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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion. There may also be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection. In the very young, old, and people with a weakened immune system, there may be no symptoms of a specific infection and the body temperature may be low or normal, rather than high. Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high blood lactate, or low urine output. Septic shock is low blood pressure due to sepsis that does not improve after fluid replacement.

Sepsis is caused by an inflammatory immune response triggered by an infection. Most commonly, the infection is bacterial, but it may also be fungal, viral, or protozoan. Common locations for the primary infection include the lungs, brain, urinary tract, skin, and abdominal organs. Risk factors include very young age, older age, a weakened immune system from conditions such as cancer or diabetes, major trauma, or burns. An older method of diagnosis was based on meeting at least two systemic inflammatory response syndrome (SIRS) criteria due to a presumed infection. In 2016, SIRS was replaced with a shortened sequential organ failure assessment score (SOFA score) known as the quick SOFA score (qSOFA) which is two of the following three: increased breathing rate, change in level of consciousness, and low blood pressure. Blood cultures are recommended preferably before antibiotics are started, however, infection of the blood is not required for the diagnosis. Medical imaging should be used to look for the possible location of infection. Other potential causes of similar signs and symptoms include anaphylaxis, adrenal insufficiency, low blood volume, heart failure, and pulmonary embolism.

I guess you are getting it right, the **"DISEASE DIAGNOSIS"** segment is all about BACTERIAL SEPTICEMIA. As a corollary, **"INTERPRETATION"** section talks about BLOOD CULTURE as is **"TROUBLE SHOOTING"** too.

Besides these you may not require anything else to deal with SEPTICEMIA. A little fun, a hefty laugh and a self induced scratch on your scalp is always due. Do take a look at **"THE BOUQUET"**.

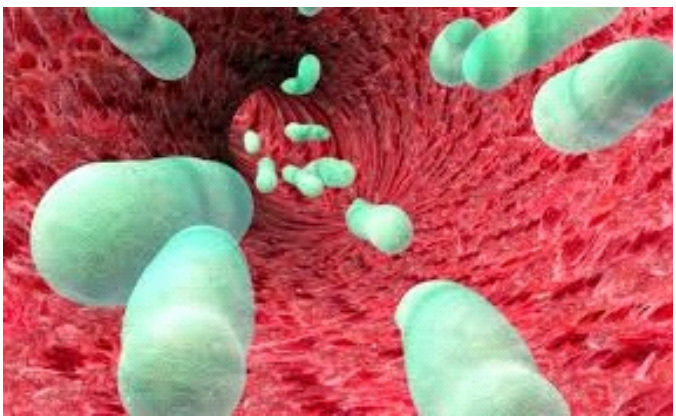
DISEASE DIAGNOSIS

BACTERIAL SEPSIS

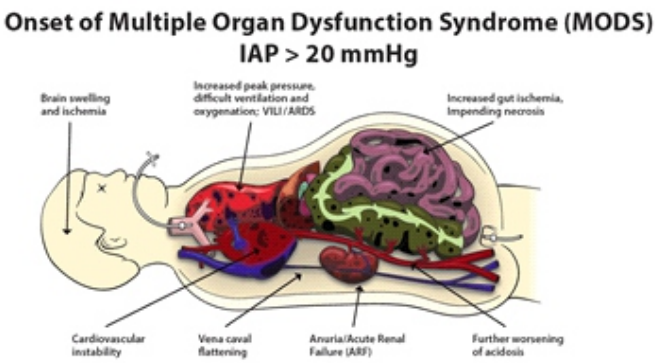
PRACTICE ESSENTIALS

Definitions

Sepsis is a life-threatening syndrome usually caused by bacterial infection. Sepsis is a response of the body's immune system that results in organ dysfunction or failure. The systemic inflammatory response syndrome (SIRS) criteria were recently replaced by the quick Sequential Organ Failure Assessment (qSOFA) in 2016, allowing for quick bedside analysis of organ dysfunction in patients with suspected or documented infection. The qSOFA score includes a respiratory rate of 22 breaths/minute or more, systolic blood pressure of 100 mm Hg or less, and altered level of consciousness. For completeness, severe sepsis is defined as sepsis complicated by organ dysfunction.



Multiple organ dysfunction syndrome (MODS) is characterized by progressive organ dysfunction in a severely ill patient, with failure to maintain homeostasis without intervention. It is the end stage in infectious conditions (sepsis, septic shock) and noninfectious conditions (eg, SIRS due to pancreatitis). The greater the number of organ failures, the higher the mortality risk, with the greatest risk associated with respiratory failure requiring mechanical ventilation. MODS can be classified as primary or secondary.



Primary MODS is the direct result of identifiable injury or insult with early organ dysfunction (eg, renal failure due to a nephrotoxic agent or liver failure due to a hepatotoxic agent). Secondary MODS is organ failure that has no attributable cause and is a consequence of the host's response (eg, acute respiratory distress syndrome [ARDS] in individuals with pancreatitis).

The following parameters are used to assess individual organ dysfunction:

- Respiratory system: Partial pressure of arterial oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ratio
- Hematology: Platelet count, coagulation panel (prothrombin time and partial thromboplastin time)
- Liver: Serum bilirubin
- Renal: Serum creatinine (or urine output)
- Brain: Glasgow coma score
- Cardiovascular: Hypotension and vasopressor requirement

Septic shock is defined as sepsis with hypotension requiring vasopressor therapy to maintain a mean blood pressure of more than 65 mm Hg and a serum lactate level exceeding 2 mmol/L (18 mg/dL) after adequate fluid resuscitation. This has a greater risk of mortality and long-term morbidity.

Pseudosepsis is defined as fever, leukocytosis, and hypotension due to causes other than sepsis. Examples might include the clinical picture seen with salicylate intoxication, methamphetamine overdose, or bilateral adrenal hemorrhage.

ETIOLOGY

Sepsis can be caused by an obvious injury or infection or a more complicated etiology such as perforation, compromise, or rupture of an intra-abdominal or pelvic structure. Other etiologies can include meningitis, head and neck infections, deep neck space infections, pyelonephritis, renal abscess (intrarenal or extrarenal), acute prostatitis/prostatic abscess, severe skin or skin structure infections (eg, necrotizing fasciitis), postsurgical infections, or systemic infections such as rickettsial infection.

CLINICAL PRESENTATION

Individuals with sepsis may present with localizing symptoms related to a specific site or source of infection or may present with nonspecific symptoms. Individuals with nonspecific symptoms are usually acutely ill with fever and may present with or without shaking chills. Mental status may be impaired in the setting of fever or hypotension. Patients with bacteremia from any source often display an increased breathing rate resulting in respiratory alkalosis. The skin of patients with sepsis may be warm or cold, depending on the adequacy of organ and skin perfusion. A detailed history and physical examination is essential in determining the likely source of the septic process. This helps the clinician to determine the appropriate treatment and antimicrobial therapy.

DIAGNOSIS

A diagnosis of sepsis is based on a detailed history, physical examination, laboratory and microbiology testing, and imaging studies.

Laboratory studies that may be considered include the following:

- Complete blood (CBC) count - May show elevated or low white blood cell count, anemia, and/or thrombocytopenia
- Chemistry studies, such as markers of liver or kidney injury - May suggest organ dysfunction
- Bacterial cultures - Blood cultures and site-specific cultures based on clinical suspicion (eg, wound culture, sputum culture, or urine culture)
- Stained buffy coat smears or Gram staining of peripheral blood - May be helpful in certain infections
- Urine studies (urinalysis, microscopy, urine culture)
- Certain biomarkers, such as procalcitonin and presepsin - May be useful in diagnosing early sepsis and in determining prognosis

Imaging modalities should be focused on areas of clinical concern, based on the history and physical examination, and may include the following:

- Chest radiography (to rule out pneumonia and diagnose other causes of pulmonary infiltrates)
- Chest CT scanning (to further evaluate for pneumonia or other lung pathology)
- Abdominal ultrasonography (for suspected biliary tract obstruction)
- Abdominal CT scanning or MRI (for assessing a suspected non-biliary intra-abdominal source of infection or delineating intrarenal and extrarenal pathology)
- Site-specific soft tissue imaging, including ultrasonography, CT scanning, or MRI (to assess for possible abscess, fluid collection, or necrotizing skin infection)
- Contrast-enhanced CT scanning or MRI of the brain/neck (to assess for possible masses, abscess, fluid collection, or necrotizing infection)

The following cardiac studies may be useful if cardiac involvement or disease is suspected as a cause or complication of infection:

- Electrocardiography (ECG) to evaluate for conduction abnormalities or delays or arrhythmias; pericarditis may be a cause of "pseudosepsis"
- Cardiac enzyme levels
- Echocardiography to evaluate for structural heart disease

Invasive diagnostic procedures that may be considered include the following:

- Thoracentesis (in patients with pleural effusion)
- Paracentesis (in patients with ascites)
- Drainage of fluid collections/abscesses
- Bronchoscopy with washing, lavage, or other invasive sampling (in patients with suspected pneumonia)

MANAGEMENTs

Initial management may include the following:

- Inpatient admission or ICU admission for monitoring and treatment
- Initiation of empiric antibiotic therapy, to be followed by focused treatment based on culture, laboratory, and imaging data
- Supportive therapy as necessary to maintain organ perfusion and respiration; timely intervention with infection source control, hemodynamic stabilization, and ventilatory support
- Transfer if requisite facilities are not available at the admitting hospital

Appropriate empiric antimicrobial therapy depends on adequate coverage of the presumed pathogen(s) responsible for the septic process, potential antimicrobial resistance patterns, and patient-specific issues such as drug allergies or chronic medical conditions. Tying sites of infection to specific pathogens should occur, as follows:

- Intravenous line infections: Consider broad-spectrum coverage for gram-positive organisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (linezolid, vancomycin, or daptomycin) and gram-negative nosocomial pathogens (especially *Pseudomonas* species and other Enterobacteriaceae [piperacillin-tazobactam, carbapenems, or cefepime]), and line removal. Some of these may be *Candida* infections.
- Biliary tract infections: Typical bacterial agents include Enterobacteriaceae, gut-associated anaerobes, and *Enterococcus.* Consider carbapenems, piperacillin-tazobactam, cephalosporins, or quinolones in combination with an anaerobic agent such as metronidazole.
- Intra-abdominal and pelvic infections: Typically Enterobacteriaceae, gut-associated anaerobes, or *Enterococcus* (carbapenems, piperacillin-tazobactam, or cephalosporins or quinolones in combination with an anaerobic agent such as metronidazole)
- Urosepsis: Typically Enterobacteriaceae or *Enterococcus* (carbapenems, piperacillin-tazobactam, cephalosporins, quinolones, or aminoglycosides)
- Pneumococcal sepsis: Third-generation cephalosporins, respiratory quinolone (levofloxacin or moxifloxacin), carbapenem, or vancomycin if resistance is suspected
- Sepsis of unknown origin: Meropenem, imipenem, piperacillin-tazobactam, or tigecycline; metronidazole plus levofloxacin, cefepime, or ceftriaxone may be alternatives

Early surgical evaluation for presumed intra-abdominal or pelvic sepsis is essential. Procedures that may be warranted depend on the source of the infection, the severity of sepsis, and the patient's clinical status, among other factors. Once an etiologic pathogen is identified, typically via culture, narrowed antibiotic therapy against the identified pathogen is appropriate (eg, penicillin for penicillin-susceptible *Streptococcus pneumoniae*).

BACKGROUND

Hippocrates, in the fourth century BCE, used the term sepsis denoting decomposition. Avicenna, in the eleventh century, called diseases causing purulence as blood rot. In the nineteenth century, the term sepsis was widely used to describe severe systemic toxicity. A closely derived term of septicemia was used for bacterial infection in the blood, which has been replaced by the term bacteremia. In the last two centuries, the processes underlying infections have been better studied and elucidated. The role of microorganisms in causing infections and the intricate mechanisms of various intrinsic and extrinsic toxins in damaging body tissues that result in fever and shock has been discovered with painstaking research. At the beginning of the twentieth century, the term endotoxin was devised by Pfeiffer to explain the causative agent in infection with cholera. It was later linked to other gram-negative bacterial pathogenicity. The initial sepsis guidelines were published in 2004 and revised in 2008 and 2012. The current clinical practice guidelines are a revision of the 2012 Surviving Sepsis Campaign (SSC) guidelines for the management of severe sepsis and septic shock.

ETIOLOGY

The etiology of sepsis is diverse, and clinical clues to various organ systems aid in appropriate workup and diagnosis. It is also pertinent to be able to distinguish between the infectious and noninfectious causes of fever in a septic patient. The following are organ system–specific etiologies of possible sepsis:

- Skin/soft tissue: Necrotizing fasciitis, cellulitis, myonecrosis, or gas gangrene, among others, with erythema, edema, lymphangitis and positive skin biopsy result
- Wound infection: Inflammation, edema, erythema, discharge of pus, with positive Gram stain and culture results from incision and drainage or deep cultures
- Upper respiratory tract: Pharyngitis, tonsillitis, or sinusitis, among others, with inflammation, exudate with or without swelling, and lymphadenopathy or positive throat swab culture or rapid test result
- Lower respiratory tract: Pneumonia, empyema, or lung abscess, among others, with productive cough, pleuritic chest pain, consolidation on auscultation, positive sputum culture result,

positive blood culture result, rapid viral testing, urinary antigen testing (eg, *Pneumococcus, Legionella*), quantitative culture of protected brush, or bronchoalveolar lavage

- Central nervous system: Meningitis, brain abscess, or infected hematoma, among others, with signs of meningeal irritation, elevated CSF cell count and protein level, reduced CSF glucose level, positive Gram stain and culture results
- Cerebrovascular system: Myocardial infarction, acute valvular dysfunction, myocarditis, pericardialis, ruptured aortic aneurysm, aortitis, or septic emboli, among others, with elevated levels of cardiac enzymes, and imaging (ultrasonography, CT scanning, or MRI) of the chest, abdomen, and/or pelvis showing vascular involvement
- Vascular catheters (arterial, venous): Redness or drainage at insertion site, positive blood culture result (from the catheter and a peripheral site), and catheter tip culture after sterile removal
- Gastrointestinal: Colitis, infectious diarrhea, ischemic bowel, or appendicitis, among others, with abdominal pain, distension, diarrhea, and vomiting; positive stool culture result and testing for toxigenic *Escherichia coli, Salmonella, Shigella, Campylobacter,* or *Clostridium difficile*
- Intra-abdominal: Renal abscess, pyelonephritis, pancreatitis, cholecystitis, liver abscess, intra-abdominal abscesses, or perforation, compromise, or rupture of an intra-abdominal or pelvic structure, among others, with specific symptoms and signs; aerobic and anaerobic culture of drained abdominal fluid collections; peritoneal dialysis (PD) catheter infection with cloudy PD fluid, abdominal pain, deranged cell count, and positive PD fluid culture result
- Urinary tract: Cystitis, pyelonephritis, urethritis, or renal abscess, among others, with urgency, dysuria, pelvic, suprapubic, or back pain; urine microscopy showing pyuria or a positive urine culture result; urosepsis has also been reported after prostatic biopsy
- Female genital tract: Pelvic inflammatory disease, cervicitis, or salpingitis, among others, with lower abdominal pain, vaginal discharge, positive results on endocervical and high vaginal swabs
- Male genital tract: Orchitis, epididymitis, acute prostatitis, balanitis, or prostatic abscess, among others, with dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness, and positive urine Gram stain and culture results
- Bone: Osteomyelitis presenting with pain, warmth, swelling, decreased range of motion, positive blood and/or bone culture results, and MRI changes
- Joint: Septic arthritis presenting with pain, warmth, swelling, decreased range of motion, positive arthrocentesis with cell counts, and positive Gram stain and culture results
- Nonspecific systemic febrile syndromes: Babesiosis, rickettsial diseases, lyme disease, typhus, or typhoid fever, among others, with multiorgan involvement, specific travel and epidemiological exposures, and associated rashes or other symptoms

There are numerous noninfectious causes of fever and organ dysfunction that can mimic sepsis:

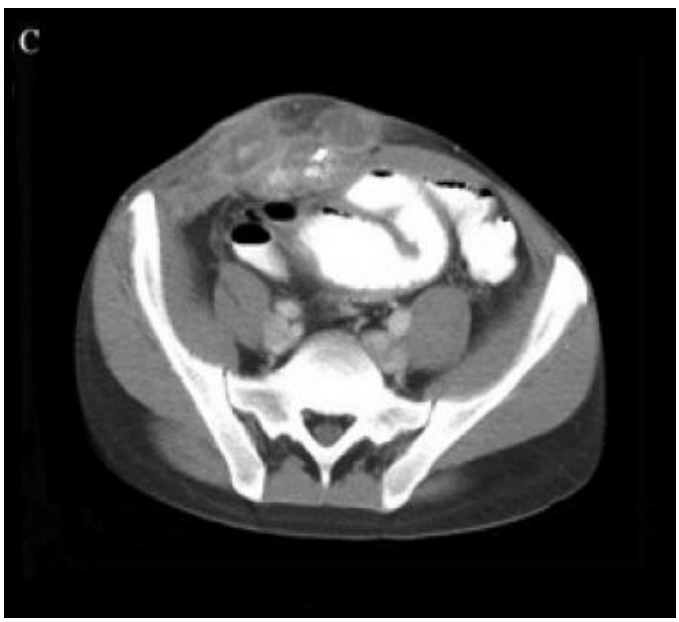
- Alcohol/drug withdrawal
- Postoperative fever (48 hours postoperatively)
- Transfusion reaction
- Drug fever
- Allergic reaction
- Cerebral infarction/hemorrhage
- Adrenal insufficiency/adrenal hemorrhage
- Myocardial infarction
- Pancreatitis
- Acalculous cholecystitis
- Ischemic bowel
- Aspiration pneumonitis
- ARDS (both acute and late fibroproliferative phase)
- Subarachnoid hemorrhage
- Fat emboli
- Transplant rejection
- Deep venous thrombosis
- Pulmonary emboli
- Gout/pseudogout
- Hematoma
- Cirrhosis (without primary peritonitis)
- Gastrointestinal hemorrhage
- Phlebitis/thrombophlebitis
- IV contrast reaction
- Neoplastic fevers
- Decubitus ulcers

Table 1. Infectious and Noninfectious Causes of Fever

System	Infectious Causes	Noninfectious Causes
Central nervous	Meningitis, encephalitis	Posterior fossa syndrome, central fever, seizures, cerebral infraction, hemorrhage, cerebrovascular accident
Cardiovascular	Central line, infected pacemaker, endocarditis, sternal osteomyelitis, viral pericarditis, myocardial/ perivalvular abscess	Myocardial infarction, balloon pump syndrome, Dressler syndrome
Pulmonary	Ventilator-associated pneumonia, mediastinitis, tracheobronchitis, empyema	Pulmonary emboli, ARDS, atelectasis (without pneumonia), cryptogenic organizing pneumonia, bronchogenic carcinoma without postobstructive pneumonia, systemic lupus erythematosus, pneumonitis, vasculitis
Gastrointestinal	Intra-abdominal abscess, cholangitis, cholecystitis, viral hepatitis, peritonitis, diarrhea (*Clostridium difficile*)	Pancreatitis, acalculous cholecystitis, ischemia of the bowel/colon, bleeding, cirrhosis, irritable bowel syndrome

System	Infectious Causes	Noninfectious Causes
Urinary tract	Catheter-associated bacteremia, urosepsis, pyelonephritis, cystitis	Allergic interstitial nephritis
Skin/soft tissue	Decubitus ulcers, cellulitis, wound infection	Vascular ulcers
Bone/joint	Chronic osteomyelitis, septic arthritis	Acute gout
Other	Transient bacteremia, sinusitis	Adrenal insufficiency, phlebitis/thrombophlebitis, neoplastic fever, alcohol/drug withdrawal, delirium tremens, drug fever, fat emboli, deep venous thrombosis, postoperative fever (48 h), fever after transfusion

An abdominal wall abscess is depicted on the CT scan below.



A right lower quadrant abdominal wall abscess and enteric fistula are observed and confirmed by the presence of enteral contrast in the abdominal wall. Organisms can be introduced via various mechanisms, including direct inoculation of microbes into the body or body site, such as in skin or soft tissue infections or bloodstream infections associated with indwelling venous catheters. Inhalational acquisition is a mode of infection in the setting of respiratory infection, as is aspiration of oral/gastric content. Ascending urinary tract infection can also cause systemic infection. The gastrointestinal tract can also be a source of infection if contents macroscopically rupture or seed the intra-abdominal compartment or if organisms translocate through the mucosal barrier. Other mucosal surfaces can also serve as entry points, including the conjunctiva, the upper respiratory tract, and the genitourinary tract. External disease-transmitting vectors, such as arthropods, can also cause infection. The pathophysiology of sepsis is complex and results from the effects of circulating bacterial products, mediated by cytokine release, caused by sustained bacteremia. Cytokines are responsible for the clinically observable effects of bacteremia in the host. Impaired pulmonary, hepatic, or renal function may result from excessive cytokine release during the septic process.

PROGNOSIS

Sepsis is a common cause of mortality and morbidity worldwide. The prognosis depends on underlying health status and host defenses, prompt and adequate surgical drainage of abscesses, relief of any obstruction of the intestinal or urinary tract, and appropriate and early empiric antimicrobial therapy. The prognosis of sepsis treated in a timely manner and with appropriate therapy is usually good, except in those with intra-abdominal or pelvic abscesses due to organ perforation. When timely and appropriate therapy has been delivered, the underlying physiologic condition of the patient determines outcome. A systematic review by Winters et al suggested that beyond the standard 28-day in-hospital mortality endpoint, ongoing mortality in patients with sepsis remains elevated up to 2 years and beyond. In addition, survivors consistently demonstrate impaired quality of life. Clinical characteristics that affect the severity of sepsis and, therefore, the outcome include the host's response to infection, the site and type of infection, and the timing and type of antimicrobial therapy.

Host-related

Abnormal host immune responses may increase susceptibility to severe disease and mortality. For example, extremes of temperature and the presence of leukopenia and/or thrombocytopenia, advanced age, presence of co-morbid conditions, hyperglycemia, bleeding diatheses, and failure of procalcitonin levels to fall have all been associated with worsened outcome. Important risk factors for mortality include the patient's comorbidities, functional health status, newly onset atrial fibrillation, hypercoagulability state, hyperglycemia on admission, AIDS, liver disease, cancer, alcohol dependence, and immune suppression. Age older than 40 years is associated with comorbid illnesses, impaired immunologic responses, malnutrition, increased exposure to potentially resistant pathogens in nursing homes, and increased use of medical devices, such as indwelling catheters and central venous lines.

Infection site

Sepsis due to urinary tract infection has the lowest mortality rate, while mortality rates are higher with unknown sources of infection, gastrointestinal sources (highest in ischemic bowel), and pulmonary sources.

Infection type

Sepsis due to nosocomial pathogens has a higher mortality rate than sepsis due to community-acquired pathogens. Increased mortality is associated with bloodstream infections due to *Staphylococcus aureus,* fungi, and *Pseudomonas,* as well as polymicrobial infections. When bloodstream infections become severe (ie, septic shock), the outcome may be similar regardless of whether the pathogenic bacteria are gram-negative or gram-positive.

Antimicrobial therapy

Studies have shown that the early administration of appropriate antibiotic therapy (ie, antibiotics to which the pathogen is sensitive) is beneficial in septic patients demonstrating bacteremia. Previous antibiotic therapy (ie, antibiotics within the prior 90 days) may be

associated with increased mortality risk, at least among patients with gram-negative sepsis. Patients who have received prior antibiotic therapy are more likely to have higher rates of antibiotic resistance, reducing the likelihood that appropriate antibiotic therapy will be chosen empirically.

Restoration of perfusion

Failure to attempt aggressive restoration of perfusion early may also be associated with an increased mortality risk. A severely elevated lactate level (>4 mmol/L) is associated with a poor prognosis in patients with sepsis.

EPIDEMIOLOGY

Incidence

The incidence of sepsis and the number of sepsis-related deaths are increasing because of an increased use of immunosuppressive medications. The incidence varies by race and sex. The highest incidence is among black males. The incidence also shows seasonal variation, with the highest number of cases in winter, probably because of the increased prevalence of respiratory infections during this season. Older patients (≥65 years) account for most (60%-85%) sepsis cases, attributable to multiple comorbidities and frequent hospitalizations.

Pathogens

The predominant infectious organisms that cause sepsis have changed over the years. Gram-positive bacteria are the most common etiologic pathogens, although the incidence of gram-negative sepsis remains substantial. The incidence of fungal sepsis has been rising with more patients on immunosuppressive therapies and more cases of HIV infection. In approximately half of sepsis cases, the organism is not identified (culture-negative sepsis).

Risk Factors

Risk factors for sepsis and septic shock include the following:

- ICU admission with subsequent nosocomial infection
- Bacteremia
- Advanced age (≥65 years)
- Immunosuppression - Conditions that impair host defenses such as seen with neoplasms, renal failure, hepatic failure, AIDS, asplenism, diabetes, autoimmune diseases, organ transplant, alcoholism, and the use of immunosuppressant medications and immunomodulators
- Community-acquired pneumonia
- Previous hospitalization and antibiotic therapy in the preceding 90 days
- Genetic factors - Defects of cellular and humoral immunity (low or absent antibody production, T cells, phagocytes, natural killer cells, complement)
- Urosepsis due to benign prostatic hypertrophy (BPH) in older males or complicated UTI
- Major trauma and burn injuries

BACTERIAL SEPSIS CLINICAL PRESENTATION

History and Physical Examination

Nonspecific signs and symptoms

The history and physical examination findings are nonspecific but may suggest the likely source of the septic process and thereby help determine the appropriate antimicrobial therapy and other interventions. General signs and symptoms of sepsis may include the following:

- Fever, with or without shaking chills (temperature >38.3ºC or < 36ºC)
- Impaired mental status (in the setting of fever or hypoperfusion)
- Increased breathing rate (>20 breaths/min) resulting in respiratory alkalosis
- Warm or cold skin, depending on the adequacy of organ perfusion and dilation of the superficial skin vessels
- Hypotension requiring pressor agents to maintain systolic blood pressure above 65 mm Hg

Systemic signs and symptoms

The clinical features depicted below may provide important diagnostic clues.

Respiratory infection

Cough, chest pain, and dyspnea may suggest pneumonia or empyema but may also be observed in patients with pulmonary embolism or pleural effusion.

Gastrointestinal (GI) or genitourinary (GU) infection

The patient may have a history of antecedent conditions predisposing to perforation or abscess. In many cases, the history is critical for diagnosis. Abdominal findings on physical examination may be absent or unimpressive.

- Patients with an intra-abdominal or pelvic source of infection usually have a history of antecedent conditions that predispose to perforation or abscess (eg, chronic or retrocecal subacute appendicitis, diverticulitis, Crohn disease, previous abdominal surgery, or cholecystitis).
- Diffuse abdominal pain may suggest pancreatitis or generalized peritonitis, whereas right upper abdominal quadrant (RUQ) tenderness may suggest a biliary tract etiology (eg, cholecystitis, cholangitis), and tenderness in the right lower abdominal quadrant (RLQ) suggests appendicitis or Crohn disease. Discrete tenderness over the left lower abdominal quadrant suggests diverticulitis, particularly in elderly patients.
- A rectal examination may reveal exquisite tenderness caused by a prostatic abscess or, more commonly, an enlarged noninflamed prostate suggestive of prostatitis.
- A urinary tract source is suggested by an antecedent history of pyelonephritis, stone disease, congenital abnormal collecting system, prostatic hypertrophy, or previous operations or procedures involving the prostate or kidneys. Costovertebral angle tenderness with a fever suggests acute pyelonephritis. Subacute or chronic pyelonephritis may manifest as only mild tenderness.

Intravenous line infection

Evidence of infection at a central IV line site suggests the probable etiology. However, it is important to note that many patients with central IV line infections do not have superficial evidence of infection at the insertion site. Always suspect IV line infections, especially when other sources of sepsis are eliminated. Central IV lines are the lines most commonly associated with bacteremia or sepsis. Peripheral venous lines and arterial lines are rarely associated with bacteremia. Thrombophlebitis may be noted at the peripheral IV line site.

Surgical wound infection

Pain, purulent exudate, or crepitus in a surgical wound may suggest wound infection, cellulitis, or abscess.

Signs of end-organ hypoperfusion

These signs include the following:

- Warm, flushed skin may be present in the early phases of sepsis. The skin may become cool and clammy with progression to shock due to redirection of blood flow to core organs. Decreased capillary refill, purpura cyanosis, or mottling may be seen.
- Altered mental status, obtundation, restlessness
- Oliguria or anuria due to hypoperfusion
- Ileus or absent bowel sounds

Special considerations

- Elderly patients may present with peritonitis and may not experience rebound tenderness of the abdomen.
- Elderly individuals, persons with diabetes, and patients on beta-blockers may not exhibit an appropriate tachycardia as blood pressure falls.
- Younger patients develop a severe and prolonged tachycardia without hypotension until acute decompensation occurs.
- Patients with chronic hypertension may develop critical hypoperfusion at a blood pressure that is higher than in healthy patients (ie, relative hypotension).
- An acute surgical abdomen in a pregnant patient may be difficult to diagnose. The most common cause of sepsis in pregnancy is urosepsis.

BACTERIAL SEPSIS DIFFERENTIAL DIAGNOSES

Diagnostic Considerations

Sepsis is often associated with or preceded by other conditions (see Table 2 below).Noninfectious conditions that present in a manner similar to that of sepsis must also be considered, as should the host's immunocompetence. Early diagnosis with rapid initiation of appropriate therapy is the cornerstone of reducing mortality and morbidity associated with sepsis. Diagnostic studies should be sent within the first 3 hours of suspected sepsis, and antibiotics should be initiated within the first 45 minutes after appropriate cultures are collected. If the blood pressure remains less than 65 mm Hg despite initial fluid resuscitation of 30 mL/kg or if the initial lactate level is 4 mmol/L (36 mg/dl) or higher within 6 hours, further hemodynamic assessments should be performed to ensure adequate organ perfusion. It is essential to reach a preliminary diagnosis within the first 12 hours of presentation to decrease the likelihood of adverse clinical outcomes.

Table 2. Clinical Conditions Associated With Sepsis

System	Associated With Sepsis	Not Typically Associated With Sepsis
GI tract	Liver Gallbladder Colon Abscess Intestinal obstruction Instrumentation	Esophagitis Gastritis Pancreatitis (may have multiorgan dysfunction but not infectious in origin) Small bowel disorders GI bleeding
GU tract	Pyelonephritis Intra- or perinephric abscess Renal calculi Urinary tract obstruction Acute prostatitis/abscess Renal insufficiency Instrumentation in patients with bacteriuria	Urethritis Cystitis Cervicitis Vaginitis Catheter-associated bacteriuria (in otherwise healthy hosts without genitourinary tract disease)
Pelvis	Peritonitis Abscess	
Upper respiratory tract	Deep neck space infection Abscess	Pharyngitis Sinusitis Bronchitis Otitis
Lower respiratory tract	Community-acquired pneumonia (with asplenia) Empyema Lung abscess	Community-acquired pneumonia (in otherwise healthy host)
Intravascular	IV line sepsis Infected prosthetic device Acute bacterial endocarditis	
Cardiovascular	Acute bacterial endocarditis Myocardial/perivalvular ring abscess	Subacute bacterial endocarditis
CNS	Bacterial meningitis	Aseptic meningitis
Skin/soft-tissue	Necrotizing fasciitis	Osteomyelitis Uncomplicated wound infections

CNS = central nervous system; GI = gastrointestinal; GU = genitourinary; IV = intravenous.

Pseudosepsis

A common medicolegal error is failure to consider pseudosepsis as a cause of the presenting syndrome. Most causes of pseudosepsis are readily treatable if recognized and managed early. Thus, before embarking on a workup for sepsis or beginning empiric antibiotic therapy, it is vital to rule out the treatable causes of pseudosepsis early in the disease process. Consider other causes or conditions that mimic the clinical and hemodynamic parameters of sepsis and differentiate between the distributive presentation versus septic shock (see Table 3 below). The causes of pseudosepsis must be identified because they require supportive, rather than antimicrobial, therapy.

Table 3. Noninfectious Conditions Mimicking Clinical and Hemodynamic Parameters of Sepsis

Clinical Presentations Mimicking Sepsis	Hemodynamic Parameters Mimicking Sepsis
Myocardial infarction	Spinal cord injury
Pancreatitis	Adrenal insufficiency
Diabetic ketoacidosis	Acute pancreatitis
Systemic lupus erythematosus flare with abdominal crisis	Hemorrhage
Ventricular pseudoaneurysm	Pulmonary embolism
Massive aspiration/atelectasis	Anaphylaxis
Systemic vasculitis	
Hypovolemia (eg, due to diuretics, dehydration)	

Pseudosepsis is a common cause of misdiagnosis in hospitalized patients, particularly in the emergency department (ED) and ICU. The most common causes of pseudosepsis include gastrointestinal (GI) hemorrhage, pulmonary embolism, acute myocardial infarction (MI), acute pancreatitis (edematous or hemorrhagic), diuretic-induced hypovolemia, and relative adrenal insufficiency. Patients with pseudosepsis may have fever, chills, leukocytosis, and a left shift, with or without hypotension. Many causes of pseudosepsis produce pulmonary artery catheter readings that are compatible with sepsis (ie, increased cardiac output and decreased peripheral resistance), which could misdirect the unwary clinician (see Table 4 below).

Table 4. Characteristics of Pseudosepsis and Sepsis

Parameters	Pseudosepsis	Sepsis
Microbiologic	No definite source PLUS ≥1 abnormalities Negative blood cultures excluding contaminants	Proper identification/process/source PLUS ≥1 microbiologic abnormalities Positive buffy coat smear result OR several positive blood culture results with a pathogenic organism
Hemodynamic	⇓ PVR ⇑ CO	⇓ PVR ⇑ CO Left ventricular dilatation
Laboratory	⇑ WBC count (with left shift) Normal platelet count ⇑ FSP ⇑ Lactate ⇑ D-dimers ⇑ PT/PTT ⇓ Albumin ⇓ Fibrinogen ⇓ Globulins	⇑ WBC count (with left shift) ⇓ Platelets ⇑ FSP ⇑ Lactate ⇑ D-dimers ⇓ PT/PTT ⇓ Albumin
Clinical	≤102°F ± Tachycardia ± Respiratory alkalosis Hypotension	≥102°F OR Hypothermia ± ±Mental status changes ± Hypotension

CO = cardiac output; FSP = fibrin split products; GI = gastrointestinal; GU = genitourinary; PT/PTT = prothrombin time/partial thromboplastin time; PVR = peripheral vascular resistance; WBC = white blood cell.

Host immunocompetence

Otherwise healthy hosts with community-acquired pneumonia virtually never present with hypotension or sepsis; however, patients with decreased or absent splenic function may present with overwhelming pneumococcal sepsis. If an otherwise healthy patient with community-acquired pneumonia presents with shock and all of the other causes of pseudosepsis are ruled out, then it must be assumed that the patient is a compromised host with impaired or absent splenic function.

Differential Diagnoses

- Acute Pancreatitis
- Diabetic Ketoacidosis
- Lower Gastrointestinal Bleeding
- Myocardial Infarction
- Overzealous diuresis
- Pulmonary Embolism
- Upper Gastrointestinal Bleeding

Bacterial Sepsis Workup

Approach Considerations

Multiple clinical, laboratory, radiologic, and microbiologic data are required for the diagnosis of sepsis and septic shock. Sepsis should never be diagnosed based on a single abnormality. However, the diagnosis is often made empirically at the bedside upon presentation or retrospectively when follow-up data return (eg, positive blood culture result) or a response to antibiotics is evident. Importantly, the identification of a pathogenic organism, although preferred, is not always feasible since the responsible organism may be unidentified in many patients.

In general, the workup for sepsis may include the following:

- Blood culture and urine analysis and culture
- Chemistry studies that can suggest organ dysfunction, such as liver or kidney function tests
- Chest radiology
- Diagnostic imaging of the chest and abdomen/pelvis
- Cardiac studies such as ECG and troponins, as indicated
- Interventions such as paracentesis, thoracentesis, lumbar puncture, or aspiration of an abscess, as clinically indicated
- Measurement of biomarkers of sepsis such as procalcitonin levels

Laboratory Studies

Complete blood cell count

A complete blood cell (CBC) count is usually not specific. Leukocytosis with a left shift is also a nonspecific diagnostic finding and can be seen in noninfectious conditions. Leukopenia, anemia, and thrombocytopenia may be observed in sepsis.

Complete metabolic profile

A complete metabolic profile identifies changes in organ function, especially the liver and kidneys.

Bacterial cultures

Obtain blood cultures in all patients upon admission. Negative blood culture results are also necessary to include pseudosepsis in the

differential diagnosis. Blood culture isolates might suggest the underlying disease process. Bacteroides fragilis suggests a colonic or pelvic source, whereas Klebsiella species or enterococci suggest a gallbladder or urinary tract source. If central intravenous (IV) line sepsis is suspected, remove the line and send the tip for semiquantitative bacterial culture. If culture of the catheter tip yields positive results and demonstrates 15 or more colonies and if the isolate from the tip matches the isolate from the blood culture, an infection associated with the central IV line is diagnosed. ICU patients are at a greater risk of colonization by MRSA, vancomycin-resistant enterococci (VRE), and carbapenem-resistant Enterobacteriaceae (CRE). It is critical to deescalate or change the empiric antibiotic regimen once the organism susceptibilities are available.

Gram staining

Buffy coat analysis of CBC may be useful in identifying certain infectious agents, although the yield is low.

Urinalysis with reflex to culture

If urosepsis is suspected, obtain a urine Gram stain, urinalysis, and urine culture. A systematic review found that in adult ICU patients, catheter-associated urinary tract infection was associated with significantly higher mortality and a longer stay.

Microbiology

Organism identification via culture in a patient who fulfills the definition of sepsis is highly supportive of a sepsis diagnosis but is unnecessary. The rationale behind its lack of inclusion in the diagnostic criteria for sepsis is that a culprit organism goes unidentified in up to half of patients who present with sepsis, and a positive culture result is not required to make a decision regarding treatment with empiric antibiotics.

Unique laboratory findings

Laboratory and clinical features that may suggest an underlying etiology of sepsis are as follows:

- Leukocytosis (WBC count >12,000/µL) or leukopenia (WBC count < 4000/µL)
- Normal WBC count with greater than 10% immature forms (left shift with bandemia)
- Hyperglycemia (plasma glucose level >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
- Plasma C-reactive protein level of more than two standard deviations above the reference value
- Arterial hypoxemia (PaO_2/FiO_2 ratio < 300 mm Hg)
- Acute oliguria (urine output < 0.5 mL/kg/hour for at least 2 hours despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 mmol/L
- Coagulation abnormalities (INR >1.5 or PTT >60 seconds)
- Thrombocytopenia (platelet count < 100,000/µL)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
- Adrenal insufficiency (eg, hyponatremia, hyperkalemia) and euthyroid sick syndrome can also be found in sepsis.
- Hyperlactatemia (serum lactate >2 mmol/L) can result from organ hypoperfusion in the presence or absence of hypotension and indicates a poor prognosis. A serum lactate level of 4 mmol/L or more (especially arterial lactate) indicates septic shock.
- Plasma procalcitonin and presepsin elevation is associated with bacterial infection and sepsis.

Procalcitonin levels

Procalcitonin (PCT) is an acute-phase reactant that is elevated in severe bacterial infections. In most clinical assays, the reference range of PCT is below detectable. Measurement of PCT and C-reactive protein (CRP) at onset and on the fourth day of treatment can predict survival of patients with ventilator-associated pneumonia. A decrease in either one of these marker values predicts survival. A study from van Nieuwkoop et al examined the use of PCT levels in predicting bacteremia in a group of 581 patients, 136 of whom had bacteremia; PCT levels successfully identified 94-99% of the patients with bacteremia. Heyland et al, in a systematic review of the economic value of PCT-guided reduction in antibiotic use in intensive care, found that with hospital mortality and length of stay unchanged, PCT testing to reduce antibiotic treatment broke even when daily antibiotics cost about $150 in Canadian dollars.

Chest Radiology and Chest CT Scan

Chest Radiography

No radiologic signs are specific to the identification of sepsis, but chest radiography can aid in identifying a specific infection site. Chest radiography is important to rule out pneumonia and diagnose other causes of pulmonary infiltrates, such as the following:

- Pulmonary drug reactions
- Pulmonary embolism
- Pulmonary hemorrhage
- Primary or metastatic pulmonary neoplasms
- Lymphangitic spread of malignancies
- Large pleural effusions
- Pneumothorax
- Hydrothorax
- Fluid overload
- Congestive heart failure (CHF)
- Acute myocardial infarction (MI)
- Acute respiratory distress syndrome

Chest CT Scanning

Chest CT scanning is a very sensitive modality for diagnosing the lung pathology listed above.

Abdominal Ultrasonography, CT Scanning, and MRI

Perform abdominal ultrasonography if biliary tract obstruction is suspected based on the clinical presentation. However, abdominal ultrasonography is suboptimal for the detection of abscesses or perforated hollow organs. Ultrasonograms in patients with cholecystitis may show a thickened gallbladder wall or biliary calculi but no dilatation of the common bile duct (CBD). Stones in the biliary tract may or may not be visible in patients with cholangitis, but the CBD is typically dilated. Use computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen if a nonbiliary intra-abdominal source of infection is suspected on the basis of the history or physical examination findings. Abdominal CT or MRI is also helpful in delineating intrarenal and extrarenal pathology. Gallium or indium scanning has no place in the initial workup of sepsis; patients with sepsis are acutely ill by definition, and rapid diagnostic tests (eg, CT or MRI of the abdomen and ultrasonography of the right upper quadrant) are time-critical, life-saving tools. However, MRI is more time consuming than CT scanning, and the latter is preferred in emergent situations.

Cardiac Studies

If acute MI is likely, perform electrocardiography (ECG) and obtain cardiac enzyme levels. Remember that certain patients may present with a silent, asymptomatic MI, which should be included in the differential diagnosis of otherwise unexplained fever, leukocytosis, and hypotension. Silent MIs are common in elderly patients and in those who have recent undergone abdominal or pelvic surgical procedures. They are also common in individuals with alcoholism, diabetes, and uremic conditions. The following cardiac studies may be useful if cardiac involvement or disease is suspected as a cause or complication of infection:

- Electrocardiography (ECG) to evaluate for conduction abnormalities or delays or arrhythmias

- Cardiac enzyme levels
- Echocardiography to evaluate for structural heart disease

Invasive Interventions

Invasive diagnostic procedures that may be considered are discussed below.

Thoracentesis/paracentesis

Perform thoracentesis for diagnostic purposes in patients with substantial pleural effusion. Perform paracentesis in patients with gross ascites.

Surgical incision and drainage

Drainage of fluid collections/abscesses is crucial in establishing good source control and in facilitating a good clinical response to subsequent antibiotic therapy.

Bronchoscopy

Bronchoscopy with washing, lavage, or other invasive sampling is performed in patients with suspected pneumonia and in patients with suspected invasive fungal infections of the lung.

Swan-Ganz catheterization

In highly selected cases, a Swan-Ganz catheter may be useful in managing the fluid status of the patient and in assessing left ventricular dysfunction. However, routine use is not recommended.

Imaging Studies

Site-specific soft tissue imaging includes ultrasonography, CT scanning, or MRI to assess for possible abscess, fluid collection, or necrotizing skin infection. These are essential for diagnostic purposes and for monitoring the response to therapy. Contrast-enhanced CT scanning or MRI of the brain/neck is performed to assess for possible masses, abscess, fluid collection, or necrotizing infection.

Bacterial Sepsis Treatment & Management

Approach Considerations

Early aggressive medical therapy is indicated in patients with suspected sepsis.

Sepsis Treatment

Patients with sepsis are generally ill and require inpatient hospitalization or admission to the intensive care unit (ICU) for monitoring and treatment. Admission to an ICU depends on the severity of the septic process and the degree of organ dysfunction. Determine the likely source of the infection, and administer intravenous (IV) empiric antimicrobial agents until culture results become available, at which point more narrow-spectrum agents can be used (see below). In addition, offer supportive therapy aimed at maintaining organ perfusion, and provide respiratory support when necessary. A recent prospective study of 5787 adult patients with severe sepsis revealed the importance of goal-directed treatment. Patients triaged and managed according to 4 clinical goals (blood cultures before antibiotics, lactate before 90 minutes, IV antibiotics before 180 minutes, and 30 mL/kg of IV fluids before 180 minutes) were significantly less likely to die in the hospital than were those for whom all 4 of these goals were not met (22.6% vs 26.5%, respectively). In a multivariate regression analysis adjusted for age, admission to the intensive care unit (ICU), vasopressor initiation, central venous catheter insertion, and monitoring of central venous pressure and central venous oxygen saturation, complete compliance with the clinical goals was associated with a survival odds ratio of 1.194 (1.04-1.37).

Surgical Intervention

Early evaluation in patients with presumed intra-abdominal or pelvic sepsis is essential, and surgical consultation should be obtained in appropriate patients.

Consultations

Obtain a consultation with a surgeon for patients with presumed intra-abdominal or pelvic sepsis. Obtain a consultation with an infectious disease specialist, as indicated, in patients with presumed or proven sepsis.

Antimicrobial Therapy

Appropriate antimicrobial therapy depends on adequate coverage of the bacteria associated with the specific organ or organ system associated with the infection. Agents suitable for empiric monotherapy regimens (depending on the source and underlying microbiology of the sepsis because the agent must be able to cover all of the likely pathogens) may include the following:

- Imipenem
- Meropenem
- Tigecycline
- Piperacillin-tazobactam
- Ampicillin-sulbactam
- Moxifloxacin

Combination therapeutic regimens include metronidazole plus either levofloxacin, aztreonam, a third- or fourth-generation cephalosporin, or an aminoglycoside. Many advocate also using antistaphylococcal coverage (eg, vancomycin) empirically. Although no drug regimen may be superior to another, time to first dose administration is very important. Mortality data suggest that early administration of appropriate antibiotics is correlated with better survival. Alternative agents may be used alone or in combination, with a good adverse-effect profile. Antibiotics are normally continued until the septic process and surgical interventions have controlled the source of infection. Ordinarily, patients are treated for approximately 2 weeks, although duration may vary according to the source, site, and severity of the infection. As soon as patients are able to tolerate medications orally, they may be switched to an equivalent oral antibiotic regimen in an IV-to-oral conversion program.

Empiric therapy for IV line infections

A detailed discussion of catheter-associated infections is available in the IDSA catheter-associated line-related infections (CRBSI) guidelines. IV line infections are most often due to *Staphylococcus aureus* (methicillin-sensitive *S aureus* [MSSA] or methicillin-resistant *S aureus* [MRSA]) ,but gram-negative bacilli can be involved. The preferred empiric therapy for these infections is meropenem or cefepime (for *Pseudomonas*) plus additional coverage for staphylococci. If MRSA is prevalent in the institution, add linezolid, vancomycin, or daptomycin. Otherwise, nafcillin, oxacillin, or cefazolin provides adequate coverage for MSSA. Unless coagulase-negative, methicillin-sensitive staphylococci are recovered from the blood, with high-level bacteremia (3 or 4 positive blood cultures out of 4), avoid vancomycin for empiric therapy if possible; these are low-virulence organisms and may represent contaminants. If treatment is advised, the duration of therapy depends on the severity and site of infection. Treatment of staphylococcal central line infection and fungal or gram-negative organisms typically requires removal of the line. Minimize the use of vancomycin in order to prevent the emergence of vancomycin-resistant enterococci (VRE).

Empiric therapy for biliary tract infections

IDSA guidelines for complicated intra-abdominal infections such as biliary tract infections are available. The main biliary tract pathogens include *Escherichia coli, Klebsiella* species, and *Enterococcus faecalis*. Coverage for staphylococci is not needed in the biliary tract. Anaerobes can also be important, especially in patients with diabetes or immunosuppression. Preferred monotherapy regimens for biliary tract infections include imipenem, meropenem, ampicillin-sulbactam, or

piperacillin-tazobactam. Cephalosporins or quinolones in combination with metronidazole are alternate first-line agents for the treatment of biliary tract infections.

Empiric therapy for intra-abdominal and pelvic infections

The main pathogens in the lower abdomen and pelvis include aerobic coliform gram-negative bacilli and *B fragilis*. Enterococci do not require special coverage unless the patient has recurrent infection or enterococci have been specifically and repeatedly isolated. Potent anti–*B fragilis* and aerobic gram-negative bacillary coverage are essential, in addition to surgical intervention when drainage or repair of intra-abdominal viscera is required. Preferred monotherapy regimens for intra-abdominal and pelvic infections include imipenem, meropenem, piperacillin-tazobactam, ampicillin-sulbactam, or tigecycline. Alternate combination therapy for intra-abdominal and pelvic infections consists of clindamycin or metronidazole plus a third- or fourth-generation cephalosporin, aztreonam, levofloxacin, or an aminoglycoside. Some authors raise concerns about the use of tigecycline.

Empiric therapy for urosepsis

The primary uropathogens include gram-negative aerobic bacilli, such as coliforms or enterococci. *Pseudomonas aeruginosa, Enterobacter* species, and *Serratia* species are rare uropathogens and are associated with urologic instrumentation. Monotherapy for urosepsis due to aerobic gram-negative bacilli may include aztreonam, levofloxacin, a third- or fourth-generation cephalosporin, or an aminoglycoside. However, preferred monotherapy for enterococcal urosepsis involves ampicillin or vancomycin. For VRE urosepsis, linezolid or daptomycin may be used. Empiric therapy for community-acquired urosepsis consists of levofloxacin, aztreonam, or an aminoglycoside plus ampicillin. For nosocomial urosepsis, a fourth-generation cephalosporin, piperacillin-tazobactam, imipenem, or meropenem, with or without an aminoglycoside, is preferred.

Empiric therapy for staphylococcal, pneumococcal, and meningococcal sepsis

S aureus sepsis is usually associated with infection caused by devices or bacterial endocarditis. Empiric therapy may be with an anti-staphylococcal penicillin (nafcillin or oxacillin), vancomycin, a cephalosporin, daptomycin, or linezolid, depending on the concern for MRSA. Pneumococcal or meningococcal sepsis may be treated with penicillin G or a beta-lactam. In patients with associated meningococcal meningitis, the antibiotic selected should penetrate the cerebrospinal fluid (CSF) and should be given in meningeal doses. Consider the regional prevalence of drug-resistant pneumococci when selecting an antibiotic.

Empiric therapy for sepsis of unknown origin

The usual sources of sepsis are the distal gastrointestinal (GI) tract, the pelvis, and the genitourinary (GU) tract. Organisms that should be covered from these areas include aerobic gram-negative bacilli (coliforms) and *B fragilis.* Enterococci are important pathogens in biliary tract sepsis and urosepsis. Preferred empiric monotherapy includes meropenem, imipenem, piperacillin-tazobactam, or tigecycline. Empiric combination therapy includes metronidazole plus levofloxacin, aztreonam, or a third- or fourth-generation cephalosporin.

Outpatient management

If orally administered antibiotics are continued at home, advise the patient about possible adverse effects. If additional antimicrobial therapy is needed outside the hospital setting, it should be given orally, not intravenously. Do not allow the total course of antibiotics to exceed 3 weeks, except for specific clinical scenarios, which may require prolonged courses of oral antibiotics for cure or complete clinical resolution.

BACTERIAL SEPSIS GUIDELINES

Guidelines Summary

The initial sepsis guidelines were published in 2004 and then revised in 2008 and 2012. The current clinical practice guidelines are a revision of the 2012 Surviving Sepsis Campaign (SSC) guidelines for the management of severe sepsis and septic shock.

Major New Recommendations in the 2012 Update

Emphasis was directed to (1) first-hour fluid resuscitation and inotrope therapy directed to goals of threshold heart rates, normal blood pressure, and capillary refill of 2 seconds or less with specific evaluation after each bolus for signs of fluid overload, as well as first-hour antibiotic administration and (2) subsequent ICU hemodynamic support directed to goals of $S_{cv}O_2$ greater than 70% and cardiac index (CI) 3.3-6 L/min/m with appropriate antibiotic coverage and source control. Another major new recommendation in the 2012 update was that hemodynamic support of septic shock should be addressed at the institutional level rather than only at the practitioner level, with well-planned coordination between the family, community, prehospital, emergency department, hospital, and ICU settings. The 2012 guidelines recommend that each institution implement their own adopted or home-grown bundles that include the following:

- Recognition bundle containing a trigger tool for rapid identification of patients with suspected septic shock at that institution
- Resuscitation and stabilization bundle to drive adherence to consensus best practice at that institution
- Performance bundle to monitor, improve, and sustain adherence to that best practice

The 2016 Surviving Sepsis Campaign Guidelines

The 2016 guidelines give a detailed overview of initial resuscitation, screening, and diagnosis of sepsis. The management decisions concerning antibiotic therapy, fluid administration, source control, administration of pressors and steroids, blood products, anticoagulants, immunoglobulins, mechanical ventilation, sedation, analgesia, glucose control, blood purification, renal replacement therapy, bicarbonate, venous thromboembolism and stress ulcer prophylaxis, nutrition, and setting goals of care are addressed. The main differences between the 2012 and 2016 guidelines are discussed in detail in the cited reference.

Unfortunately, a consensus could not be reached between some of the sponsoring organizations. A position paper issued by the IDSA does not endorse the Society of Critical Care Medicine/European Society of Intensive Care Medicine (SCCM/ESICM) 2016 Surviving Sepsis Campaign guidelines for the management of sepsis and septic shock, despite the IDSA's participation in the development of the guidelines. In particular, while the IDSA agrees that the SCCM/ESICM recommendations are life-saving for patients with septic shock, they may lead to overtreatment in those with milder variants of sepsis and sepsis syndromes. The IDSA does not endorse routine initiation of antibiotic therapy within one hour of suspecting sepsis nor administration of combination antibiotic therapy and a 7- to 10-day course of antibiotic therapy for all patients, regardless of presentation factors. The IDSA also notes unclear recommendations for removal of catheters when considered as the source of sepsis and for the role of procalcitonin when monitoring therapeutic response. As more research related to timing of therapy is completed, further guideline refinement is expected, and perhaps a consensus regarding the treatment approach can be achieved.

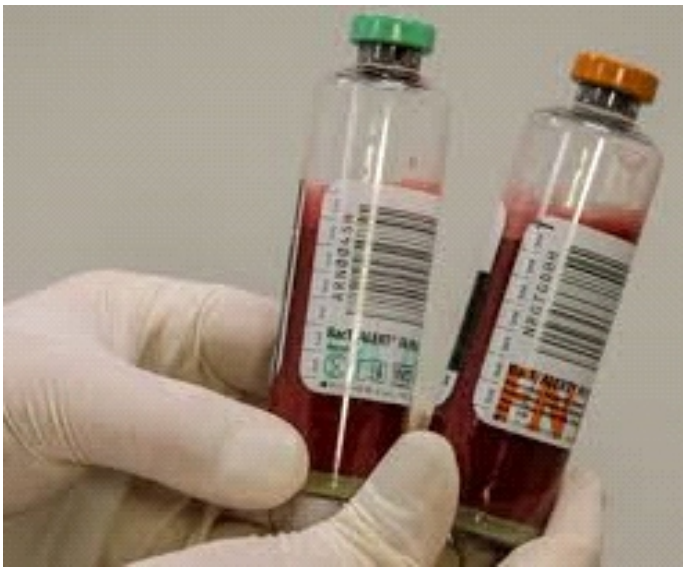
Medication Summary

The goals of pharmacotherapy are to eradicate the infection, reduce morbidity, and prevent complications.

INTERPRETATION

BLOOD CULTURE

The reference range for blood culture is no growth.



Interpretation

True infection is almost always present if the culture is positive for one of the following organisms:[1,2]

- Streptococci (non-viridans)
- Aerobic and facultative gram-negative rods [3]
- Anaerobic cocci
- Anaerobic gram-negative rods
- Yeast

Negative growth does not rule out infection.

Suspect contamination if only one of several cultures is positive, if detection of bacterial growth is delayed (≥5 d), or if multiple organisms are isolated from one culture.[4]

Common contaminants include the following:

- *Staphylococcus epidermidis*[5]
- *Bacillus species*
- *Propionibacterium acnes*
- *Corynebacterium species*
- *Clostridium perfringens*
- *Viridans Streptococcus*
- *Candida tropicalis*

Collection and Panels

Specifics for collection and panels are as follows:

- Specimen type - Whole blood
- Container - Culture bottles (one aerobic and one anaerobic) for blood and green-top tube (heparin) for fungus and mycobacteria (if warranted by clinical suspicion)
- Collection method - Venipuncture
- Specimen volume - Adults: 10-20 mL per culture set; Pediatric patients: 1.0-3.0 mL

Other instructions are as follows:

- Collect specimens as soon as possible after onset of chills or fever and before beginning antibiotic therapy.
- Use aseptic technique (eg, clean venipuncture sites and culture vial tops with 2% chlorhexidine/70% isopropyl alcohol swabs before collection).
- Draw 2-3 sets of cultures from separate sites at least 30-60 min apart (no more than 4 sets per 24-hour period).
- Do not draw from IV catheter unless other sites unavailable.
- Related tests - Complete blood count (CBC), urine culture, bacterial wound culture, gram stain, CSF analysis, fungal tests, susceptibility testing, sputum culture

BACKGROUND

Description

Blood cultures are used to identify microorganisms in the blood and to assist in guiding antimicrobial therapy. Common sources of bacteremia include the following: [6,7]

- Genitourinary tract
- Respiratory tract
- Abscesses
- Surgical wounds
- Biliary tract
- Prosthetic cardiac valves

Indications/Applications

Indications for blood culture include symptoms of bacteremia or sepsis, such as the following:

- Fever, chills
- Rapid breathing and heart rate
- Confusion
- Severe hypotension
- Decreased urine output

TROUBLESHOOTING

BLOOD CULTURES

HOW TO OBTAIN, PROCESS, REPORT, AND INTERPRET

The detection and identification of microorganisms circulating in the bloodstream of patients is arguably one of the most important functions of the clinical microbiology laboratory. Effective implementation of this function requires careful consideration of specimen collection and processing, culture techniques, result reporting, and, perhaps most importantly, result interpretation by the physician. The purpose of this review is to provide a synopsis of the current state of the art for each of these areas, with the intention of providing adequate information to enable clinical laboratory personnel and physicians to critically evaluate and, if required, improve their current blood culture practices.

Introduction

Bloodstream infections (BSIs) represent an important cause of human morbidity and mortality. The evaluation of patients suspected of having a BSI routinely includes blood cultures, which optimally yield an aetiological diagnosis and provide the opportunity to perform antimicrobial susceptibility testing to guide therapeutic intervention when necessary. The clinical significance of positive blood cultures has been extensively evaluated over the past several decades . These studies have served to define the most frequent aetiological agents responsible for BSIs and the range of agents, and have improved our understanding of the risks and outcomes associated with such infections. As the baseline characteristics of patients have changed with advances in medicine (e.g. more immunocompromised hosts, more indwelling catheters and other intravascular devices, and changes in therapy for human immunodeficiency virus), the epidemiology of BSIs has also evolved, with more infections occurring in patients with intravascular devices and in outpatient settings. Additionally, there appears to be a trend towards improved outcomes in patients with BSIs, perhaps as a consequence of earlier therapeutic intervention, whereas the number of BSIs appears to be increasing, especially those occurring in populations that were previously less affected (outpatients). Because BSIs remain an important cause of morbidity and mortality, and prompt targeted therapeutic intervention may improve patient outcomes, there has been significant interest in improving the speed and accuracy of blood culture methods in the clinical microbiology laboratory. Despite these efforts, little has changed since the introduction of continuous-monitoring blood culture systems in the 1990s, but incremental advances in more rapid identification and susceptibility prediction have occurred, especially for some particularly troublesome pathogens. Moreover, greater advances appear to be on the horizon.

Blood Culture Collection

The utility of blood culture for detecting BSI is directly influenced by the collection of optimal specimens only from patients with clinical findings compatible with BSI; routine 'surveillance' blood cultures are costly and of little clinical value [7, 8, 9]. Clearly, venipuncture is the preferred method for blood culture collection. Arterial blood samples do not increase diagnostic yield, and blood specimens obtained from intravascular lines have demonstrated increased rates of contamination in some studies [10]. The American College of Physicians guidelines recommend that collecting blood for culture from intravascular devices be avoided, and the CLSI recommends that, if one must collect a blood culture from an intravenous line, it should be paired with a culture that is obtained via venipuncture to assist in the interpretation of positive results [11,12]. The timing of blood culture collection does not appear to significantly affect the recovery of clinically relevant microorganisms, and most authorities therefore recommend collecting multiple sets simultaneously or over a short period of time, except when documentation of continuous bacteraemia is required for patients with endovascular infection [12,13]. Whenever possible, two to four sets of blood specimens should be collected from independent venipuncture sites, and, for adult patients, each set should consist of 20–40 mL of blood . The volume of blood drawn from infants and children is less well prescribed, but should be based on the child's age and not exceed 1% of the patient's total blood volume. It is clear that the total volume of blood cultured from adult patients is directly proportional to the yield of microorganisms recovered. This is a consequence of the fact that most adult patients with BSIs have very low circulating concentrations of viable microorganisms. Inadequate blood volume or the collection of a single blood culture set significantly reduces the sensitivity of the test, and also makes the interpretation of results far more difficult. Collection of multiple sets of blood cultures from a single venipuncture or intravascular line should also be avoided. For optimal recovery of diverse BSI aetiological agents, each set of blood cultures should include paired aerobic and anaerobic blood culture bottles, and the aerobic bottle should be filled first. Proper skin antisepsis prior to collection of blood cultures via peripheral venipuncture is paramount, to reduce blood culture contamination rates and facilitate result interpretation for the clinician. A variety of skin disinfectants have been clinically evaluated, and reports comparing their relative efficacy have been published . On the basis of these data, current guidance documents conclude that tincture of iodine, chlorine peroxide and chlorhexidine gluconate are superior to povidineiodine preparations, and that tincture of iodine and chlorhexidine gluconate are probably equivalent for skin antisepsis prior to blood culture collection . Although chlorhexidine gluconate is an adequate disinfectant for older infants, children, and adults, it should not be used on infants <2 months of age, and an alternative is therefore required in centres where this disinfectant is otherwise routinely employed. Once optimal blood culture specimens are collected according to the principles outlined above, they should be sent to the laboratory as promptly as possible. These specimens should never be refrigerated or frozen, and should be held at room temperature for no more than a few hours if necessary. Although an extended delay between blood culture collection and incubation in a continuous-monitoring blood culture instrument is not recommended, a significant diminution in pathogen recovery has only been experimentally observed when blood culture bottles have been held for >24 h at 4°C or room temperature and for >12 h at 37°C . Lengthy incubation of blood culture bottles prior to entering them into a continuous-monitoring blood culture instrument may delay or impede the detection of growth by the instrument, and is discouraged.

Laboratory Techniques for Blood Culture

In the vast majority of institutions, most blood culture specimens delivered to the laboratory are entered into an incubation protocol on a continuously monitored blood culture device. There are several manufacturers of such devices, and their performance characteristics are similar. These devices incubate the blood culture bottles for a

prescribed period of time (determined by the user) and signal audibly and/or visually if growth is detected. Each automated blood culture system has its own associated medium formulations that must be selected by the user. The blood culture bottles typically contain proprietary mixtures of culture medium, an anticoagulant, and, in many cases, resins or charcoal mixtures to reduce the effects of antimicrobials and other toxic compounds. Generally, combinations of medium formulations that are complementary to each other are chosen to enhance the recovery of the most diverse range of microorganisms. Medium combinations typically include aerobic and anaerobic formulations and, in select circumstances, a formulation containing reagents that are ideal for recovering mycobacteria and/or yeasts may be inoculated as well. Controlled studies comparing the performance of media with and without the addition of antimicrobial binding or absorbing agents (resins and/or charcoal compounds) have repeatedly demonstrated that the latter formulations are clearly superior for the recovery of microorganisms, especially staphylococci and yeasts. Blood cultures entered into automated, continuous-monitoring protocols should routinely be incubated for 5 days. Multiple studies have shown that this incubation time is adequate for the detection of the majority of pathogens, including fastidious bacteria that belong to the Haemophilus, Actinobacillus, Cardiobacterium, Eikinella and Kingella (HACEK) group, and that incubation beyond 5 days increases the number of contaminants recovered . Longer incubation times may be required when dimorphic fungaemia or bacteraemia caused by Legionella, Brucella, Bartonella or Nocardia spp. is suspected. Blood cultures for Mycobacterium spp. should be incubated for 4 weeks. The detection of some microorganisms is enhanced by employing blood culture techniques in addition to or in place of standard instrumented blood culture systems. The most common example of this principle is the utilization of the Isolator blood culture system (Wampole Laboratories, Cranbury, NJ, USA) for the enhanced detection of dimorphic fungi and Bartonella spp.. This system is unique in that it is non-broth-based. Instead, blood samples obtained by venipuncture are collected into a tube that contains a lysing solution. The tubes are then transported to the laboratory, where they are centrifuged. The supernatant is discarded, and the pellet is inoculated onto solid medium, the composition of which may be tailored to recover the organisms (bacteria, fungi, and/or mycobacteria) that are most likely or highly suspected on the basis of clinical findings. Although there are clear advantages to using this approach in select circumstances (suspicion of BSI caused by dimorphic fungi or Bartonella spp.), it is not routinely employed, as it is quite labour-intensive, it poses a greater risk of laboratory-acquired infection to technologists, and it is inferior to standard blood culture methods for the detection of anaerobes, Haemophilus spp., and pneumococci .

Special Considerations for Select Microorganisms

Fungal blood cultures

Fungi represent an emerging group of organisms that are responsible for BSI with increasing frequency. The growth requirements for fungi often differ from those for bacteria, most notably with regard to optimal growth temperature and media. For example, most yeasts grow best at 37°C, whereas filamentous fungi often grow best at lower (27–30°C) temperatures. Most routine manual and automated blood culture systems are able to support the growth of yeasts such as Candida spp. However, if suspicion is high for a BSI being caused by yeast, and routine blood cultures are negative, then it may be reasonable to consider a request for alternative test methods that are optimally designed to support the growth of most yeasts. Moulds, and especially dimorphic fungi, often grow poorly in typical instrumented blood culture systems. Furthermore, the recovery of moulds such as Aspergillus spp. is often of unclear clinical significance when they are isolated with these methods . In cases where fungaemia caused by a mould is suspected, alternative blood culture methods should be employed, such as the lysis centrifugation method, in which the lysed and pelleted blood specimen can be plated on medium that specifically supports the growth of moulds and dimorphic fungi. Some fungi require highly specialized medium supplements, the most noteworthy example being the requirement for lipid supplementation for Malasezzia furfur, which is often achieved by overlaying fungal medium with olive oil.

Mycobacterial blood cultures

Mycobacterial BSIs occur in immunocompromised patients (either as a consequence of iatrogenic immunosuppression, or associated with an immunosuppressive condition) and patients with long-term vascular access devices. Investigation tailored to the recovery of mycobacterial blood isolates should thus generally be limited to patients with such characteristics. As mycobacteria are commonly located intracellularly, approaches to growing them in vitro often include lysis of leukocytes prior to incubation in a rich medium that contains fatty acids. Mycobacteria may be optimally recovered, with extended incubation of 4 weeks, with manual methods such as lysis centrifugation or the use of commercial 'lytic' media in manual or instrumented systems. These blood culture formulations typically contain a proprietary mixture of fatty acids that support mycobacterial growth, along with antimicrobial agents. Limited comparisons between formulations suggest some variability in the performance of lytic culture media, but comprehensive comparative studies of all formulations have not been performed .

Fastidious microorganisms

Fastidious microorganisms are rarely implicated in BSI in clinical practice, but when they are isolated from blood cultures they often represent serious infection. In some cases, the observation of signal-positive Gram stain-negative blood culture results provides a clue that a fastidious microorganism might be implicated as the BSI aetiological agent. In those cases, collaboration between the laboratory and clinician is essential to ensure that appropriate steps are taken to increase the odds of isolation of such organisms. Some organisms may be small or of unusual morphology, and not readily recognized by the technologist. In other cases, the organism may not stain well with standard Gram stain protocols (e.g. Mycoplasma and Campylobacter). In those cases, alternative staining techniques may be employed, including the use of acridine orange (to stain bacterial nucleic acids) or the use of carbol fuschin as an alternative to safranin as a counterstain in the Gram stain protocol to enhance the staining of Campylobacter, Helicobacter, and Brucella. Perhaps the most frequently encountered fastidious bacteria are the members of the HACEK group as the aetiological agents for subacute bacterial endocarditis. As noted above, in the vast majority of cases, these organisms are isolated with standard blood culture techniques without the need for special protocols or procedures. This is also generally true for Brucella spp., Campylobacter spp., and Francisella spp., but is not true for all fastidious bacteria. Abiotrophia and Granulicatella are usually detected with automated blood culture instruments, but do not grow well on standard, unsupplemented solid media, as they require pyridoxal or cysteine for growth. This can be

accomplished by co-cultivation with staphylococci, by the use of pyridoxalimpregnated disks placed on the surface of standard blood agar plates, or by the use of specially supplemented or enriched media. The yield of standard blood culture media for the cultivation of Bartonella spp. is typically low. Special techniques, including lysis centrifugation methods and/or serological investigations, are thus indicated for the diagnosis of BSI caused by Bartonella spp. Legionella spp. require buffered charcoal yeast extract (BCYE) for optimal growth. Recovery of Legionella can be achieved by subculturing standard blood culture medium that has been incubated according to the standard protocol for 5 days into BCYE, or by utilizing BCYE in conjunction with lysis centrifugation methods. A detailed description of all of the special techniques required for the culture of other rarely encountered fastidious organisms (e.g. Helicobacter and Leptospira) is beyond the scope of this review, and has been provided elsewhere .

ISOLATION, IDENTIFICATION, AND SUSCEPTIBILITY TESTING

Once blood cultures become positive for growth, either by manual subculture techniques or signalling from automated systems, a Gram stain is performed. A positive Gram stain result should be regarded as a critical value, and immediately phoned to the ordering clinician or another responsible member of the healthcare team providing care to the patient. Subcultures are performed at this point, and these allow identification and, if indicated, susceptibility testing to be performed, typically over the next 24–48 h. Laboratories should have a comprehensive protocol in place to guide the appropriate work-up of organisms isolated from blood cultures. To optimally utilize resources, complete organism identification and organism-specific susceptibility testing should only be performed on clinically important isolates, and not on organisms that probably represent contaminants [57,58]. Isolates that are probably associated with true BSI (as per the laboratory protocol) should be saved in the laboratory (by serial subculture) for several days to allow additional testing if required, and may be retained for longer periods of time (in a frozen archive) to allow investigation of recurrent BSIs in appropriate patients.

Interpretation of Positive Blood Cultures

The interpretation of positive blood culture results is often straightforward, but sometimes presents a significant dilemma for physicians and clinical microbiologists. For the latter circumstance, a variety of laboratory data must be evaluated in the context of the clinical picture to arrive at an accurate interpretation. The pattern of positivity of blood cultures is often useful; when the majority of or all blood culture sets obtained by independent venipuncture are positive for the same microorganism, the likelihood that this represents true BSI is exceedingly high, regardless of the organism's identity . Likewise, the identities of organisms isolated from positive blood cultures also have value. Staphylococcus aureus, Streptococcus pneumoniae, Enterobacteriaceae, Pseudomonas aeruginosa and Candida albicans are almost always predictive of true BSI. Conversely, Corynebacterium spp. and Propionibacterium spp. almost always represent contamination. The recovery of viridans group streptococci, coagulase-negative staphylococci (CoNS) and enterococci is more difficult to interpret, as some studies have demonstrated that they represent true BSI in 38%, 15% and 78% of cases, respectively [1]. Notably, CoNS represent one of the most commonly encountered blood culture contaminants, but also constitute an important cause of BSI in the ever-expanding population of patients with implanted devices and indwelling catheters. Interpretation for these cases may be aided by identifying CoNS to the species level when more than one set of blood cultures becomes positive. If the same species of CoNS is isolated from multiple blood culture sets, the odds that it represents true bacteraemia as opposed to contamination increase . Without this additional information, using the number of positive blood culture sets that are generically positive for CoNS is a less reliable predictor. Finally, some have suggested that the number of blood culture bottles (as opposed to the number of sets) has predictive value, in that the more that are positive for CoNS, the more likely it is that the patient has bacteraemia caused by CoNS. However, systematic evaluations of this approach have proven it to be unreliable .

Rapid Methods for Identification and Susceptibility Testing of Isolates from Positive Blood Cultures

Prompt detection, identification and susceptibility testing of the aetiological agents responsible for BSIs is critical, as it allows clinicians to make the most informed decisions about possible therapeutic interventions. Blood cultures incubated in modern instrumented systems that are ultimately positive for most bacterial pathogens typically signal positive in a median time of 12–36 h, whereas the time to positivity from collection to detection is longer for some fastidious bacteria, anaerobes, and fungi . Following detection, Gram stain rapidly provides some information to the clinician that may be useful for determining the significance of the positive result and/or determining initial antimicrobial therapy. Standard microbiological protocols that rely on biochemical identification of microorganisms plus phenotypic antimicrobial susceptibility testing follow, and may take an additional 48–72 h, assuming that the results obtained are easily interpreted. It may take days longer to generate final results for organisms that are difficult to identify biochemically or grow slowly in vitro. Given the usual delay of 3–5 days from the collection of blood cultures to the time at which final identification and susceptibility results are obtained, there has been keen interest in reducing this interval by employing a variety of rapid methods. In some cases, the time to delivery of results may be reduced by employing traditional microbiological protocols earlier in the work-up. For example, the coagulase test, which is traditionally used to distinguish CoNS isolates from coagulase-positive isolates, may be performed directly on signal-positive blood culture broths that show Gram-positive cocci in clusters on Gram staining . This approach allows rapid distinction between CoNS and coagulase-positive staphylococci (which are mostly S. aureus), and may influence the ability of clinicians to interpret the clinical significance of a positive blood culture result and their ability to begin appropriate antimicrobial therapy. Obviously, this is not a complete solution, as it does not definitively identify the organism and nor does it provide susceptibility information. To augment such an approach, some laboratories may couple direct coagulase testing with the use of chromogenic agar medium, which allows identification of methicillin-resistant S. aureus isolates within 18–24 h . Clearly, this solution represents an improvement over traditional methods, but applies only to one specific organism and gives susceptibility results for only one drug. More robust approaches to improving the turn-around time for the laboratory diagnosis of BSIs have focused largely on newer or novel technology. Molecular methods, including nucleic acid amplification assays (NAATs), DNA sequencing approaches, DNA microarrays, and probe hybridization, have emerged as useful tools for microorganism identification, and, in some cases, the prediction of

antimicrobial susceptibility for select antibiotics . Novel phenotypic approaches have also been shown to reduce turn-around time for the identification and limited susceptibility testing of select organisms. Finally, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, which has already demonstrated widespread utility in the routine identification of microorganisms in the clinical microbiology laboratory, appears to be a very promising approach to the rapid identification of organisms directly from signal-positive blood culture broths . The major drawback of this approach, like most of the others, is the lack of rapid susceptibility information to accompany the organism identity. It is not yet clear when or if this capability will be possible with matrix-assisted laser desorption ionization time-of-flight mass spectrometry or other rapid methods, and the actual clinical utility of microorganism identification in the absence of susceptibility information is narrow and unproven.

Rapid Methods for Detection of Microorganisms Directly in Blood Specimens

Although technological improvements have led to reductions in the time required for identification and (in limited cases) susceptibility testing of isolates from signal-positive blood cultures, a further improvement would obviously be the ability to rapidly and directly detect and identify microorganisms in blood samples from patients with a suspected BSI. Currently available solutions involve the use of NAATs that are designed to detect specific microorganisms in blood samples [68]. Controlled trials evaluating the performance of such solutions as compared with standard blood cultures have demonstrated reasonably good performance, with the obvious limitation that NAATs will only detect a subset of possible BSI pathogens, and provide no susceptibility information . As conventional phenotypic susceptibility testing requires isolated organisms, if the direct NAAT is positive and the corresponding culture is negative, susceptibility information may never be available. Thus, at the present time, such an approach may serve only as an adjunct to standard of care protocols. As is the case for rapid methods for blood culture isolate identification, the actual clinical impact of rapid methods for direct pathogen detection in blood specimens has not been extensively studied.

Conclusions

Technological advances have resulted in the ability to more rapidly identify and, in some cases, predict the susceptibility of the aetiological agents of BSIs to a limited extent. Although these methods hold great promise for the future, conventional blood culture methods remain the dominant approach to diagnosing most patients with BSIs. Therefore, the traditional principles of patient selection, adequate and careful specimen collection, appropriate cultivation and accurate result interpretation remain critical to the delivery of the most effective care for our patients with suspected BSIs.

BOUQUET

Brain Teasers

1. **What constitutes extractable nuclear antigens (ENA).**
   A. Sm, RNP
   B. SS-A, SS-B
   C. Scl-70 and Jo-1
   D. All of the above.

2. **Hepatitis D coexists with.**
   A. Hepatitis A
   B. Hepatitis B
   C. Hepatitis C
   D. Hepatitis E.

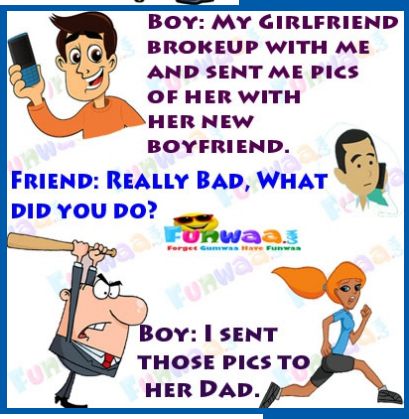
3. **In hepatitis B infection, which is the first detectable viral marker?**
   A. HbsAg
   B. HbeAg
   C. HBV DNA
   D. None of the above.

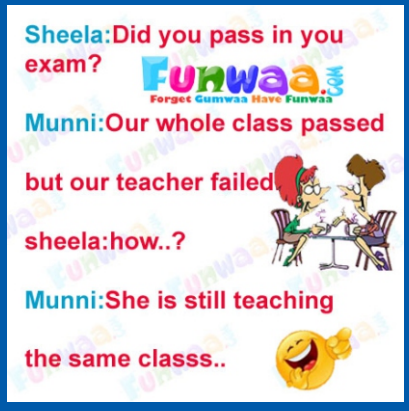
4. **In relation to hepatitis B, the presence of indicates recovery and immunity in a previously infected individual.**
   A. Anti-HbsAb
   B. Anti-HbcAb
   C. Both of the above
   D. None of the above.

ANSWER: 1. D, 2. B, 3. A, 4. C

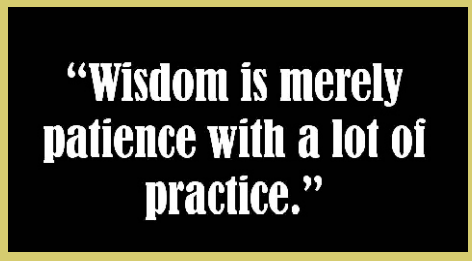
BOUQUET

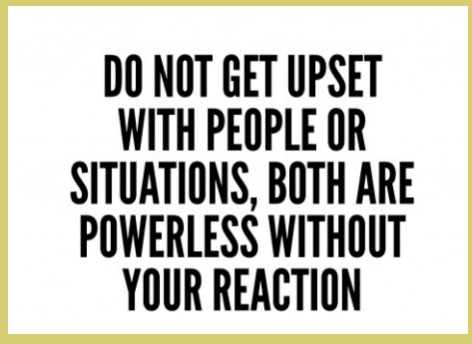
In Lighter Vein

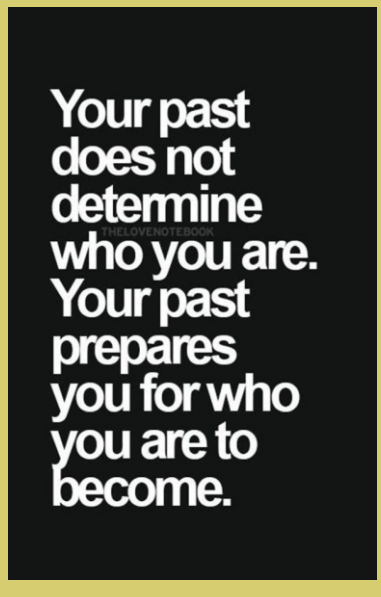


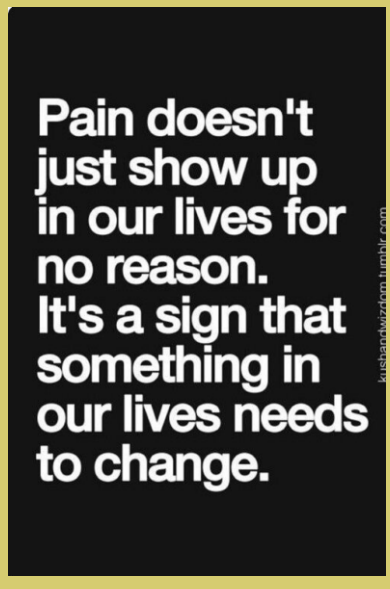


Wisdom Whispers









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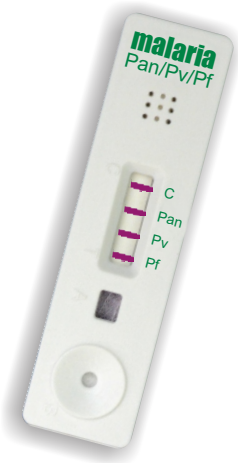

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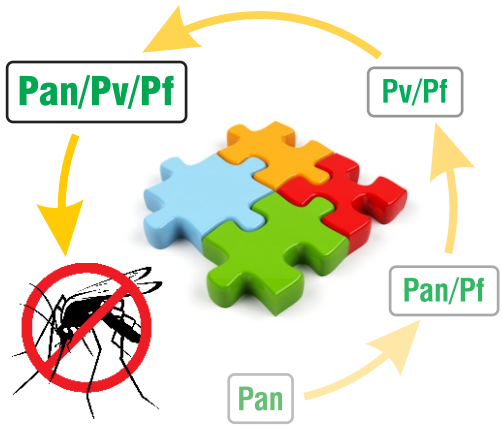

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Fax: (0832) 2458544. E-mail: sales@tulipgroup.com Website: www.tulipgroup.com