surface (endocarditis or aneurysms), infected devices (AV fistulas, indwelling cannulas, intra arterial catheters) [20].

- Bacteremia can be primary or secondary:

1. PRIMARY BSI: BSI is called primary if the point of entry of infection or focus cannot be determined or if it arises from an intravascular catheter [catheter related BSI (CRBSI)].

2. SECONDARY BSI: BSI is called secondary if any distant site other than an Intravenous catheter is established as the portal of entry or origin.

- Bacteremia can be community acquired or nosocomial depending on epidemiological settings [23]:

1. COMMUNITY ACQUIRED BACTEREMIA: It is detected within 48 hours of admission and the patients should not be hospitalized within previous 30 days and there should not be any recent history of invasive procedures (e.g. Foley catheter, IV catheter, Central venous catheter or dialysis)

2. NOSOCOMIAL ACQUIRED BACTEREMIA: It is detected after 48 hours of admission in hospital and is associated with long term hospital stay, invasive procedures, long term antibiotic therapy.

- The major classification of blood stream infection is:

1. INTRAVASCULAR INFECTION: Infection that originates within cardiovascular system contributes to intravascular infection. It includes infective endocarditis, Mycotic aneurysm, Catheter related bacteremia and Suppurative thrombophlebitis. These infections are life threatening and leads to serious illness.

2. EXTRAVASCULAR INFECTION: Here the bacteria invade the circulation through the lymphatic system. Most cases of clinically significant BSI are due to extravascular infection.

The most common routes of extravascular infection are genitourinary tract (25%), respiratory tract (20%), abscesses (10%), surgical wound infection (5%), biliary tract (5%) and other unknown sites (25%). In one third of bacteremia source of infection is not identified. Organisms causing BSI through extravascular sites are members of the family Enterobacteriaceae, *Streptococcus pneumoniae*, *Staphylococcus aureus*, anaerobic cocci, *Neisseria gonorrhoeae*, *Clostridium* spp, Bacteroides, Beta haemolytic *Streptococci* and *Pseudomonas* [11].

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RISK FACTORS:

The risk factors & underlying conditions of BSI are immunosuppression, irrational use of antibiotics that leads to emergence of resistance to drugs, invasive procedures that allow microorganisms to enter the host, surgical procedures, underlying organ failure and Malignancy [18].

CLINICAL FEATURES:

The clinical features or presentation ranges from mild symptoms occurring from transient bacteremia to fulminant sepsis leading to Septic shock, DIC, high mortality and life-threatening complications. Continuous bacteremia is associated with endocarditis (intravascular) or other extravascular infection like typhoid fever (for first week) or brucellosis. Transient bacteremia occurs following any minor surgeries or manipulation.

Intermittent bacteremia is commonly secondary to any local abscess. Fever is the most common presenting symptoms in almost all patients with intermittent and continuous bacteremia. Other clinical features include increased respiratory rate, heart rate and decreased blood pressure. Bryan emphasized that patients with positive blood cultures are 12 times more likely to die during hospitalization than patients with negative blood cultures [26].

MICROBIAL PATHOGENS IN BSI:

In the recent studies done by Pittet et al, Valles et al 2009, about 50-60% were caused by gram negative organisms and 20-30% by gram positive organisms. Fungi mainly *Candida* contribute to 6-10% of episodes. The most common organisms in BSI are; Coagulase Negative *Staphylococci, Staphylococcus aureus, Enterococci, Candida spp., E. coli, Klebsiella spp., P. aeruginosa, Enterobacter spp., Acinetobacter spp.* [27].

LABORATORY DIAGNOSIS OF BLOOD STREAM INFECTIONS

Blood cultures are important diagnostic tool in patients with conditions that predispose to BSI [11]. The growth of bacteria can be detected using manual techniques and automated methods. Many automated systems are available now which gives rapid results. Once growth is isolated, the organism is identified and tested for its susceptibility for various antimicrobial agents [23].

SPECIMEN COLLECTION & TRANSPORT:

Blood cultures are obtained using a sterile needle or syringe. About 5- 10 ml of blood should be drawn aseptically by single venepuncture, inoculated into the blood culture bottle containing medium and incubated. After 18-24 hrs of incubation the bottles are checked for presence of microorganisms. Blood cultures should not be obtained from indwelling intravascular catheters as there is greater risk of recovering skin organisms. If indwelling catheters are considered as source of BSI, then blood samples are collected from the catheter site [11].

SITE OF COLLECTION:

Since there is increased incidence of bacteremia from bacteria that are part of normal skin flora such as Coagulase Negative S*taphylococci*, *Corynebacteria* and *Bacillus* species, appropriate asepsis should be followed while collecting samples of blood. Blood is collected from peripheral vein (e.g. cubital vein). Contamination is more in femoral vein and arterial blood are of no use in recovering pathogens (Tenney et al, Vaisanen et al. 1985). The rate of contamination is higher from IV catheter blood samples since colonizers present in catheter gives false positive results. In fact, catheter blood sample is useful when catheter related blood stream infection (CRBSI) is considered [11].

ASEPTIC PRECAUTION:

The skin site over the vein is disinfected with the 70% isopropyl alcohol in a circle rubbed vigorously. Then from the centre of circle, 2% tincture of iodine (or povidone-iodine) is applied in circles and allowed to dry on the skin for at least 1 minute. Gloves should be used by the person collecting the blood. It is important to use both alcohol and iodine compound to disinfect the venepuncture site [14,28].

TIME OF COLLECTION

Blood should be collected during febrile episodes or as soon as after the onset of fever and chills. It is also essential to collect blood samples before starting antibiotic therapy or end of a dosing interval [29].

SPECIMEN VOLUME

Adults: In adults with BSI the colony forming units (CFU) per milliliter of blood is very low. Therefore, a sufficient sample volume of blood is required for the successful detection of bacteremia. The rate of isolation is greater, when more blood is cultured [29].

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Results from a study suggested that the yield increases by 3.2% for every milliliter of blood cultured. For adults 10-20mL of blood per culture is required to increased the yield by 30 percent [14].

Children: It is unsafe to obtain the large volumes of blood from children, particularly infants. In spite of low level of bacteremia in infants and children it is safe to obtain as much as 4% to 4.5% of patient's blood volume for culture. The relationship between blood volumes for culture from infants and children by Baron and colleagues [30].

NUMBER OF BLOOD CULTURES

The rate of detection increases with the number of blood cultures. The first blood culture should be obtained at the same time and inoculated into two different media and at two different temperatures. The second set of culture should be obtained in the same way & this increases the sensitivity rate to 99% [13,14,30,31]. There is no current recommendation for ideal time difference between two blood culture [32].

CULTURE MEDIA:

The media used for Blood culture should be nutritionally enriched with Tryptic or Trypticase soy, brain heart infusion, Columbia Agar and Brucella broths are used commonly. These commercially available media contain the anticoagulant Sodium ployanethol sulfonate (SPS, Liquoid) (Wilson et al. 1994), 0.025% to 0.05% concentration [20]. Bacteria cannot survive well in the clot and so anticoagulants are used. SPS inactivates neutrophils & inhibit antibiotics including Streptomycin, Kanamycin, Gentamycin, and Polymyxin. The side effects of SPS is that it inhibits the growth of certain bacteria like *Neisseria gonorrhoea, Neisseria meningitidis, Peptostreptococcus anaerobius* [11]. This inhibitory effect of SPS can be neutralized by addition of gelatin (1%) to the medium. The use of resin in blood culture media significantly increases the recovery of pathogens such as members of the family Enterobacteriaceae, *Enterococcus spp, S. pneumoniae* and *S. viridans*. Antimicrobial agents normally present in human blood are neutralized by adding adsorbents such as resins, activated charcoal and fuller's earth [20].

TRANSPORT

Refrigeration of blood cultures are not recommended. Rapid transportation of blood cultures and immediate processing in the laboratory is done for appropriate recovery of pathogens [33].

SAMPLE PROCESSING

Processing of the blood cultures includes incubation, gram staining and subcultures. There are manual and automated blood culture systems available for processing.

SYSTEMS FOR PROCESSING BLOOD CULTURES: MANUAL BLOOD CULTURE SYSTEMS:

The two commercially available manual Blood culture systems are variations of classic biphasic media bottles known as Castaneda bottles. They are-

1. The Oxoid Signal System: The Oxoid (Ogelensburg, N4) signal system is a single bottle blood culture system where the bacterial growth is determined by the production of CO_2.The blood culture bottle is connected to a second plastic chamber, called signal chamber fitted at the bottom with a long needle. Bacterial growth and metabolism produces CO_2. Weinstein et al designed new bottle with increased head – gas space which increased the yield of organisms [34].
2. BBL Septi – Check Blood Culture System: The Septi-Check biphasic agar slide system (BD Diagnostic system, sparks, MD) uses blood culture bottle containing brain heart infusion broth or Trypticase Soy broth [35]. The slide contains paddle with agar surface. After inoculation, the plastic contained "slide" is screwed on. The agar surface is flooded with the broth for few minutes and then again placed upright for continuous incubation. The bottle is inverted at regular intervals and sub cultured after incubating at 37^0C for 4 - 6hrs.
3. Lysis centrifugation blood culture system: (Wampole Isostat / Isolator Microbial System): The isolator microbial system (Wampole laboratories, Princeton, NJ) is a special tube contains Saponin A, a chemical which lyse the white and red blood cells, Propylene glycol to decrease foaming, SPS as an anticoagulant, EDTA to chelate calcium and a small amount of Fluorochrome [20]. This is an alternative blood culture method used for

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recovery of fastidious (or) slow growing organisms (*Bortonella henselae*) [20], Filamentous moulds, dimorphic fungi, *Malassezia furfur* and *Legionella spp*. [11]. The mean recovery time of yeasts and *Histoplasma capsulatum* is reduced from 4.9 days and 24.14 days to 2.12 and 8 days respectively with the isolator [20]. Increased rate of contamination is the major problem with isolator system and it can be decreased by using dry agar plates, proper disinfection of work area and sample processing in a Laminar hood.

- EXAMINATION OF MANUAL SYSTEMS: Blood culture bottles are incubated at 37-degreeC for 16 to 18 hrs. and examined for haemolysis, production of gas, or turbidity. Blind subcultures are made after 24 hrs. of incubation and microscopic examination should be performed. For microscopic examination Gram stain or Acridine orange stains are used. Acridine orange stains detect 10^4 CFU/ml whereas Gram stain detects 10^5 CFU/ml [36]. Tierney et al reported 16.8 percent increase in the detection of bacteremia using Acridine orange stain while the broth is macroscopically negative.

AUTOMATED AND COMPUTERIZED BLOOD CULTURE SYSTEMS-

The first automated system was BACTEC 460 (Becton Dickinson), was introduced in the 1970s. The results are rapid and obtained within a day. After positive culture is obtained, bottles are removed for gram stain and sub culture [11].

1. BACT/ALERT MICROBIAL DETECTION SYSTEM: This system contains CO_2 sensitive chemical sensor separated by unidirectional CO_2 permeable membrane which is bonded to the bottom of every bottle. The growth of microorganisms in the blood broth produces CO_2, which makes the color sensor to turn from green to yellow.
2. THE BACTEC 9240/9120 BLOOD CULTURE SYSTEM: This system is similar to BACT/Alert but the only difference is the use of fluorescent, rather than spectral light for detecting change in CO_2 concentration.
3. THE TREK ESP CULTURE SYSTEM: The ESP blood culture system (TREK diagnostic system, Cleveland, OH) is different from the above two systems by:

- The CO_2 production, monitored manometrically.
- Monitoring both gas consumption and production.
- In addition to CO_2 production H_2 and O_2 concentration changes are also monitored (testing multiple gas production) [27].

ANTIMICROBIAL SUSCEPTIBILITY TESTING:

After identification of the causative organisms the management of BSI includes early and appropriate treatment by antimicrobial therapy.

✓ Antibacterial susceptibility testing:

Antibiotic sensitivity testing (ABST) is usually done by Kirby Bauer disc diffusion method, using 0.5 McFarland's turbidity on the Mueller Hinton agar plates Commercially Available Hi-media antibiotic discs are used.

✓ Antifungal susceptibility testing:

It was performed on Mueller Hinton agar plate supplemented with the 2% glucose and 0.5 µg/ml methylene blue. Commercially available Hi-media antifungal discs are generally used.

Blood culture (BC) is considered as the gold standard for the detection of bacteremia. Blood cultures being one of the most important laboratory test performed in the diagnosis of serious infection and leads to a definitive diagnosis against the causative organisms yet the problem of blood culture contamination persists [13]. Appropriate detection of microorganisms and low rate of contaminants are two major goals for BC diagnostics. There is considerable increase in incidence of vascular infection caused by bacteria that are normally considered a virulent. So it is important to distinguish between contaminants & pathogen [37]. When such organisms are present, interpretation of the culture result involves taking into account the person's

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clinical condition and whether or not multiple cultures are positive for the same organism.

Thus the accurate differentiation of a contaminant from a true pathogen relies on a multidisciplinary approach and the clinical judgement of experienced practitioners [38].

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