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**Disclaimer**
Findings are generally non-specific and secondary to primary infection. They include malaise, leukocytosis, tachypnoea, and pulse >90 bpm.

Sepsis can progress rapidly to multi-organ failure and shock, and is often fatal. Survival is dependent on a high index of suspicion of sepsis, early recognition and immediate intervention.

Patients with evidence of sepsis, including signs of organ dysfunction, require immediate hospital assessment.

Empirical broad-spectrum antibiotic therapy (based on the most probable pathogens) should be administered as soon as possible, and always within the first hour following recognition.

Blood cultures, as well as cultures of all wounds or other potentially infected body fluids, should be performed as indicated by symptoms and the risk profile of the patient, ideally before the initiation of antimicrobial treatment.

Any source of infection should be controlled as a matter of urgency, preferably within 6 hours following recognition.

Evidence of hypoperfusion or shock should be identified and treated with immediate intravenous fluid challenges, if present. Shock that fails to respond to fluid challenges necessitates urgent critical care referral for consideration of vasopressors and/or inotropes.
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection.[1] The definition of sepsis was updated in 2016 following publication of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1]

The 2016 consensus definitions also recommend that the Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) criteria and ‘quick’ (q)SOFA criteria be used to identify sepsis, in place of the currently used systemic inflammatory response syndrome (SIRS) criteria, which were the basis for the previous definition of sepsis.[1] [2] SOFA is an ICU-based mortality score and qSOFA is a rapid, shortened version of SOFA designed for use outside the ICU. The SOFA scores are not in themselves clinical predictors of sepsis, and they rely on clinical suspicion for the scores to be assessed. Furthermore, qSOFA has not been prospectively validated, and its place in clinical practice has not been fully established. Although the SIRS criteria are no longer recommended and have limitations, they are well established after many years of use.[3] At present it is unclear which clinical score will best guide sepsis care; therefore, the SIRS criteria remain the current standard for identifying sepsis and are likely to remain relevant in medical care, at least in the short term.

SIRS is a multi-system response that can result from infection (localised or general), as well as from non-infectious causes (e.g., trauma, burns, or pancreatitis).[4] [5] [6] [7] [8] It is defined by the presence of 2 or more criteria from the following: temperature >38.3°C (101°F) or <36.0°C (96.8°F); tachycardia >90 bpm; tachypnoea >20 breaths/minute or PaCO2 <4.3 kPa (32 mmHg); hyperglycaemia (blood glucose >7.7 mmol/L [>140 mg/dL]) in the absence of diabetes mellitus; acutely altered mental status; leukocytosis (WBC count >12×10^9/L [12,000/microlitre]); leukopenia (WBC count <4×10^9/L [4000/microlitre]); or a normal WBC count with >10% immature forms.[5] [Surviving Sepsis Campaign: evaluation for severe sepsis screening tool]

When using the SIRS criteria, sepsis is the presence of SIRS (i.e., 2 or more SIRS criteria) resulting specifically from an infection.

In the first international consensus definitions, which date from 1991, severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension; septic shock was defined as sepsis with hypotension despite adequate fluid replacement.[5] These definitions remain clinically established in many clinical settings.

However, the 2016 third international consensus (Sepsis-3) definitions state that the term ‘severe sepsis’ should be made redundant in light of the revisions to the definition of sepsis.[1] Septic shock has also been redefined as a subset of sepsis, in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.[1]

In 2016, the National Institute for Health and Care Excellence (NICE) published guidance on the recognition, diagnosis, and early management of sepsis, which highlighted that the Sepsis-3 international consensus definitions of sepsis have limited use in the early identification of people at risk of sepsis.[9] The NICE guidelines propose a move away from using the SIRS criteria, and do not immediately support the use of the SOFA/qSOFA criteria. Instead NICE proposes a risk stratification approach to categorise patients into 3 groups according to their risk of severe illness or death from sepsis: high risk; moderate to high risk; or low risk. The risk stratification is based on the patient’s: history (e.g., altered mental state; urine output; impaired immunity; or recent trauma, surgery, or invasive procedure), appearance (e.g., signs of potential infection; mottled or ashen appearance; cyanosis of skin, lips, or tongue; or non-blanching rash of skin), and clinical
Sepsis in adults

**Basics**

Evaluation (e.g., temperature, heart rate, respiratory rate, blood pressure, level of consciousness, and oxygen saturation).

**Epidemiology**

Sepsis is estimated to affect 31.5 million people worldwide every year, with an estimated 5.3 million deaths annually.[11] The population-based incidence of sepsis is estimated to be as high as 176 to 380 cases per 100,000 per year. [12] [13] [14] [15] The annual incidence of sepsis in the EU has been estimated at 90.4 cases per 100,000 population.[16] However, incidence rates depend on the definition of sepsis, with rates in Canada cited as 15.7 cases per 100,000 population per year requiring admission to ICU.[17]

The incidence of sepsis is likely to be rising. In England, data from the Hospital Episode Statistics (HES) released by the Health and Social Care Information Centre (HSCIC) in 2015 shows there were nearly 123,000 cases of sepsis with 36,800 associated deaths recorded in 2013/14,[18] up from around 25,100 in 2010.[19]

Most epidemiological studies find sepsis to be more common in men than in women. Patients older than 65 years of age are particularly susceptible, with one study finding almost two-thirds of cases to be in people over 65.[20]

**Aetiology**

Causative agents vary significantly depending on the region, hospital size, season, and type of unit (neonatal, transplantation, oncology, or haemodialysis units).[21] [22] [23] [24] [25] [26] [27] [28] [29] [30]

It should be noted that pathogenic organisms are identified in only around half of cases of sepsis.[31] Where organisms are identified, bacteria (gram-positive and gram-negative) are identified as the causative organism in approximately 90% of cases, with gram-positive bacteria and fungal infections increasing in frequency.[32] Since the mid-1980s, the frequency of gram-positive sepsis (mainly caused by *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and streptococci) has surpassed that of gram-negative sepsis (mainly caused by Enterobacteriaceae, especially *Escherichia coli* and *Klebsiella pneumoniae*, and by *Pseudomonas aeruginosa*). However, *E coli* remains the most prevalent pathogen causing sepsis.[4] [17] [21] [33] [34] Some experts believe that the host response to some viral infections so closely mimics sepsis that it should be considered as such.

In the majority of cases of sepsis arising in the community, the causative organisms will be sensitive, frequently endogenous bacteria. In the UK, a report of the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) study in sepsis published in November 2015 highlighted that nearly 75% of cases of sepsis arose as a result of community-acquired infection.[31] However, it should be acknowledged that resistance patterns of organisms continue to change and can differ greatly according to region. For example, in one large multi-centre European study, >50% of isolates in ICU were methicillin-resistant *S aureus* (MRSA).[35] Over the last two decades, vancomycin-resistant enterococci (VREs) have emerged, with >10% of enterococci being VREs.[36] Just as concerning is the significant number of *E coli* isolates that are now resistant to amoxicillin/clavulanic acid (around 40%).[37] MRSA is increasingly prevalent in the community, with community-acquired MRSA presenting as a severe pneumonia, often with cavitation, in patients with a recent coryzal illness. In the UK, sepsis is the most common direct cause of maternal death, ahead of venous thromboembolism.[38] Following pregnancy (in the 6-week postnatal period), group A streptococci are the most common causative agent.[39]
Sepsis in adults

Basics

Studies tend to broadly concur on the relative frequencies of sources of infection. [10] [35] In the SOAP study, the respiratory tract accounted for 60%; the bloodstream 20%; abdomen 26%; skin 14%; and urinary system 12%. [35] The Surviving Sepsis Campaign observational study of over 15,000 patients showed slightly fewer patients with respiratory sources (44.4%) and a greater frequency of urosepsis (20.8%). [10] However, in 20% to 30% of patients, a definite source of infection is not found. [20]

The leading fungal pathogen causing sepsis has been identified as Candida. [21] In a European point-prevalence study, fungi were isolated from 17% of ICU patients with nosocomial infection. [40] Fungi are more prevalent as isolates in patients with secondary or tertiary peritonitis, with Candida identified in up to 20% of patients with GI tract perforation. [41] Risk factors include faecal soiling of the peritoneum, recurrent GI perforation, immunosuppressive therapy for neoplasm or in post-transplant patients, and the presence of inflammatory diseases. These patients carry a high risk of mortality. [42]

Pathophysiology

Sepsis is a syndrome comprising an immune system-mediated collection of physiological responses to an infectious agent. Clinical signs such as fever, tachycardia, and hypotension are common but the clinical course depends on the type and resistance profile of infectious organism, the site and size of the infecting insult, and the genetically determined or acquired properties of the host’s immune system.

Immune-system activation:

- Pathogen entry and survival is facilitated by tissue contamination (surgery or infection), foreign body insertion (catheters), and immune status (immunosuppression). [43]
- The innate immune system is activated by bacterial cell wall products, such as lipopolysaccharide, binding to host receptors, including Toll-like receptors (TLRs). [44] [45] These are widely found on leukocytes and macrophages, and some types are found on endothelial cells. [46] At least 10 TLRs have been described in humans. These have specificity for different bacterial, fungal, or viral products, and genetic polymorphisms are associated with a predisposition to shock with gram-negative organisms. [47]
- Activation of the innate immune system results in a complex series of cellular and humoral responses, each with amplification steps: [7]
  - Pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha and interleukins 1 and 6 are released, which in turn activate immune cells.
  - Reactive oxygen species, nitric oxide (NO), proteases, and pore-forming molecules are released, which bring about bacterial killing. NO is responsible for vasodilatation and increased capillary permeability, and has been implicated in sepsis-induced mitochondrial dysfunction. [48]
  - The complement system is activated, and mediates activation of leukocytes, attracting them to the site of infection where they can directly attack the organism (phagocytes, cytotoxic T lymphocytes), identify it for attack by others (antigen presenting cells, B lymphocytes), ‘remember’ it in case of future infection (memory cells, B lymphocytes), and cause the increased production and chemotaxis of more T helper cells. [49]

The endothelium and coagulation system:

- The vascular endothelium plays a major role in the host’s defence to an invading organism, but also in the development of sepsis. Activated endothelium not only allows the adhesion and migration of
Sepsis in adults

Basics

• Stimulated immune cells, but becomes porous to large molecules such as proteins, resulting in the tissue oedema.

• Alterations in the coagulation systems include an increase in procoagulant factors, such as plasminogen activator inhibitor type I and tissue factor, and reduced circulating levels of natural anticoagulants, including antithrombin III and activated protein C (APC), which also carry anti-inflammatory and modulatory roles.[50] [51]

Inflammation and organ dysfunction:

• Through vasodilatation (causing reduced systemic vascular resistance) and increased capillary permeability (causing extravasation of plasma), sepsis results in relative and absolute reductions in circulating volume.

• A number of factors combine to produce multiple organ dysfunctions. Relative and absolute hypovolaemia are compounded by reduced left ventricular contractility to produce hypotension. Initially, through an increased heart rate, cardiac output increases to compensate and maintain perfusion pressures, but as this compensatory mechanism becomes exhausted, hypoperfusion, and shock may result.

• Impaired tissue oxygen delivery is exacerbated by pericapillary oedema. This means that oxygen has to diffuse a greater distance to reach target cells. There is a reduction of capillary diameter due to mural oedema and the pro-coagulant state results in capillary microthrombus formation.

• Additional contributing factors include disordered blood flow through capillary beds, resulting from a combination of shunting of blood through collateral channels and an increase in blood viscosity secondary to loss of red cell flexibility.[52] As a result, organs may become hypoxic, even though gross blood flow to an organ may increase. These abnormalities may lead to lactic acidosis, cellular dysfunction, and multi-organ failure.[53]

• Cellular energy levels fall as metabolic activity begins to exceed production. However, cell death appears to be uncommon in sepsis, implying that cells shut down as part of the systemic response. This could explain why relatively few histological changes are found at autopsy, and the eventual rapid resolution of severe symptoms, such as complete anuria and hypotension, once the systemic inflammation resolves.[54]

Classification

Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (2016)[1]

• Sepsis has been redefined as life-threatening organ dysfunction caused by a dysregulated host response to an infection.

• Owing to revisions to the definition of sepsis, the term 'severe sepsis' (as previously defined in the 1991/2001 international consensus definitions) should be made redundant.

• Septic shock has also been re-defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Septic shock can be defined clinically as a patient diagnosed with sepsis, with persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP)≥ 65 mmHg, and a lactate level> 2 mmol/L (>18 mg/dL), despite adequate fluid resuscitation.
First International Consensus Definitions for Sepsis and Septic Shock (1991)[5] [8] [10]

- In the 1991 definitions (which were reviewed in 2001) sepsis is defined as a systemic inflammatory response to a new infection, and severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.
- Sepsis with hypoperfusion is defined by the presence of acute circulatory failure, characterised by arterial hypotension (systolic BP <90 mmHg, reduced by >40 mmHg from baseline or mean arterial pressure [MAP] of <65 mmHg), or other evidence of hypoperfusion, such as serum lactate >2 mmol/L (>18 mg/dL).
- Septic shock is defined as being present when hypoperfusion persists for at least 1 hour despite adequate fluid resuscitation and is unexplained by other causes. However, hypoperfusion is in itself a clinical emergency and should be corrected as soon as is practicable. The distinction between hypoperfusion and shock in this context is theoretical; in reality the urgency is identical.

Although the 1991 definitions have been superseded by the 2016 Sepsis-3 definitions, these changes have prompted much debate and the 1991 definitions remain in widespread clinical use while the controversies are resolved.

Sepsis: recognition, diagnosis and early management (National Institute for Health and Care Excellence, 2016)[9]

In 2016, the UK National Institute for Health and Care Excellence (NICE) published guidelines on sepsis recommending that patients with suspected sepsis should be stratified according to risk of severe illness or death from sepsis (i.e., low risk, moderate to high risk, and high risk).
Case history

Case history #1

A 78-year-old woman presents to hospital for an elective right haemicolectomy. She has a past medical history of hypertension, angina on exertion, and diabetes mellitus. She is independently mobile, does her own shopping, and has a 30-pack-a-year history of smoking. The operation was uncomplicated. On day 5 post-surgery, she becomes confused. On examination, she has a Glasgow Coma Scale score of 14/15. She has a temperature of 38.5°C (101.3°F), a respiratory rate of 28 breaths/minute, and oxygen saturations of 92% on 2 L of oxygen. She is tachycardic at 118 bpm, and her BP is 110/65 mmHg. On chest auscultation, she has coarse crackles in the right lower zone. Her surgical wound appears to be healing well and her abdomen is soft and not tender.

Other presentations

Sepsis may complicate benign primary infections found in any age group and requires a high suspicion for the clinical signs of systemic inflammatory response (tachycardia, fever, tachypnoea, or respiratory compromise).

Altered mental status may also be a presenting feature, especially in older patients. Mild disorientation or confusion is common with more severe presentations, including significant anxiety, agitation, and loss of consciousness.

Other features that may be present include reduced urine output; a mottled or ashen appearance; cyanosis of skin, lips, or tongue; or presence of a non-blanching rash on the skin.[9]

Step-by-step diagnostic approach

Sepsis is a spectrum of disease, where there is a systemic and dysregulated host response to an infection.[1] Presentation may range from non-specific or non-localised symptoms (e.g., feeling unwell with a normal temperature), to severe signs with evidence of multi-organ dysfunction and septic shock. Risk of progression to fulminant disease is determined by various factors, including:

- Magnitude and nature of the infective focus
- Timing and quality of interventions
- Genetic and acquired predisposition of the patient.

Early recognition and diagnosis is essential because early treatment is associated with significant short- and long-term benefits in outcome.[58] [59] [60] [61] [62] [9]

Diagnostic criteria

There is ongoing debate about the most appropriate criteria for diagnosing sepsis in clinical practice, with several different approaches suggested. These include use of the systemic inflammatory response syndrome (SIRS) criteria in the presence of infection; the Sequential (or sepsis-related) Organ Failure Assessment (SOFA) score recommended by the Sepsis-3 international consensus group; and use of a risk stratification system as recommended by guideline groups in the US and UK.
In practice, sepsis is usually diagnosed by the clinical identification of an infection in a patient who meets the clinical criteria for SIRS. According to the international consensus definition published in 1991 (and reviewed in 2001), SIRS is defined by the presence of two or more criteria from a collection of clinical signs and laboratory investigations as follows. (Hyperglycaemia and acutely altered mental status are not part of the original criteria for SIRS, but have since been included by the Surviving Sepsis Campaign in their screening tool.)[5] [Surviving Sepsis Campaign: evaluation for severe sepsis screening tool]

- Temperature > 38.3°C (101°F) or < 36.0°C (96.8°F)
- Tachycardia > 90 bpm
- Tachypnoea > 20 breaths/minute or PaCO2 < 4.3 kPa (32 mmHg)
- Leukocytosis (WBC count > 12x10^9/L [12,000/microlitre])
- Leukopenia (WBC count < 4x10^9/L [4000/microlitre])
- Normal WBC count with > 10% immature forms.
- Hyperglycaemia (blood glucose > 7.7 mmol/L (>140 mg/dL)) in the absence of diabetes mellitus
- Acutely altered mental status.

In 2016, the definition of sepsis was updated by the Third International Consensus Group (Sepsis-3) to reflect greater understanding of the disease. This step was taken because the SIRS criteria were found to be too non-specific to be useful in defining sepsis: they defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to an infection. Rather than using the SIRS criteria to identify these patients (upon which the previous definition was based), the Sepsis-3 advised that sepsis should be defined using the SOFA criteria.[1] The SOFA score is calculated based on the assessment of the following systems (with a score of ≥2 in a patient with a suspected infection being suggestive of sepsis):[1]
As the SOFA score has primarily been validated on patients in an ICU setting and requires multiple laboratory test results, the Third International Consensus Group suggested the use of the 'quick SOFA' (qSOFA) as a bedside assessment to identify those at risk of deterioration due to sepsis. This is a simple clinical assessment that assesses for the presence of at least 2 of the following:[1]

- Altered mental state
- Systolic blood pressure ≤100 mmHg
- Respiratory rate ≥22 breaths/minute.

However, since the introduction of qSOFA, a large study in the US found that it had poor sensitivity (particularly when compared with other bedside early warning scores and the SIRS criteria) and was a late indicator of deterioration.[63]

Further studies will be needed to determine the optimal screening methods for early recognition of sepsis.

The 2016 Sepsis-3 definitions also recommend that the term 'severe sepsis', as previously defined, should be made redundant in light of revisions to the definition of sepsis.[1] Septic shock has also been redefined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.[1] According to the 2016 international consensus definition, septic shock should be defined as sepsis with both of the following (despite adequate volume resuscitation):[1]

- Persistent hypotension requiring vaspressors to maintain mean MAP ≥65 mmHg,
- Serum lactate > 2 mmol/L (>18 mg/dL).

Patients with septic shock (as defined by the Sepsis-3) are associated with hospital mortality rates greater than 40%. [1]

In 2016, the National Institute for Health and Care Excellence (NICE) published guidelines which focus on the early recognition and identification of sepsis.[9] In a move away from the SIRS and SOFA criteria recommended by the international consensus definitions, the NICE guidelines recommend a risk stratification approach to identify early those patients at highest risk. The approach involves categorising a patient as being at low risk, moderate to high risk, or high risk of severe illness or death from sepsis, based on the following criteria:

- History (altered behaviour; altered mental state; functional ability; impaired immunity; or recent trauma, surgery, or invasive procedure)
- Respiratory (respiratory rate; new need for oxygen to maintain saturation)
- Systolic blood pressure
- Circulation and hydration (raised heart rate; urine output)
- Skin (signs of infection; mottled or ashen appearance; cyanosis of skin, lips, or tongue; non-blanching rash of skin).

This focus on early identification of patients at risk of sepsis is shared with the American College of Emergency Physicians (ACEP) Expert Panel on Sepsis in their tool DART (Detect, Act, Reassess, Titrate).[64] The NICE guidelines also provide further recommendations for in-hospital clinical assessment and laboratory investigations (e.g., venous blood test for blood gas, including glucose and lactate.
measurement; blood culture; FBC; CRP; urea and serum electrolytes; creatinine; and coagulation) in patients with suspected sepsis based on their risk profile and symptoms.\[9\]

There are multiple scoring systems and definitions for sepsis and sepsis with organ dysfunction. None is perfect and many seek to measure similar variables. Furthermore, the NICE sepsis guidelines published in the UK have highlighted a limitation of the international consensus definitions in that they are unproven in the early identification of people at risk of sepsis.\[9\] At present, SIRS and the earlier international consensus definitions of sepsis, severe sepsis, and septic shock remain clinically established in most clinical settings.

**Initial evaluation**

Sepsis may present initially with non-specific, non-localised symptoms, such as feeling unwell with normal temperature. Sepsis should be considered if a patient presents with signs or symptoms that indicate possible infection, regardless of temperature.\[9\] This is because, although fever is frequently associated with sepsis, hypothermia is a common presenting sign and carries a worse prognosis.\[65\] Initial assessment includes identifying the likely source of infection, identifying risk factors for sepsis, determining the need for urgent source control (e.g., incision and drainage of an abscess), and identifying abnormalities of behaviour, circulation, or respiration.

As for all acutely ill patients, initial evaluation should follow the ABCDE format, to include assessment of the airway, respiratory, and circulatory sufficiency, and conscious level (Glasgow Coma Scale or AVPU [Alert, responds to Voice, responds to Pain, Unresponsive]). Attention should be paid to seeking other signs of organ dysfunction (jaundice, purpura fulminans, cyanosis), and signs of circulatory insufficiency including oliguria, mottling of the skin, and prolonged capillary refill times. Oxygen saturation, respiratory rate, heart rate, BP, temperature, and accurate hourly fluid balance (including urine output) should be monitored. It is important to seek clinical evidence for the source of infection. This will aid diagnosis and provide vital information as to the patient’s risk factors for sepsis. Risk factors strongly associated with sepsis include: underlying malignancy, impaired immunity (e.g., due to illness or drugs), recent surgery or other invasive procedures, breached skin integrity (e.g., wounds, skin infection), indwelling catheter, intravenous drug misuse, age >65 years or frailness, pregnancy or recent pregnancy, haemodialysis, hx of alcoholism, immunocompromise, and diabetes mellitus.

**Investigations**

Initial investigations cover 4 purposes:

- To identify causative organisms
- To evaluate for organ dysfunction
- To identify the source of infection
- To prognosticate, to aid in the selection of an appropriate level of care.
Priority should be given to those investigations that will help to answer important clinical questions, such as the source of infection and severity of illness. Cultures of blood and other fluids will take 48 to 72 hours to yield sensitivities of causative organisms (if identified), but are far less sensitive if delayed until after antimicrobial administration.

Investigations to identify causative organisms:

- Blood cultures should be taken immediately, and preferably before antibiotics are started, provided their sampling will not delay administration of antibiotics. Ideally, at least one set should be taken percutaneously, and one set from any vascular access device that has been in situ for more than 24 hours.[66] [67] Other cultures (e.g., sputum, cerebrospinal fluid (CSF), pleural fluid, joint fluid, stool, and urine) should be taken as clinically indicated.
- If no localising signs are present, examination and culture of all potential sites of infection including wounds, catheters, prosthetic implants, epidural sites, and pleural or peritoneal fluid, as indicated by the clinical presentation and history, is required.
- If meningitis is suspected (e.g., headache, photophobia, neck stiffness, vomiting), a lumbar puncture (LP) for CSF microscopy and culture should be performed. A CT scan prior to performing an LP to exclude raised intracranial pressure is required if there is any clinical suspicion of this.

[VIDEO: Diagnostic lumbar puncture in adults: animated demonstration ]

- If an enclosed collection such as an abscess or empyema is suspected, it is recommended that this be drained and cultured early in the course of the illness (within 6 hours following identification).[74]
- Intubated patients in whom there is a suspicion of pneumonia should have tracheal aspirates, broncho-alveolar lavage, or protected brush specimens taken.

Evaluation for organ dysfunction:

- Baseline assessment of liver function tests (notably bilirubin), an FBC (with differential), coagulation (INR, PTT), serum creatinine, and blood urea.
- Serum electrolytes and glucose are frequently deranged, and should be measured at baseline and regularly until the patient improves.
- Elevated serum lactate highlights tissue hypoperfusion, and is most reliably assessed using an arterial blood gas (ABG) sample.[75] However, in practice, a venous blood gas (VBG) sample is generally used, as it is generally easier and quicker to obtain compared with ABG. Most patients do not undergo ABG sampling unless there is respiratory compromise.
- Markers of inflammation, including CRP and procalcitonin, are of use in determining clinical progress and response to therapy. Serial measures of procalcitonin can be useful as a guide to the need to continue or stop empiric antibiotics.[76] However, evidence for the prognostic value of procalcitonin is unclear,[77] and the use of procalcitonin in the identification of sepsis is excluded from many guidelines.

Investigations to identify the source of the infection:

- The source of infection may be immediately evident; for example, with classical signs and symptoms of pneumonia (purulent sputum, dyspnoea, tachypnoea, cyanosis) or peritonism (abdominal pain, guarding, distension, tenderness, absent bowel sounds). However, in many patients the origin must be actively sought.
Sepsis in adults

Diagnosis

- Diagnostic studies may identify a source of infection that requires removal of a foreign body or drainage to maximise the likelihood of a satisfactory response to therapy. Chest x-rays and ultrasound scans can be performed at the bedside. Examinations such as CT scanning require transfer of potentially unstable patients and the benefit should be weighed against the risk.
- In patients at risk of, or with symptoms compatible with, bacterial endocarditis, a transthoracic or transoesophageal echocardiogram is useful. This is also helpful to differentiate between hypovolaemic, cardiac, and septic shock, as well as alternative diagnoses such as valvular abnormalities, pulmonary embolus, myocardial ischaemia (with segmental or global dysfunction), hypovolaemia, and pulmonary hypertension. If readily available, an echocardiogram may also be appropriate in patients with sepsis of unknown origin.
- An ECG should be arranged to help exclude other differential diagnoses, including MI, pericarditis, and myocarditis. Sepsis also predisposes to myocardial dysfunction (particularly in septic shock)[78] and arrhythmias (e.g., atrial fibrillation).[9]

Certain investigations carry prognostic value and can help determine the need for critical care:

- Lactate measurement is a useful assessment of perfusion once a diagnosis of sepsis has been established. Increasing levels of lactate are associated with increasing levels of anaerobic metabolism. Persistently elevated lactate levels may parallel the degree of hypoperfusion or organ failure. High lactate carries adverse prognostic value if elevated to >2 mmol/L (>18 mg/dL), and still worse outcomes are associated with levels >4 mmol/L (>36 mg/dL).[9] Lactate clearance (the rate at which lactate is cleared over a period of 6 hours) has been demonstrated to be as useful as more invasive tests, such as central venous oxygen saturation, in determining a patient’s response to treatment.[79] [80]
- Studies with trauma patients have evaluated lactate levels against Acute Physiology and Chronic Health Evaluation (APACHE) scores and lactate clearance rates and found lactate levels to be inferior in informing the prognosis. However, an APACHE score takes 24 hours to calculate.[81]
- An alternative measure is serum procalcitonin levels. However, evidence for the prognostic value of procalcitonin is unclear.[82] and the use of procalcitonin in the identification of sepsis is excluded from many guidelines. Changes in procalcitonin levels may occur later than that of lactate, although changes in both markers combined are highly predictive of outcome between 24 and 48 hours.[83]
  It may, therefore, have greater utility in permitting early cessation of antimicrobial therapy.[77] [84]
- Some experts recommend the use of shock index (heart rate divided by systolic BP) as a predictor of requirement for critical care, with one group finding an index >0.9 to be predictive.[85]
- More recently, non-invasive impedance echocardiography has been shown, if a cardiac index of <2 is identified, to predict poor outcome.[86]

Patients suffering from septic shock who have not responded to initial fluid resuscitation will require invasive monitoring and treatment in high dependency units.

Emerging tests

The PhenoTest™ BC Kit can identify 14 species of bacteria and 2 species of yeast that commonly cause bloodstream infections, while also providing guidance on antibiotic sensitivity. The test compares the organism’s DNA to a database, and then uses time-lapse images to analyse the organism’s response to antibiotics. It can identify a positive blood culture in 1.5 hours and guide antibiotic treatment in 6.5 hours. However, the test has been associated with false positive results.[87]
A number of other rapid detection methods for early pathogen detection and antimicrobial susceptibility testing are in clinical testing at present. Such assays could be of significant value in the personalised care of septic patients in the near future.

## Risk factors

### Strong

**underlying malignancy**

- Incidence rates of sepsis are up to 995 cases per 100,000 per year in patients with malignancy. Immunosuppression (including both the severity and duration of neutropenia where present), recurrent infections, invasive catheterisations, and treatment of resistant organisms contribute to the increased risk (odds ratio [OR] 9.77, 95% confidence interval [CI] 9.67 to 9.88).[34]

**age >65 years**

- Associated with an increased risk of sepsis (relative risk [RR] 7.0, 95% CI 5.6 to 8.7).[17]
- Risk of sepsis is particularly high in people aged >75 years or those who are frail.[9]

**immunocompromise**

- Associated with an increased risk of sepsis.
- Immunocompromise may arise from treatment (e.g., chemotherapy, corticosteroids, or other immunosuppressants), underlying disease (e.g., diabetes, sickle cell), or surgery (e.g., splenectomy).[9] [55]

**haemodialysis**

- Associated with an increased risk of sepsis (RR 208.7, 95% CI 142.9 to 296.3).[17]

**alcoholism**

- Associated with an increased risk of sepsis (RR 5.6, 95% CI 3.8 to 8.0).[17]

**diabetes mellitus**

- Decreased resistance to infections, complications of diabetes, and increased surgical complications play a role (RR 5.9, 95% CI 4.4 to 7.8).[17]

**recent surgery or other invasive procedures**

- Risk of sepsis is high in people who have had surgery or other invasive procedures in the past 6 weeks.[9]
- Risk of sepsis is particularly high following oesophageal, pancreatic, or elective gastric surgery.[56]

**breached skin integrity**

- Risk of sepsis is high in people with any breach of skin integrity (e.g., cuts, burns, blisters, or skin infection).[9]

**indwelling lines or catheters**

- Risk of sepsis is high in people with indwelling lines or catheters.[9]
Sepsis in adults

**Diagnosis**

**intravenous drug misuse**
- Risk of sepsis is high in people who misuse drugs intravenously.[9]

**pregnancy**
- Pregnancy or recent pregnancy is a risk factor for the development of sepsis.[9] In the UK, the estimated incidence of sepsis in pregnancy has been reported to be 47 cases per 100,000 maternities per year,[57] whereas the estimated annual incidence among people aged 18 to 19 years in a general population has been reported to be around 29.6 cases per 100,000.[20]
- Risk of sepsis among women may be higher if they have impaired immunity, gestational diabetes, diabetes (or other comorbid condition), needed invasive procedures during pregnancy (e.g., caesarean section, forceps delivery, removal of retained products of conception), had prolonged rupture of membranes during pregnancy, have or have been in close contact with people with group A streptococcal infection (e.g., scarlet fever), or have continued vaginal bleeding or an abnormal vaginal discharge with odour.[9]

**Weak**

**urban residence**
- May predispose to increased exposure to infections and drug-resistant pathogens (RR 2.4, 95% CI 1.2 to 5.6).[17]

**lung disease**
- Weakly associated with sepsis (RR 3.8, 95% CI 2.6 to 5.4).[17]

**male sex**
- May be at greater risk (OR 1.28, 95% CI 1.24 to 1.32).[12]

**non-white ancestry**
- May be at increased risk (OR 1.90, 95% CI 1.80 to 2.00).[12]

**winter season**
- Seasonal infections (e.g., respiratory infections in winter) are weakly associated with sepsis.
- Sepsis is 1.4 times more likely to occur in the winter than in the autumn.[27]

**History & examination factors**

**Key diagnostic factors**

**presence of risk factors (common)**
- Key risk factors include: underlying malignancy, age older than 65 years, immunocompromise, haemodialysis, alcoholism, and diabetes mellitus.

**high (>38°C) or low (<36°C) temperature (common)**
- Temperature should not be used as the sole predictor of sepsis and should not be used to rule sepsis either in or out.
Sepsis in adults

**Diagnosis**

- Fever may not be apparent in the following groups of people with sepsis: older people or those who are very frail, people undergoing treatment for cancer, immunocompromised people, and severely ill people with sepsis.
- Temperature rise can result from a physiological response (e.g., after surgery or trauma).

**tachycardia (common)**
- Heart rate >90 bpm (>100 bpm in pregnant women).

**tachypnoea (common)**
- Respiratory rate >20 breaths/minute.

**acutely altered mental status (common)**
- Due to impaired cerebral perfusion and inflammatory cytokines.

**poor capillary refill, mottling of the skin, or ashen appearance (common)**
- Signs of circulatory insufficiency.

**signs associated with specific source of infection (common)**
- The source of infection may be immediately evident; for example, with classical signs and symptoms of pneumonia (purulent sputum, dyspnoea, tachypnoea, cyanosis) or peritonism (abdominal pain, guarding, distension, tenderness, absent bowel sounds). However, in many patients the origin must be actively sought.

**low oxygen saturation (common)**
- Sign of circulatory insufficiency.

**arterial hypotension (common)**
- Systolic BP <90 mmHg, mean arterial pressure (MAP) <65 mmHg, or reduction in systolic BP >40 mmHg from baseline.
- May be present when sepsis leads to organ dysfunction.
- The use of vasopressor agents to correct hypotension does not exclude shock.

**decreased urine output (common)**
- Urine output <0.5 mL/kg/hour for at least 2 hours, or no urine passed in the last 18 hours.
- May be present when sepsis leads to organ dysfunction.

**cyanosis (common)**
- Sign of circulatory insufficiency.

**Other diagnostic factors**

**purpura fulminans (common)**
- Sign of organ dysfunction.

**jaundice (uncommon)**
- Sign of organ dysfunction.
Sepsis in adults

ileus (uncommon)
- May be present when sepsis leads to organ dysfunction.

## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBC with differential</strong></td>
<td>WBC count &gt;12×10^9/L (12,000/microlitre) (leukocytosis); WBC count &lt;4×10^9/L (4000/microlitre) (leukopenia); or a normal WBC count with &gt;10% immature forms; low platelets</td>
</tr>
<tr>
<td>- WBC count is sensitive but not specific for the diagnosis of sepsis.</td>
<td>serums electrolytes frequently deranged; blood urea may be elevated</td>
</tr>
<tr>
<td>- Non-infectious injury (e.g., crush injury), cancer, and immunosuppressive agents can also cause either increased or decreased WBC counts.</td>
<td></td>
</tr>
<tr>
<td>- Thrombocytopenia of non-haemorrhagic origin may occur in patients who are severely ill with sepsis.</td>
<td></td>
</tr>
<tr>
<td><strong>blood urea and serum electrolytes</strong></td>
<td>serum electrolytes frequently deranged; blood urea may be elevated</td>
</tr>
<tr>
<td>- Blood urea is performed with serum creatinine to evaluate for renal dysfunction.</td>
<td></td>
</tr>
<tr>
<td>- Serum electrolytes should be measured at baseline and regularly until the patient improves.</td>
<td></td>
</tr>
<tr>
<td><strong>serum creatinine</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>- Elevated creatinine may occur in sepsis associated with renal dysfunction.</td>
<td></td>
</tr>
<tr>
<td><strong>LFT</strong></td>
<td>elevated bilirubin, ALT, AST, alkaline phosphatase, and gamma-GT</td>
</tr>
<tr>
<td>- Baseline test.</td>
<td></td>
</tr>
<tr>
<td>- Sepsis can originate from hepatic or peri-hepatic infections.</td>
<td></td>
</tr>
<tr>
<td>- Comorbidity of underlying hepatic disease can affect drug metabolism and outcome in sepsis.</td>
<td></td>
</tr>
<tr>
<td>- Septic shock can compromise hepatic blood flow and metabolism, including lactate.</td>
<td></td>
</tr>
<tr>
<td><strong>coagulation studies (INR, aPTT)</strong></td>
<td>may be prolonged</td>
</tr>
<tr>
<td>- Baseline test, especially before central line placement.</td>
<td></td>
</tr>
<tr>
<td><strong>serum glucose</strong></td>
<td>may be elevated or, more rarely, low</td>
</tr>
<tr>
<td>- May be elevated, with or without known history of diabetes, due to the stress response and to altered glucose metabolism.</td>
<td></td>
</tr>
<tr>
<td>- Hyperglycaemia is associated with increased morbidity and mortality.</td>
<td></td>
</tr>
<tr>
<td>- Spontaneous or iatrogenic hypoglycaemia also poses significant dangers.[88] [89]</td>
<td></td>
</tr>
<tr>
<td>- The Surviving Sepsis Campaign recommends the maintenance of normoglycaemia (above lower limit of normal, but &lt;10 mmol/L [180 mg/dL]), preferably with the use of an insulin infusion protocol.[84]</td>
<td></td>
</tr>
<tr>
<td>- Rarely, glucose may be low, suggesting acute liver failure.</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosis of Sepsis in Adults

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>lactate levels</strong></td>
<td>Elevated serum lactate highlights tissue hypoperfusion, and is most</td>
</tr>
<tr>
<td></td>
<td>reliably assessed using an ABG sample.[75]</td>
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<tr>
<td></td>
<td>Increasing levels of lactate are associated with increasing levels of</td>
</tr>
<tr>
<td></td>
<td>anaerobic metabolism. Persistently elevated lactate levels may</td>
</tr>
<tr>
<td></td>
<td>parallel the degree of malperfusion or organ failure.</td>
</tr>
<tr>
<td></td>
<td>High lactate carries adverse prognostic value if elevated to &gt;2 mmol/</td>
</tr>
<tr>
<td></td>
<td>L (&gt;18 mg/dL), and still worse outcomes are associated with levels &gt;4</td>
</tr>
<tr>
<td></td>
<td>mmol/L (&gt;36 mg/dL).</td>
</tr>
<tr>
<td></td>
<td>Lactate clearance (the rate at which lactate is cleared over a period</td>
</tr>
<tr>
<td></td>
<td>of 6 hours) has been demonstrated to be as useful as more invasive</td>
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<tr>
<td></td>
<td>tests, such as central venous oxygen saturation, in determining a</td>
</tr>
<tr>
<td></td>
<td>patient’s response to treatment.[79] [80]</td>
</tr>
<tr>
<td></td>
<td>may be elevated; levels &gt;2 mmol/L (&gt;18 mg/dL) associated with adverse</td>
</tr>
<tr>
<td></td>
<td>prognosis; even worse prognosis with levels &gt;4 mmol/L (&gt;36 mg/dL)</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>elevated</td>
</tr>
<tr>
<td><strong>blood culture</strong></td>
<td>may be positive for organism</td>
</tr>
<tr>
<td></td>
<td>Baseline test. A marker for inflammation.</td>
</tr>
<tr>
<td></td>
<td>Blood cultures should be taken immediately, and preferably before</td>
</tr>
<tr>
<td></td>
<td>antibiotics are started, provided their sampling will not delay</td>
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<tr>
<td></td>
<td>administration of antibiotics.</td>
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<tr>
<td></td>
<td>Ideally, at least one set should be taken percutaneously, and one set</td>
</tr>
<tr>
<td></td>
<td>from any vascular access device that has been in situ for more than</td>
</tr>
<tr>
<td></td>
<td>24 hours.[66] [67]</td>
</tr>
<tr>
<td>**other cultures (e.g., of sputum, stool, urine, wounds, catheters,</td>
<td>may be positive for organism</td>
</tr>
<tr>
<td></td>
<td>prosthetic implants, epidural sites, pleural or peritoneal fluid)</td>
</tr>
<tr>
<td></td>
<td>Other cultures (for example, of sputum, stool, and urine) should be</td>
</tr>
<tr>
<td></td>
<td>taken as clinically indicated.</td>
</tr>
<tr>
<td></td>
<td>If meningitis is suspected, a lumbar puncture (LP) for CSF</td>
</tr>
<tr>
<td></td>
<td>microscopy and culture should be performed. A CT scan prior to</td>
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<tr>
<td></td>
<td>performing a LP to exclude raised intracranial pressure is required if</td>
</tr>
<tr>
<td></td>
<td>there is any clinical suspicion of this.</td>
</tr>
<tr>
<td>[VIDEO: Diagnostic lumbar puncture in adults: animated demonstration]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If an enclosed collection such as an abscess or empyema is</td>
</tr>
<tr>
<td></td>
<td>suspected, it is recommended that this be drained and cultured early</td>
</tr>
<tr>
<td></td>
<td>in the course of the illness (within 6 hours following identification).[74]</td>
</tr>
<tr>
<td></td>
<td>Intubated patients, in whom there is a suspicion of pneumonia,</td>
</tr>
<tr>
<td></td>
<td>should have tracheal aspirates, broncho-alveolar lavage, or protected</td>
</tr>
<tr>
<td></td>
<td>brush specimens taken.</td>
</tr>
<tr>
<td></td>
<td>If no localising signs are present, examination and culture of all</td>
</tr>
<tr>
<td></td>
<td>potential sites of infection, including wounds, catheters, prosthetic</td>
</tr>
<tr>
<td></td>
<td>implants, epidural sites, and pleural or peritoneal fluid, as indicated by the clinical presentation and history, is required.</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| arterial blood gas (ABG) or venous blood gas (VBG) | • ABG evaluation facilitates optimisation of oxygenation, and is indicative of metabolic status (acid-base balance).  
  • In ventilated patients, it helps to determine optimal positive end-expiratory pressure (PEEP), while minimising adverse levels of inspiratory pressure and unnecessarily high FiO2.  
  • Differentiation of respiratory from metabolic acidosis allows metabolic demands to be identified and treated.  
  • Lactate levels are most reliably assessed using an ABG sample. However, in practice, a venous blood gas (VBG) sample is often used, as it is generally easier and quicker to obtain compared with ABG. Most patients do not undergo ABG sampling unless there is a respiratory component.  
  • Repeat blood gases are indicated depending on the clinical state of the patient.  
  • PaCO2 <4.3 kPa (32 mmHg) is one of the diagnostic criteria for systemic inflammatory response syndrome (SIRS); may be hypoxaemia, hypercapnia |
| chest x-ray                                | • Required to look for cause of sepsis.  
  • A chest x-ray is always indicated after central venous pressure and endotracheal tube placement to rule out malposition and complications.  
  • May show evidence of infection, such as consolidation or pleural effusion, cardiac abnormalities, or a pneumothorax |
| ECG                                       | • An ECG should be arranged to help exclude other differential diagnoses, including myocardial infarction, pericarditis, and myocarditis. Sepsis also predisposes to myocardial dysfunction (particularly in septic shock)[78] and arrhythmias (e.g., atrial fibrillation).[9]  
  • May show evidence of ischaemia, atrial fibrillation, or other arrhythmia; may be normal |
### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>lumbar puncture</td>
<td>elevated WBC count, presence of organism on microscopy, and positive culture</td>
</tr>
<tr>
<td>- Performed if meningitis suspected, provided no suspicion of raised intracranial pressure. A CT scan is required prior to performing an LP to exclude raised intracranial pressure if there is any clinical suspicion of this.</td>
<td></td>
</tr>
<tr>
<td>- Bacterial meningitis: WBC count &gt;1×10^9/L (1000/microlitre); protein is elevated; glucose is normal or reduced; cell differential is predominantly neutrophils.</td>
<td></td>
</tr>
<tr>
<td>- Viral meningitis may be associated with lower WBC counts and predominant lymphocytes.</td>
<td></td>
</tr>
<tr>
<td>[VIDEO: Diagnostic lumbar puncture in adults: animated demonstration ]</td>
<td></td>
</tr>
<tr>
<td>echocardiogram (transthoracic or transoesophageal)</td>
<td>inadequate left ventricular filling suggests hypovolaemia; vegetations, if endocarditis is cause of sepsis</td>
</tr>
<tr>
<td>- A transthoracic or transoesophageal echocardiogram is useful in patients at risk of, or with symptoms compatible with, bacterial endocarditis.</td>
<td></td>
</tr>
<tr>
<td>- If readily available, may also be appropriate in patients with sepsis of unknown origin.</td>
<td></td>
</tr>
<tr>
<td>- Also helpful to differentiate between hypovolaemic, cardiac, and septic shock.</td>
<td></td>
</tr>
<tr>
<td>- May determine alternative diagnoses, such as valvular abnormalities, pulmonary embolus, myocardial ischaemia, segmental or global dysfunction, hypovolaemia, and pulmonary hypertension.</td>
<td></td>
</tr>
<tr>
<td>ultrasound scan</td>
<td>may demonstrate abscess, fluid collection, pneumoperitoneum from perforated viscus, obstruction of GI/renal/biliary tracts</td>
</tr>
<tr>
<td>- Including but not limited to abdominal ultrasound scan.</td>
<td></td>
</tr>
<tr>
<td>- May indicate source of infection (e.g., dilated common bile duct indicating biliary obstruction).</td>
<td></td>
</tr>
<tr>
<td>CT chest or abdomen</td>
<td>abscess, effusion may be demonstrated</td>
</tr>
<tr>
<td>- If clinically indicated to establish source of infection.</td>
<td></td>
</tr>
<tr>
<td>- Requires transfer of potentially unstable patients and the benefit should be weighed against the risk.</td>
<td></td>
</tr>
<tr>
<td>serum procalcitonin</td>
<td>elevated</td>
</tr>
<tr>
<td>- Where available, measurement of serum procalcitonin should be considered in all patients with sepsis to guide antibiotic therapy. Among patients with acute respiratory infections (including those resulting in sepsis), procalcitonin-guided therapy was associated with a 2 day reduction in the antibiotic course, a 27% reduction in antibiotic related side-effects, and a 10% reduction in 30 day mortality rate.[90]</td>
<td></td>
</tr>
<tr>
<td>- However, evidence for the prognostic value of procalcitonin alone is unclear,[82] and its use in the identification of sepsis is excluded from many guidelines. In addition, changes in procalcitonin levels may occur later than that of lactate, although changes in both markers combined are highly predictive of outcome between 24 and 48 hours.[83]</td>
<td></td>
</tr>
</tbody>
</table>
Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhenoTest™ BC Kit</td>
<td>may be positive for organism and guide antimicrobial therapy</td>
</tr>
<tr>
<td>• Can identify 14 species of bacteria and 2 species of yeast that commonly cause bloodstream infections, while also providing guidance on antibiotic sensitivity.</td>
<td></td>
</tr>
<tr>
<td>• Compares the organism’s DNA to a database, and then uses time-lapse images to analyse the organism’s response to antibiotics.</td>
<td></td>
</tr>
<tr>
<td>• Can identify a positive blood culture in 1.5 hours and guide antibiotic treatment in 6.5 hours.</td>
<td></td>
</tr>
<tr>
<td>• Has been associated with false positive results.[87]</td>
<td></td>
</tr>
</tbody>
</table>

Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infectious causes of systemic inflammatory response syndrome (SIRS)</td>
<td>• SIRS can result as a non-specific finding from a host of other disease states, including postoperative recovery, trauma, burns, transplant rejection, hyperthyroidism, Addisonian crisis, blood product transfusion reactions, serum sickness, immunisations, and CNS infarction or haemorrhages.</td>
<td>• Specific tests are directed by clinical suspicion of underlying cause.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Associated medical interventions (e.g., catheterisation, surgical procedures, ventilation) can subsequently lead to superimposed infections to make sepsis a continual threat and possibility.</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>• Symptoms suggesting MI are central, squeezing chest pain radiating down the left arm or into the jaw. Pain may be felt in the epigastric region. Patients may present in cardiogenic shock.</td>
<td>• Ischaemic changes on ECG. Elevated CK-MB and troponin.</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>• Patients present with sharp, stabbing, pleuritic chest pain (typically better on sitting up and leaning forward, and worse with lying down).</td>
<td>• ECG may have upward concave ST-segment elevation globally and PR-segment depression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Echo may demonstrate a pericardial effusion; absence of LV wall motion abnormalities.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Myocarditis               | • Patients typically present with a viral prodrome, dyspnoea, or underlying autoimmune condition, such as SLE.  
  • Medications such as antibiotics, thiazide diuretics, antiepileptics, digoxin, lithium, amitriptyline, and dobutamine may be suggestive of drug aetiology.                                                                                                                                                      | • ECG may show non-specific ST-segment and T-wave abnormalities.  
  • Inflammatory markers may be elevated.  
  • Two-dimensional echo demonstrates global and regional LV motion abnormalities and dilatation.                                                                                                                                                    |
| Acute pancreatitis        | • May present with abdominal pain and hypovolaemia.  
  • There may be a history of gallstones, alcohol use, or viral infections (e.g., mumps).                                                                                                                                                                                                                                                                         | • Elevated serum amylase, lipase, glucose; low calcium.                                                                                                                                                                                                                                               |
| Massive pulmonary embolism| • Presents with acute dyspnoea, pleuritic chest pain, and hypotension.                                                                                                                                                                                                                                                                                                                                                           | • CT pulmonary angiogram shows a filling defect in the pulmonary arteries.                                                                                                                                                                                                                           |
| Leukaemia                 | • May present with fever, leukocytosis, anaemia, tachycardia, multi-organ dysfunction, and dyspnoea and thus meet diagnostic criteria for (suspected) sepsis.  
  • The immunocompromise may additionally facilitate development of infections or the increased clinical suspicion of undiagnosed infection.                                                                                                                                                             | • Biopsies of blood smear, bone marrow, tumour, or lymph nodes may identify neoplastic cells.  
  • Identification of a specific infectious agent is definitive in differentiating sepsis from SIRS.                                                                                                                                                                                                   |
| Malignant hyperthermia    | • This is a rare condition characterised by severe hyperthermia (>41.1 °C [106 °F]) and muscle rigidity following administration of anaesthetic agents (e.g., succinylcholine for intubation). Lactic acidosis, hyperkalaemia, rhabdomyolysis, hypoxia, and arrhythmias may also occur.                                                                                       | • The caffeine-halothane contracture test (CHCT) is most commonly used to screen for susceptibility, as ryanodine receptor gene (RYR1) identification is gaining in clinical importance.[92]  
  • The CHCT requires muscle biopsy and testing in select regional laboratories after resolution of the episode.  
  • Neither test is clinically useful to direct therapy in the acute situation.                                                                                           |

[91]  
[92]  

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jan 31, 2018.  
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### Diagnostic criteria

There are multiple scoring systems and definitions for sepsis and sepsis with organ dysfunction. None is perfect and many seek to measure similar variables. The systemic inflammatory response syndrome (SIRS) criteria and the 1991/2001 international consensus definitions of sepsis, severe sepsis, and septic shock remain clinically established in most clinical settings. The Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score is recommended in the 2016 international consensus.

**Third International Consensus definitions for sepsis and septic shock (Sepsis-3) (2016)**[1]

1. **Sepsis:** the third international consensus definition of sepsis published in 2016 redefines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. According to the 2016 consensus definitions, an increase in SOFA score of 2 or more constitutes organ dysfunction. The SOFA score is calculated based on the assessment of the following systems in the ICU setting:

   - Respiratory (PaO2/FiO2 ratio)
   - Neurological (as assessed by the Glasgow coma scale)
   - Cardiovascular (mean arterial pressure [MAP] or administration of vasopressors)
   - Coagulation (platelet count)
   - Renal (creatinine level and urine output)
   - Hepatic (bilirubin level).

The 2016 consensus definitions recommend that the SOFA criteria should replace the previously recommended SIRS criteria. Furthermore, the ‘quick’ (q)SOFA criteria are recommended for use outside of the ICU setting to promptly identify patients with suspected infection who are likely to have a poor outcome. According to the 2016 consensus definitions, patients with 2 or more of the following qSOFA criteria are likely to have poor outcomes typical of sepsis:

   - Alteration in mental status
   - Systolic blood pressure ≤100 mmHg
   - Respiratory rate ≥22 per minute.

2. **Severe sepsis:** in light of the revisions to the definition of sepsis, the 2016 consensus definitions recommend that the term ‘severe sepsis’ (as defined in the 1991/2001 consensus definitions) should be made redundant.
3. Septic shock: the definition of septic shock has been redefined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.[1] According to the 2016 consensus definitions, septic shock is defined as sepsis with both:

- Persistent hypotension requiring vasopressors to maintain MAP $\geq$65 mmHg, and
- Serum lactate level $>2$ mmol/L ($>18$ mg/dL) despite adequate volume resuscitation.

**Revised International Consensus definitions for sepsis and septic shock: SIRS in the presence of infection (2001)**[5]

These criteria have in principle been superseded by the Sepsis-3 definitions. However, they remain in widespread use in clinical practice.

1. Definitive diagnosis requires clinical identification of infection in a patient who also meets the clinical criteria for SIRS. According to the revised consensus conference definition published in 2001, SIRS is defined by the presence of 2 or more criteria from a collection of clinical signs and laboratory investigations as follows: [Surviving Sepsis Campaign: evaluation for severe sepsis screening tool]

- Temperature $>38.3^\circ$C (101°F) or $<36.0^\circ$C (96.8°F)
- Tachycardia $>90$ bpm
- Tachypnoea $>20$ breaths/minute or PaCO2 $<4.3$ kPa (32 mmHg)
- Hyperglycaemia (blood glucose $>7.7$ mmol/L [$>140$ mg/dL]) in the absence of diabetes mellitus
- Acutely altered mental status
- Leukocytosis (WBC count $>12 \times 10^9$/L [12,000/microlitre])
- Leukopenia (WBC count $<4 \times 10^9$/L [4000/microlitre])
- Normal WBC count with $>10\%$ immature forms.

2. Sepsis: when SIRS is present in an individual patient and the cause is thought likely to be an infection, sepsis is present.

3. Severe sepsis: present when sepsis leads to dysfunction of 1 or more organ systems, and includes the subset septic shock. Organ dysfunction variables are:

- Arterial hypoxaemia (PaO2/FiO2 ratio $<300$) with new pulmonary infiltrates
- A new or increased oxygen requirement to maintain SpO2 $>90\%$
- Acute oliguria (urine output $<0.5$ mL/kg/hour for at least 2 hours)
- Serum creatinine $>176.8$ micromol/L (2.0 mg/dL)
- Coagulation abnormalities (INR $>1.5$ or aPTT $>60$ seconds)
- Thrombocytopenia (platelets $<100 \times 10^9$/L [100,000/microlitre])
- Hyperbilirubinaemia (total bilirubin $>68.42$ micromol/L [4 mg/dL])
- Arterial hypotension (systolic BP $<90$ mmHg, mean BP $<65$ mmHg, or reduction in systolic BP $>40$ mmHg from baseline)
- Serum lactate $>2$ mmol/L ($>18$ mg/dL).

4. Septic shock is defined as:

- Arterial hypotension (systolic BP $<90$ mmHg, mean BP $<65$ mmHg, or reduction in systolic BP $>40$ mmHg from baseline) persisting for at least 1 hour, despite adequate fluid resuscitation, or
- Serum lactate $>4$ mmol/L ($>36$ mg/dL) after adequate fluid resuscitation.

The use of vasopressor agents to correct hypotension does not exclude shock.
Sepsis: recognition, diagnosis and early management (National Institute for Health and Care Excellence, 2016)[9]

In the UK, the National Institute for Health and Care Excellence (NICE) has published guidance on the recognition, diagnosis, and early management of sepsis, which includes specific criteria for risk stratification of adults with suspected sepsis. The criteria are as follows:

Low risk of severe illness or death from sepsis:

- Normal behaviour
- No history of acute deterioration of functional ability, impaired immunity, or trauma/surgery in the past 6 weeks
- Normal respiratory rate (i.e., <21 breaths per minute) and no oxygen requirement to maintain saturation
- Normal blood pressure (i.e., systolic blood pressure >100 mmHg)
- Normal heart rate (i.e., ≤90 beats per minute; <100 beats per minute in pregnant women) and no new onset arrhythmias
- Normal urine output in the past 18 hours
- Normal temperature
- No non-blanching rash.

Moderate to high risk of severe illness or death from sepsis:

- History of new onset of altered behaviour or mental state (reported by patient, friend, or relative)
- History of acute deterioration of functional ability
- Impaired immunity (e.g., from illness or drugs)
- Trauma, surgery, or invasive procedures in the past 6 weeks
- Respiratory rate 21-24 breaths per minute
- Systolic blood pressure 91-100 mmHg
- Heart rate 91-130 beats per minute (100-130 beats per minute in pregnant women), or new onset arrhythmia
- No urine passed in previous 12-18 hours (for catheterised patients, 0.5-1.0 mL/kg of urine passed per hour)
- Tympanic temperature <36°C
- Signs of potential infection (e.g., redness, swelling or discharge at surgical site, or breakdown of wound).

High risk of severe illness or death from sepsis:

- Objective evidence of new altered mental state
- Respiratory rate ≥25 breaths per minute
- New need for oxygen (>40% FiO2) to maintain saturation >92% (or >88% in known chronic obstructive pulmonary disease)
- Systolic blood pressure ≤90 mmHg, or systolic blood pressure >40 mmHg below normal
- Heart rate >130 beats per minute
- No urine passed in previous 18 hours (for catheterised patients, <0.5 mL/kg of urine passed per hour)
- Mottled or ashen appearance; cyanosis of skin, lips, or tongue; non-blanching rash of skin.
Acute Physiology and Chronic Health Evaluation II score (APACHE II)[93]

The APACHE score is commonly used to establish illness severity in the ICU and predict the risk of death.

[VIDEO: APACHE II scoring system ]

There is a high risk of death if the score is ≥25.

Other sepsis risk-scoring models

Several other models have been developed for use in the ICU, including APACHE III, the Simplified Acute Physiology Score, and Mortality Probability Model II.[33] [94] [95]

Patient group-specific scoring systems have also been developed. For example, the Predisposition Insult Response and Organ failure (PIRO) and Mortality in Emergency Department Sepsis (MEDS) scores have been developed to risk-stratify patients with sepsis or septic shock who are admitted to the accident and emergency department;[96] the Sepsis in Obstetrics Score (SOS) has been developed to risk-stratify pregnant or postnatal women with sepsis.[97] These scoring systems can assist in the identification and management of sepsis in specific patient groups.[98]

There are numerous ongoing studies investigating techniques for ‘staging’ the severity of sepsis using a variety of blood-borne markers.[82] [99] Although some techniques have shown initial promise, the evidence base remains weak, and they have an unclear role in future clinical practice.
Step-by-step treatment approach

Early recognition and treatment of sepsis is key to improving outcomes. Treatment guidelines have been produced by the Surviving Sepsis Campaign and remain the most widely accepted standards. Current best practice is based upon evidence for care bundles in sepsis. They include:

- Obtain blood cultures prior to administration of antibiotics
- Administer broad-spectrum antibiotics that target the suspected pathogen(s)
- Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L (≥36 mg/dL)
- Obtain serial measurement of blood lactate
- Use vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg in patients refractory to fluid therapy
- In patients with an initial lactate ≥4 mmol/L (≥36 mg/dL), or who are persistently hypotensive (i.e., MAP <65 mmHg), assess volume status and perfusion using either a repeat focused examination (including vital signs and cardiopulmonary, capillary refill, pulse, and skin findings), or 2 of the following methods:
  - Measurement of central venous pressure (CVP)
  - Measurement of central venous oxygen saturation (ScvO2)
  - Bedside cardiovascular ultrasound
  - Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines recommend administering crystalloid if the patient has a lactate ≥2 mmol/L (≥18 mg/dL) and at least one high risk criterion. Crystalloids are also recommended if the patient has a lactate >2 mmol/L (>18 mg/dL) and at least two moderate to high risk criteria, or evidence of acute kidney injury. Crystalloid can be considered in patients with a lactate <2 mmol/L (<18 mg/dL) if they have at least one high risk criterion.

The Sepsis Six

One bundle dealing with basic therapies, the ‘Sepsis Six’, has been shown to improve outcomes in septic patients. If the 6 factors are completed within the first hour following recognition of sepsis, the associated mortality has been reported to reduce by as much as 50%. The 6 factors are as follows:

- Administer high-flow oxygen to maintain target oxygen saturations greater than 94% (or 88%-92% in people at risk of hypercapnic respiratory failure)
- Take blood cultures
- Give intravenous antibiotics
- Start intravenous fluid resuscitation
- Check lactate level
- Monitor hourly urine output.

Patients who are refractory to initial treatments, in particular those with septic shock, may require invasive monitoring and consideration for organ support (e.g., central venous catheter and vasopressors), so management on a high dependency unit or ICU may well be required.

One aspect of basic intervention, the delivery of appropriate rapid fluid challenges, is intended to restore the imbalance between oxygen supply and demand to the tissues. Patients who fail to respond to the rapid delivery of adequate volumes of intravenous fluids are in septic shock. The immediate priority in this group of patients is the restoration of the circulation and oxygen delivery.
Early goal-directed fluid therapy has previously been the gold standard of care,[6] [58] [61] [88] [84] [102] [103] but several randomised, prospective studies have found no discernible benefit with this therapy over usual care.[104] [105] [106] [107] [108] However, the central tenets of early goal-directed therapy (e.g., restoration of circulating volume, correction of hypotension, and assessing cardiac output) remain important to the management of sepsis and have now become standard practice in many emergency departments.

Monitoring of vital signs and response to fluid therapy is essential. Assessment of oxygenation via pulse oximetry and serial lactate measurements should be performed, along with monitoring of urinary output. A failure of lactate to improve with therapy is indicative of a poor outcome. Lactate clearance has been shown to correlate positively with survival.[79] All patients receiving vasopressors should have an arterial catheter inserted as soon as it is practical to do so to aid more accurate monitoring of arterial blood pressure.[84]

**Antibiotic therapy**

Broad-spectrum intravenous antibiotics should be given before a pathogen is identified.[84] [109] [110] They are recommended within the first hour once sepsis is diagnosed, preferably after cultures have been taken.[84] [9] The delivery of appropriate antibiotics within the first hour is of critical importance in maximising chances of survival.[62] [111] [112] [113]

Knowledge of locally prevalent pathogens and their antibiotic resistance patterns are important when deciding empirical therapy.[109] [114] Empirical antibiotic recommendations will be necessarily individualised at the institutional level, based on local antibiotic protocols. Once culture and sensitivity results are available, antibiotics can be tailored to the known pathogens. Cultures should be repeated (e.g., at 6-hour to 8-hour intervals) if there are persistent or repeated fever spikes, or there is the identification of a new site of infection. Antibiotics should be given targeted to the presumed site of infection. If there is no clinical evidence to suggest a site of infection, empirical broad-spectrum antibiotics should still be given.

Empirical antibiotics should be narrowed as soon as a pathogen has been identified and sensitivities are available.[84]

**Respiratory source**

Respiratory infections account for approximately 30% to 50% of cases. Monotherapy appears as effective as combination therapy in community-acquired pneumonia, although some units prefer combination therapy in patients with severe pneumonia requiring critical care admission.[115] Treatment regimens should cover common respiratory pathogens and atypical organisms such as *Legionella pneumophila*.

Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Combination therapy should include a beta-lactam (such as benzyl penicillin, cefotaxime, or amoxicillin/clavulanate), with a macrolide (such as azithromycin). A suitable monotherapy treatment regimen is to use a respiratory quinolone, such as moxifloxacin or levofloxacin, or alternatively, doxycycline. These monotherapy regimens are suitable for patients with penicillin allergy.

Risk factors for the presence of multiple drug-resistant pathogens (MDRPs) for *Pseudomonas aeruginosa* and for methicillin-resistant *Staphylococcus aureus* (MRSA) will affect choice of antimicrobial agents and should be evaluated. These include hospitalisation (for >48 hours, including
Sepsis in adults

Treatment

residence in nursing home) or systemic antibiotic use within the previous 90 days. A history of MRSA infection or colonisation should be sought. Recently, increasing numbers of cases of community-acquired MRSA pneumonia have been reported, particularly in association with influenza virus infection. Mortality rates appear somewhat higher than for non-MRSA severe pneumonia at 33%.[116]

MRSA should be considered in patients presenting with particularly severe community-acquired pneumonia, especially in the presence of haemoptysis, shock, and an influenza-like prodromal illness.[117] [118] [119]

In high-risk patients, a broader spectrum of cover can be achieved using a carbapenem such as imipenem/cilastatin, or an antipseudomonal penicillin such as piperacillin/tazobactam in combination with an aminoglycoside such as gentamicin. Tigecycline is an alternative for patients with penicillin allergy; however, monotherapy with this drug should be used with caution as it may be associated with an increased risk of mortality. Expert advice should be sought before using tigecycline.[120] In patients at risk of MRSA, or with unusual severity of pneumonia with haemoptysis, vancomycin or linezolid should be added to one of the above regimens. In patients with significant risk factors for *Pseudomonas* infection (bronchiectasis, systemic corticosteroid use, malnourishment) consideration should be given to the addition of ciprofloxacin to one of the above regimens.

**Urinary tract source**

Urinary tract infections account for approximately 10% to 20% of cases. Ensuring patency of the urinary tract is vital. Cover should include gram-negative coliforms and *Pseudomonas*. Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. A suitable treatment regimen is to use a combination of either ampicillin or a cephalosporin, such as cefotaxime with gentamicin. Ciprofloxacin is a suitable alternative in patients with penicillin allergy.

**Abdominal source**

Infection arising from abdominal sources accounts for approximately 20% to 25% of cases. Gram-positive and gram-negative organisms including anaerobes should be covered. Peritonitis or intra-peritoneal abscesses require urgent surgical drainage or (where appropriate) percutaneous drainage.

Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Treatment with ampicillin or cefotaxime with metronidazole and gentamicin is a suitable regimen, or alternatively piperacillin/tazobactam with gentamicin. A regimen of tigecycline and gentamicin is a suitable choice in patients with penicillin allergy.

Patients with recurrent perforation of the large intestine are at increased risk of invasive fungaemia. Anazole, such as fluconazole, or an echinocandin, such as micafungin, should be added to the antibacterial cover. Non-albicans species of *Candida* are increasingly resistant to azoles.[41] [42] [121]

**Soft-tissue and joint source**

This heterogeneous group of infections includes septic arthritis, wound infections, cellulitis, and acute super-infections arising from chronic ulceration, and accounts for approximately 5% to 10% of cases. A high index of suspicion should also be held for necrotising fasciitis, which requires immediate surgical intervention (as does septic arthritis). Most infections are polymicrobial, and broad-spectrum cover against gram-positive and gram-negative organisms including anaerobes should be used.
Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. A suitable regimen is to use flucloxacillin (or tigecycline in penicillin-allergic patients) together with metronidazole. Alternatively, clindamycin may be used. If the patient has risk factors for MRSA, vancomycin (or alternatively linezolid) should be added.

If necrotising fasciitis is suspected, clindamycin together with flucloxacillin or tigecycline would be a sensible choice.

**CNS source**

CNS infections are a relatively uncommon but potentially devastating cause of sepsis, accounting for under 5% of cases. Meningococcal septicaemia can be extremely rapidly fatal, and if survived, can lead to greater morbidity than other forms. Immediate antibiotic therapy in suspected cases is essential.

Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Suspected meningitis or meningococcal septicaemia should be treated immediately using a third-generation cephalosporin, such as ceftriaxone or cefotaxime. For patients with penicillin allergy, vancomycin with chloramphenicol is a suitable alternative. Some suggest the addition of rifampicin to either regimen to aid penetration.

For patients over 50 years, and those with a history of alcoholism or other debilitating illness, or at increased risk of infection with *Listeria*, cephalosporins alone provide inadequate cover. Ampicillin should be added to the regimen, provided the patient is not allergic to penicillin. For those allergic to penicillin, erythromycin or trimethoprim/sulfamethoxazole can be substituted.

Patients with a more insidious onset of CNS symptoms should be suspected as having viral encephalitis. Viruses cause sepsis extremely rarely, but early use of antiviral agents such as acyclovir may improve outcome.

Corticosteroids for bacterial meningitis can improve neurological outcomes.[122]

**Sepsis of unknown origin**

Intensive efforts, including imaging, should be undertaken to attempt to evaluate the source of infection. Urgent broad-spectrum coverage to include all common pathogens should be administered.

Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Carbapenems give appropriately broad cover, with imipenem or meropenem being suitable choices. Piperacillin/tazobactam with gentamicin is an alternative. If the patient has risk factors for MRSA, vancomycin should be added.

**Fluid resuscitation**

Early, vigorous fluid resuscitation in sepsis-induced hypoperfusion is needed with at least 30 mL/kg body weight of crystalloid given within the first 3 hours.[84] Additional fluid may be required, but this should be guided by thorough clinical assessment of the patient's haemodynamic status.[84]

Repeated fluid boluses of crystalloid (typical volume 500 mL) given over 5 to 30 minutes may be effective in correcting hypotension secondary to hypovolaemia. Boluses of a colloid solution (typical volume
250-300 mL) may be used as an alternative, but no evidence supports the use of colloids over other fluids such as crystalloids or albumin solution.[123] [124] [125] [126] [127] [128] [129] [130] [131] Solutions containing starch may be harmful and should be avoided.[84] Evidence has shown that solutions containing hydroxyethyl starch (HES) are associated with a greater risk of renal dysfunction and adverse outcome.[132] [133] [134] [135] [136] [137] [138] HES solutions for infusion have been suspended from the market across the European Union owing to patient safety concerns related to the increased risk of kidney injury and death in certain patient groups, including critically ill patients and those with sepsis. The market suspension followed a January 2018 review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee that found HES solutions were still being used in these patient groups despite restrictions introduced in 2013. [139]

Normal saline and albumin should be given according to local protocols. Current evidence suggests that resuscitation using albumin-containing solutions is safe, but evidence of its efficacy is insufficient to recommend its use over crystalloids.[131] [140] [141] Red cell or plasma transfusion may be considered to target specific deficiencies but should not be used for volume augmentation. Aggressive red cell transfusion has not been shown to improve outcomes.[142]

Patients should be monitored closely for signs of fluid overload (e.g., pulmonary or systemic oedema).[143] Changes in inferior vena cava (IVC) diameter during respiration (visualised using bedside ultrasound) have been shown to be an accurate means of judging fluid responsiveness, and requirement for further intravenous fluids. In the spontaneously breathing patient, a collapsed or collapsing IVC suggest that cardiac output will improve with additional fluid resuscitation. In the mechanically ventilated patient, an increase in IVC size >18% (or visible to the naked eye) with positive pressure ventilation, fluid responsiveness is expected.[144] [145] One systematic review has shown passive leg raising to be an accurate predictor of fluid responsiveness in ventilated patients, regardless of ventilator mode or technique, and with flow variables (e.g., cardiac output) having greater accuracy compared with pulse pressure.[146]

**Glycaemic control in the critically ill**

There has been a shift of opinion and practice regarding glycaemic control in the critically ill. Since 2001, the use of tight glycaemic control in septic patients has been advocated. However, more recent evidence suggests an increase in adverse events (e.g., severe hypoglycaemia) in patients managed with tight glycaemic control (target blood glucose 6.1 mmol/L).[134] [147] An international randomised controlled trial demonstrated an increase in the absolute risk of death at 90 days by 2.6 percentage points in the patient group managed with intensive glycaemic control compared with the group managed with conventional glycaemic control (blood glucose target of 10 mmol/L [180 mg/dL]).[148] The American Diabetes Association recommends a general glucose goal of 7.8 to 10.0 mmol/L (140-180 mg/dL) in critically ill diabetic patients, preferably with use of an insulin infusion protocol.[149] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <10 mmol/L (180 mg/dL).[84]

**Persistent haemodynamic instability**

If hypotension persists, with a MAP of <65 mmHg, a vasopressor should be started.[84] [150] Noradrenaline (norepinephrine) administered via a central venous catheter is the drug of choice as it increases MAP. Vasopressin or adrenaline can be added to noradrenaline to achieve the target MAP (≥65 mmHg), or vasopressin can be added to wean noradrenaline.[84] Dopamine is an option, but should only be given to highly selected patients as it has been associated with higher mortality than...
noradrenaline.[84] [151] [152] All infusions of vasoactive medications to correct shock should be given via a secure catheter in a central vein with high flow, such as via a central venous catheter, unless resources do not permit this and the situation is urgent. The use of low-dose dopamine for renal protection is not recommended.[84]

**Adjunctive therapies**

In patients with low cardiac output despite adequate fluid resuscitation, inotropes (e.g., dobutamine) can be added. Low cardiac output suspected through clinical examination (prolonged capillary refill times, low urine output, poor peripheral perfusion) can be confirmed through the use of cardiac output monitoring or by sampling central venous or pulmonary arterial blood to measure oxygen saturations. Heart rate should be kept <100 bpm to minimise myocardial oxygen demand.[150]

Current guidelines recommend that low-dose corticosteroids are given only to patients whose BP is poorly responsive to both fluid resuscitation and vasopressor therapy.[84] However, evidence for giving corticosteroids to patients with sepsis or septic shock is mixed.[153] [154] [155] [156] [157] [158] [159] In a large randomised controlled trial published in January 2018, patients with septic shock who received infusions of hydrocortisone had no significant improvement in 28-day or 90-day mortality rates compared with those who received placebo (90-day mortality of 27.9% in the hydrocortisone group vs 28.8% for placebo). Those who received hydrocortisone did experience faster resolution of shock (median 3 vs 4 days) and were less likely to need a blood transfusion (37.0% vs 41.7%) but there were no significant differences in length of ICU stay or need for renal replacement therapy.[160]

Other more novel therapies include bathing patients with chlorhexidine washes, which may decrease the rate of hospital-acquired infections,[161] and antioxidants such as acetylcysteine. These agents have been used as an adjuvant therapy in sepsis with the aim of decreasing the levels of reactive oxygen species. However, they have been found to be ineffective and their use is not currently recommended.[162]

**Standard ICU supportive care**

All patients with sepsis should be considered for admission to the high dependency unit or ICU.[58] [143]

General intensive care measures include stress ulcer prophylaxis with histamine H2 receptor antagonists or proton pump inhibitors (in patients at risk of GI bleeding), DVT prophylaxis (with heparin and compression stockings), enteral or parenteral nutrition, and glycaemic control.[84] [102] [163]

Transfusion of packed cells may be required. Despite studies of early goal-directed therapy transfusing to a target haemoglobin concentration of >100 g/L (10 g/dL), it is recommended that a lower threshold of 70 g/L (7 g/dL) be used.[84] Reasons for this include resource usage and a number of studies in the general critical care population showing no improvement with a higher haemoglobin threshold compared with a lower haemoglobin threshold.[142] and potential harm associated with liberal transfusion.[164] A higher haemoglobin level may be necessary in certain circumstances (myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis).[84] In the initial resuscitative phase, particularly with the application of early goal-directed therapy, a higher haematocrit of ≥30% may be appropriate.[58]

Patients requiring prolonged ventilatory support should receive lung-protective ventilation using minimal peak inspiratory pressures (<30 cmH2O) and permissive hypercapnia to specifically limit pulmonary compromise.[165] FiO2 should be titrated to lowest effective levels to prevent oxygen toxicity and maintain
central venous oxygen tension. Patients should be placed in a semi-recumbent position with the head elevated to 30° to 45°.[84]

[VIDEO: Tracheal intubation animated demonstration ]

### Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

<table>
<thead>
<tr>
<th>Acute</th>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
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<tbody>
<tr>
<td></td>
<td>presumed or confirmed sepsis</td>
<td>1st</td>
<td>antibiotics</td>
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<tr>
<td></td>
<td></td>
<td>plus</td>
<td>fluid resuscitation</td>
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<td></td>
<td></td>
<td>adjunct</td>
<td>standard supportive ICU care</td>
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<td></td>
<td></td>
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<td>vasopressors</td>
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<td>dobutamine</td>
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<td>adjunct</td>
<td>corticosteroids</td>
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<td></td>
<td>likely source of infection: pneumonia, without risk factors for multiple drug-resistant pathogens or MRSA</td>
<td>plus</td>
<td>broad-spectrum respiratory pathogen cover to include atypicals</td>
</tr>
<tr>
<td></td>
<td>likely source of infection: pneumonia, with risk factors for multiple drug-resistant pathogens</td>
<td>plus</td>
<td>broad-spectrum cover of respiratory pathogens to include multiple drug-resistant pathogens (MDRPs)</td>
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<td>antibiotic coverage for MRSA</td>
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<td>antipseudomonal quinolone</td>
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<tr>
<td></td>
<td>likely source of infection: UTI</td>
<td>plus</td>
<td>broad-spectrum cover for predominant gram-negative coliforms and Pseudomonas</td>
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<tr>
<td></td>
<td>likely source of infection: intra-abdominal</td>
<td>plus</td>
<td>broad-spectrum cover for gram-positive and gram-negative organisms, including anaerobes</td>
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<td></td>
<td>likely source of infection: intra-abdominal</td>
<td>adjunct</td>
<td>azole or echinocandin</td>
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### Acute

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Soft-tissue or joint infection (not necrotising fasciitis), MRSA not suspected</td>
<td>plus</td>
</tr>
<tr>
<td>Soft-tissue or joint infection (not necrotising fasciitis), MRSA suspected</td>
<td>plus</td>
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<tr>
<td>Necrotising fasciitis suspected</td>
<td>plus</td>
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<td>CNS</td>
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<td>adjunct</td>
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Sepsis in adults

Treatment

Treatment options

<table>
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<th>antibiotics</th>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>» Once culture and sensitivity results are known, antibiotics should be narrowed if it is possible to do so. [84]</td>
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<tr>
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<td></td>
<td>» When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered. [53] [109]</td>
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<tr>
<td>plus</td>
<td>fluid resuscitation</td>
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Acute Treatment

Patient group | Tx line | Treatment
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Recommended if the patient has a lactate >2 mmol/L (>18 mg/dL) and at least two moderate to high risk criteria, or evidence of acute kidney injury. Crystalloid can be considered in patients with a lactate <2 mmol/L (<18 mg/dL) if they have at least one high risk criterion.

- Solutions containing starch may be harmful and should be avoided. Evidence has shown that solutions containing hydroxyethyl starch (HES) are associated with a greater risk of renal dysfunction and adverse outcome. HES solutions for infusion have been suspended from the market across the European Union owing to patient safety concerns related to the increased risk of kidney injury and death in certain patient groups, including critically ill patients and those with sepsis. The market suspension followed a January 2018 review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee that found HES solutions were still being used in these patient groups despite restrictions introduced in 2013.

- Red cell or plasma transfusion may be considered to target specific deficiencies but should not be used for volume augmentation. Aggressive red cell transfusion has not been shown to improve outcomes.

- Normal saline and albumin should be given according to local protocols. Current evidence suggests that resuscitation using albumin-containing solutions is safe, but evidence of its efficacy is insufficient to recommend its use over crystalloids.

- Patients should be monitored closely for signs of fluid overload (e.g., pulmonary or systemic oedema).

adjunct standard supportive ICU care

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Sepsis in adults

### Treatment

<table>
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<tr>
<th>Acute Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>glucose goal of 7.8 to 10.0 mmol/L (140-180 mg/dL) in critically ill diabetic patients, preferably with use of an insulin infusion protocol.[149] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of &lt;10 mmol/L (180 mg/dL).[84]</td>
</tr>
</tbody>
</table>

- Transfusion of packed cells may be required. Despite studies of early goal-directed therapy transfusing to a target haemoglobin concentration of >100 g/L (>10 g/dL), it is recommended that a lower threshold of 70 g/L (7 g/dL) be used.[84] Reasons for this include resource usage and a number of studies in the general critical care population showing no improvement with a higher haemoglobin threshold compared with a lower haemoglobin threshold,[142] and potential harm associated with liberal transfusion.[164] A higher haemoglobin level may be necessary in certain circumstances (myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis).[84] In the initial resuscitative phase, particularly with the application of early goal-directed therapy, a higher haematocrit of ≥30% may be appropriate.[58]

- Patients requiring prolonged ventilatory support should receive lung protective ventilation using minimal peak inspiratory pressures (<30 cmH2O) to specifically limit pulmonary compromise.[165] FiO2 should be titrated to lowest effective levels to prevent oxygen toxicity and maintain central venous oxygen tension. Patients should be placed in a semi-recumbent position with the head elevated to 30° to 45°.[84]

**adjunct vasopressors**

- Patients unresponsive to fluid resuscitation may be treated with vasopressors. Patients requiring vasoactive support (those with septic shock) are identified by a systolic BP <90 mmHg, mean arterial pressure (MAP) <65 mmHg, or lactate ≥4 mmol/L (≥36 mg/dL), persisting after adequate fluid resuscitation.[84]

- MAP should be maintained between 65 and 90 mmHg.

- Noradrenaline (norepinephrine) administered via a central venous catheter is the drug of choice as it increases MAP. Vasopressin or
## Acute

### Patient group

### Tx line

### Treatment

Adrenaline can be added to noradrenaline to achieve the target MAP (≥65 mmHg).[84]

» Dopamine is an option, but should only be given to highly selected patients as it has been associated with higher mortality than noradrenaline.[84] [151] [152]

» The use of low-dose dopamine for renal protection is not recommended.[84]

#### Primary options

- noradrenaline (norepinephrine): 0.02 to 0.5 micrograms/kg/minute intravenously initially, titrate to effect, maximum 30 micrograms/minute

OR

#### Primary options

- noradrenaline (norepinephrine): 0.02 to 0.5 micrograms/kg/minute intravenously initially, titrate to effect, maximum 30 micrograms/minute

- AND-

- vasopressin: 0.01 to 0.03 units/minute intravenously initially, titrate to effect

- OR

- adrenaline (epinephrine): 0.05 to 2 micrograms/kg/minute intravenously initially, titrate to effect

#### Secondary options

- dopamine: 5-20 micrograms/kg/minute intravenously, titrate to effect

#### Adjunct

- dobutamine

- Dobutamine is the first choice inotrope for patients with low cardiac output and adequate left ventricular filling pressure (or adequate fluid administration) and adequate mean arterial pressure (MAP).[84] [143]

#### Primary options

- dobutamine: 0.5 to 1 microgram/kg/minute intravenously initially, followed by 2-20 micrograms/kg/minute

#### Adjunct

corticosteroids
### Treatment

**Sepsis in adults**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Treatment</strong></td>
</tr>
</tbody>
</table>
| | » Current guidelines recommend that low-dose corticosteroids are given only to patients whose BP is poorly responsive to both fluid resuscitation and vasopressor therapy.[84] Fludrocortisone may or may not be added to hydrocortisone therapy. However, current evidence for giving corticosteroids to patients with sepsis or septic shock is mixed.[153][154][155][156][157][158][159] In a large randomised controlled trial published in January 2018, patients with septic shock who received infusions of hydrocortisone had no significant improvement in 28-day or 90-day mortality rates compared with those who received placebo (90-day mortality of 27.9% in the hydrocortisone group vs 28.8% for placebo).[160]  

**Primary options** |
| » hydrocortisone: 50 mg intravenously every 6 hours |
| OR |
| **Primary options** |
| » hydrocortisone: 50 mg intravenously every 6 hours |
| » fludrocortisone: 0.05 mg orally daily |

**likely source of infection: pneumonia, without risk factors for multiple drug-resistant pathogens or MRSA**

plus **broad-spectrum respiratory pathogen cover to include atypicals**

» Monotherapy appears as effective as combination therapy in community-acquired pneumonia, although some units prefer combination therapy in patients with severe pneumonia requiring critical care admission.[115]

» For patients with suspected pneumonia, risk factors for the presence of multiple drug-resistant pathogens (MDRPs) and for methicillin-resistant *Staphylococcus aureus* (MRSA) will affect choice of antimicrobial agents, and should be evaluated. Risk factors include hospitalisation for >48 hours (including residence in nursing home), or systemic antibiotic use within the previous 90 days.

» When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.[53] Antibiotics listed are suggested as guidance only. Local or national policy, which
### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
</tr>
</tbody>
</table>

#### Primary options

**no penicillin allergy**

- **cefotaxime**: 1-2 g intravenously every 8 hours
- **amoxicillin/clavulanate**: 1.2 g intravenously every 8 hours
  
  Dose consists of 1 g amoxicillin plus 0.2 mg clavulanate.

--- **AND** ---

- **azithromycin**: 500 mg intravenously every 24 hours
- **clarithromycin**: 500 mg intravenously every 12 hours

**OR**

#### Secondary options

**penicillin allergy**

- **moxifloxacin**: 400 mg intravenously every 24 hours

**OR**

#### Secondary options

**penicillin allergy**

- **levofloxacin**: 500 mg intravenously every 12 hours

**OR**

#### Secondary options

**penicillin allergy**

- **doxycycline**: 100 mg intravenously every 12 hours

--- **likely source of infection: pneumonia, with risk factors for multiple drug-resistant pathogens**

**plus**

**broad-spectrum cover of respiratory pathogens to include multiple drug-resistant pathogens (MDRPs)**

- For patients with suspected pneumonia, risk factors for the presence of MDRPs will affect choice of antimicrobial agents, and should be evaluated. Risk factors include hospitalisation for >48 hours (including residence in nursing home), or systemic antibiotic use within the previous 90 days.
### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>» When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.[53] Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Tigecycline is an alternative for patients with penicillin allergy; however, monotherapy with this drug should be used with caution as it may be associated with an increased risk of mortality. Expert advice should be sought before using tigecycline.[120]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td>no penicillin allergy</td>
<td></td>
<td>- imipenem/cilastatin: 1 g intravenously every 8 hours &lt;br&gt;Dose refers to imipenem component. &lt;br&gt;-or- &lt;br&gt;» piperacillin/tazobactam: 4.5 g intravenously every 8 hours &lt;br&gt;Dose consists of 4 g piperacillin plus 0.5 g tazobactam. &lt;br&gt;--AND--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» gentamicin: 5 mg/kg intravenously every 24 hours</td>
</tr>
<tr>
<td>penicillin allergy</td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>antibiotic coverage for MRSA</td>
<td></td>
<td>Secondary options</td>
</tr>
<tr>
<td>likely source of infection: pneumonia, with risk factors for multiple drug-resistant pathogens</td>
<td></td>
<td>- tigecycline: 100 mg intravenously initially, followed by 50 mg every 12 hours</td>
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<tr>
<td></td>
<td></td>
<td>OR</td>
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<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- vancomycin: 1 g intravenously every 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
</tbody>
</table>

**Primary options**

**no penicillin allergy**

- imipenem/cilastatin: 1 g intravenously every 8 hours  
  Dose refers to imipenem component.  
- or-  
- piperacillin/tazobactam: 4.5 g intravenously every 8 hours  
  Dose consists of 4 g piperacillin plus 0.5 g tazobactam.  
--AND--  
- gentamicin: 5 mg/kg intravenously every 24 hours  

**Secondary options**

**penicillin allergy**

- tigecycline: 100 mg intravenously initially, followed by 50 mg every 12 hours  

**antibiotic coverage for MRSA**

- Patients presenting with particularly severe community-acquired pneumonia, especially if there is a history of haemoptysis, and patients with recent hospitalisation or history of MRSA infection should receive additional coverage for MRSA.[118]  
- Vancomycin levels need to be monitored.  

**Primary options**

- vancomycin: 1 g intravenously every 12 hours  

OR
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>likely source of infection: pneumonia, with risk factors for multiple drug-resistant pathogens</td>
<td>adjunct antipseudomonal quinolone</td>
<td>Patients with bronchiectasis, those who take systemic corticosteroids, or those who are malnourished are at risk of infection with <em>Pseudomonas aeruginosa</em> and should be additionally treated with an antipseudomonal quinolone. [168]</td>
</tr>
<tr>
<td>likely source of infection: UTI</td>
<td>plus broad-spectrum cover for predominant gram-negative coliforms and <em>Pseudomonas</em></td>
<td>If urinary stasis is present, drainage is of immediate importance. When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient’s immune status need to be considered. [53] Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
</tr>
</tbody>
</table>

**Primary options**

- linezolid: 600 mg intravenously every 12 hours

**Secondary options**

- ciprofloxacin: 400 mg intravenously every 8-12 hours

**Primary options**

- ampicillin: 1-2 g intravenously every 6 hours
- or-
- cefotaxime: 1-2 g intravenously every 8 hours
- or-
- amoxicillin/clavulanate: 1.2 g intravenously every 8 hours
  Dose consists of 1 g amoxicillin plus 0.2 mg clavulanate.

- OR-
- gentamicin: 5 mg/kg intravenously every 24 hours

**Secondary options**

penicillin allergy
## Treatment

### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>likely source of infection: intra-abdominal</td>
<td>plus</td>
<td>broad-spectrum cover for gram-positive and gram-negative organisms, including anaerobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control and drainage of an intra-abdominal source of infection is of immediate importance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered. Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
</tr>
</tbody>
</table>

#### Primary options

**no penicillin allergy**

- amoxicillin: 1 g intravenously every 6 hours
- cefotaxime: 1-2 g intravenously every 8 hours
- **AND**
  - metronidazole: 500 mg intravenously every 8 hours
- **AND**
  - gentamicin: 5 mg/kg intravenously every 24 hours

OR

#### Primary options

**no penicillin allergy**

- piperacillin/tazobactam: 4.5 g intravenously every 8 hours
  - Dose consists of 4 g piperacillin plus 0.5 g tazobactam.
  - **AND**
    - gentamicin: 5 mg/kg intravenously every 24 hours

OR

#### Secondary options

**penicillin allergy**

- tigecycline: 100 mg intravenously initially, followed by 50 mg every 12 hours
  - **AND**
## Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>adjunct</td>
<td>azole or echinocandin</td>
</tr>
<tr>
<td>likely source of infection: intra-abdominal</td>
<td></td>
<td>Patients with recurrent perforation of the large intestine are at increased risk of invasive fungaemia. An azole, such as fluconazole, or an echinocandin, such as micafungin, should be added to the antibacterial cover. Non-albicans species of <em>Candida</em> are increasingly resistant to azoles. [41] [42] [121]</td>
</tr>
<tr>
<td>Primary options</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluconazole: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td>micafungin: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>likely source of infection: soft-tissue or joint infection (not necrotising fasciitis), MRSA not suspected</td>
<td>plus</td>
<td>broad-spectrum gram-positive and gram-negative cover, including anaerobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered. [53] Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Metronidazole should be considered as empirical therapy if anaerobic infection is suspected.</td>
</tr>
<tr>
<td>Primary options</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no penicillin allergy</td>
<td></td>
<td>flucloxacillin: 2 g intravenously every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nafcillin: 1-2 g intravenously every 4-6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>metronidazole: 500 mg intravenously every 8 hours</td>
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<tr>
<td>OR</td>
<td></td>
<td>Secondary options</td>
</tr>
<tr>
<td>penicillin allergy</td>
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</table>
**Acute**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>likely source of infection: soft-tissue or joint infection (not necrotising fasciitis), MRSA suspected</td>
<td>OR</td>
<td>clindamycin: 300-600 mg intravenously every 6 hours</td>
</tr>
<tr>
<td></td>
<td>Secondary options</td>
<td>penicillin allergy</td>
</tr>
<tr>
<td></td>
<td>tigecycline: 100 mg intravenously initially, followed by 50 mg every 12 hours</td>
<td>and-</td>
</tr>
<tr>
<td></td>
<td>metronidazole: 500 mg intravenously every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>broad-spectrum cover to include MRSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.</td>
<td>and-</td>
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<tr>
<td></td>
<td>Antibiotics listed are suggested as guidance only.</td>
<td>Mineral ions</td>
</tr>
<tr>
<td></td>
<td>Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In cases of suspected MRSA-associated soft-tissue or joint infections, vancomycin or linezolid is typically added to the antibiotic therapy.</td>
<td>Mineral ions</td>
</tr>
<tr>
<td>likely source of infection: necrotising fasciitis suspected</td>
<td>Primary options</td>
<td>vancomycin: 1 g intravenously every 12 hours</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>linezolid: 600 mg intravenously every 12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>broad-spectrum cover to include group A Streptococci and gram-negative organisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If necrotising fasciitis is suspected, surgical control and debridement is of immediate importance.</td>
<td>and-</td>
</tr>
<tr>
<td></td>
<td>Once culture and sensitivity results are known, antibiotics should be adjusted if required; 90% of cases are polymicrobial.</td>
<td>and-</td>
</tr>
<tr>
<td></td>
<td>When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.</td>
<td>and-</td>
</tr>
<tr>
<td></td>
<td>Antibiotics listed are suggested as guidance only.</td>
<td>Local or national policy, which</td>
</tr>
</tbody>
</table>
Sepsis in adults

Treatment

<table>
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<tr>
<th>Acute</th>
<th>Tx line</th>
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<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Tx line</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>no penicillin allergy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» flucloucillin: 2 g intravenously every 6 hours</td>
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<td></td>
<td></td>
<td>-or-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» nafcillin: 1-2 g intravenously every 6 hours</td>
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<td></td>
<td>--AND--</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» clindamycin: 300-600 mg intravenously every 6 hours</td>
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<tr>
<td></td>
<td>OR</td>
<td><strong>Secondary options</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>penicillin allergy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» tigecycline: 100 mg intravenously initially, followed by 50 mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-and-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» clindamycin: 300-600 mg intravenously every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>likely source of infection:</strong> CNS plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>broad-spectrum cover to include Neisseria meningitidis, Streptococcus pneumoniae, and other common gram-positive causative agents</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Suspected meningitis or meningococcal septicaemia should be treated immediately using a third-generation cephalosporin, such as ceftriaxone or cefotaxime. For patients with penicillin allergy, vancomycin with chloramphenicol is a suitable alternative. Some suggest the addition of rifampicin to either regimen to aid penetration.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» When choosing empirical therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.[53] Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>no penicillin allergy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» ceftriaxone: 2 g intravenously every 12 hours</td>
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<td></td>
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<td><strong>OR</strong></td>
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</tbody>
</table>
### Acute Sepsis in Adults

**Patient group** | **Tx line** | **Treatment**
--- | --- | ---
**Primary options**

- **no penicillin allergy**
  - cefotaxime: 2 g intravenously every 6 hours

**Secondary options**

- **penicillin allergy**
  - vancomycin: 1 g intravenously every 12 hours
  - chloramphenicol: 1 g intravenously every 6 hours

**likely source of infection:** CNS

- **adjunct** rifampicin
  - Some experts suggest the addition of rifampicin to the standard antibiotic regimen to aid penetration.

  **Primary options**
  - rifampicin: 600 mg intravenously every 24 hours

**likely source of infection:** CNS

- **adjunct** antibiotic cover for *Listeria*
  - For patients over 50 years and those with history of alcoholism or other debilitating illness, or at increased risk of infection with *Listeria*, cephalosporins alone provide inadequate cover. Ampicillin should be added to the regimen, provided the patient is not allergic to penicillin. For those allergic to penicillin, erythromycin or trimethoprim/sulfamethoxazole can be substituted.

  **Primary options**
  - **no penicillin allergy**
    - ampicillin: 2 g intravenously every 6 hours

  **Secondary options**
  - penicillin allergy
    - erythromycin: 1 g intravenously every 6 hours

  **Secondary options**
  - penicillin allergy
### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>likely source of infection:</td>
<td>adjunct</td>
<td><strong>antiviral cover for HSV</strong></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td>» For patients in whom HSV encephalitis is suspected (symptoms of confusion, seizure or with CSF findings consistent with viral meningitis), empirical coverage with acyclovir is recommended.</td>
</tr>
<tr>
<td>sepsis of unknown source or where source is unclear, MRSA not suspected</td>
<td>plus</td>
<td><strong>primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>aciclovir</strong>: 5-10 mg/kg intravenously every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose refers to aciclovir component.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>imipenem/cilastatin</strong>: 1 g intravenously every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose refers to imipenem component.</td>
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<td><strong>or</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>meropenem</strong>: 1 g intravenously every 8 hours</td>
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<td></td>
<td></td>
<td><strong>or</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» <strong>piperacillin/tazobactam</strong>: 4.5 g intravenously every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose consists of 4 g piperacillin plus 0.5 g tazobactam.</td>
</tr>
</tbody>
</table>
Sepsis in adults

### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>sepsis of unknown source or where source is unclear, MRSA suspected</td>
<td>plus</td>
<td>broad-spectrum cover to include MRSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Intensive efforts, including imaging, should be undertaken to attempt to evaluate the source of infection. Urgent broad-spectrum coverage to include all common pathogens should be administered.</td>
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<td>» When choosing empiric therapy, the suspected source of infection or causative organism, local resistance patterns, and the patient's immune status need to be considered.[53] Antibiotics listed are suggested as guidance only. Local or national policy, which may take into account specialist knowledge of sensitivity patterns, should be sought and adhered to when possible. Vancomycin is used if MRSA is suspected.</td>
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### Primary options

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<tbody>
<tr>
<td></td>
<td>» vancomycin: 1 g intravenously every 12 hours</td>
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<td></td>
<td>--AND--</td>
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<tr>
<td></td>
<td>» imipenem/cilastatin: 1 g intravenously every 8 hours</td>
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<td></td>
<td>Dose refers to imipenem component.</td>
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<td>-or-</td>
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<tr>
<td></td>
<td>» meropenem: 1 g intravenously every 8 hours</td>
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**Recommendations**

### Monitoring

Standard monitoring of vital signs, pulse oximetry, ECG, regular laboratory tests, and urinary output by catheterisation are routinely performed. All patients receiving vasopressors should have an arterial catheter inserted as soon as it is practical to do so, to aid more accurate monitoring of arterial blood pressure.[84]

Patients with evidence of circulatory dysfunction or shock should be managed in a critical care or higher dependency area. Central venous catheters will be required to ensure reliable delivery of vasoactive medication. The principles of Early Goal-Directed Therapy[58] remain relevant in ongoing care for patients with shock.

Central venous pressure (CVP) may be used in combination with clinical assessment and other monitoring modalities to guide ongoing fluid resuscitation. Additional monitoring techniques include the use of stroke volume variability (an index of change in stroke volume with each contraction), cardiac ejection time (corrected for heart rate) and changes in inferior vena cava (IVC) diameter during respiration (visualised using bedside ultrasound).[144] [145] Mechanical ventilation can alter cardiac filling pressures and affect measurement. CVP values must be corrected with increasing levels of positive end-expiratory pressure (PEEP) or haemodynamic parameters.[58] [179] In the spontaneously breathing patient, a collapsed or collapsing IVC suggest that cardiac output will improve with additional fluid resuscitation. In the mechanically ventilated patient, if IVC size increases by >18% (or visible to the naked eye) with positive pressure ventilation, fluid responsiveness is expected. One systematic review has shown passive leg raising to be an accurate predictor of fluid responsiveness in ventilated patients, regardless of ventilator mode or technique, and with flow variables (e.g., cardiac output) having greater accuracy compared with pulse pressure.[146]

Central venous catheters may also be used to sample central venous oxygen saturation (ScvO2), which gives a global indication of the balance between tissue oxygen demand and supply. If ScvO2 is low (<70%), it is likely that oxygen delivery is inadequate and the need for blood transfusion (to increase oxygen carrying capacity) or inotropes (to increase cardiac output) should be assessed. Other measures of the adequacy of oxygen delivery are increasingly used, including the use of lactate clearance rate over the first 6 hours. Lactate clearance has been shown to correlate positively with survival.[79]

The use of pulmonary artery catheters may be an advantage in selected patients with suspected cardiac compromise or complicated presentations. It is not considered to be essential as a first-line routine monitor, and its use in clinical practice has been largely superseded by less invasive cardiac output monitoring modalities, including oesophageal Doppler, arterial pulse contour analysis, and thermodilution/indicator dilution techniques.

### Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>renal dysfunction</td>
<td>short term</td>
<td>high</td>
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</table>

Transient oliguria is common and is related to hypotension. Rarely, anuria occurs.[173] Acute kidney injury is relatively common but is rarely associated with histological change or with any need for long-term renal replacement therapy.

Correction of volume depletion and hypotension generally reverses oliguria.[173]
Sepsis in adults

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypotension</td>
<td>short term</td>
<td>high</td>
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Volume depletion is caused by reduced oral intake, increased venous capacitance, increased fluid losses due to pyrexia, capillary leakage leading to oedema, tachypnoea, diarrhoea, and possibly bleeding. Persistent hypotension is often due to a combination of low systemic vascular resistance, hypovolaemia and reductions in cardiac output from myocardial failure, excessive PEEP, or acidosis.

Fluid resuscitation is given with either colloids or crystalloids, and early central venous pressure (CVP) monitoring is indicated if rapid response is not achieved. Vasopressors can be started for persistent hypotension or inotropes for myocardial failure. Caution is required to prevent tachyarrhythmia.

ARDS | short term | medium

ARDS may resolve completely or can progress to fibrosing alveolitis with persistent hypoxaemia.[172]

Intubation and ventilation reduce respiratory muscle oxygen demand and the risk of aspiration and cerebral anoxia.[173] Lung protective ventilation (low tidal volumes) should be used.[4] Tidal volumes should be reduced over 1 to 2 hours to a target of 6 mL/kg of predicted body weight. Minimum positive end-expiratory pressure (PEEP) is recommended to prevent lung collapse at end expiration.[84]

Myocardial dysfunction and failure | short term | medium

Myocardial dysfunction with biventricular dilatation is a recognised complication of sepsis, but is usually transient and not commonly severe. Death from myocardial failure is rare.[143] Circulating myocardial depressant factors are thought responsible.

After adequate filling pressures have been achieved, inotropic agents should be considered to maintain an adequate cardiac index, mean arterial pressure (MAP), mixed venous oxygen saturation, and urine output.

Clinicians should define specific goals and desired endpoints of inotropic therapy in patients with sepsis and titrate therapy to those end points. These end points should be refined at frequent intervals as patient's clinical status changes.[143]

Multiple organ system failure | short term | medium

The inflammatory response in sepsis causes widespread tissue injury. Multi-organ dysfunction may be partly caused by apoptosis of immune, epithelial, and endothelial cells and a shift to an anti-inflammatory phenotype, compounded by impaired organ perfusion due to hypotension, low cardiac output states, circulatory microthrombi, a disordered microcirculation, and tissue oedema.[4]

Failure of each additional organ increases the average risk of death by 15% to 20%. Lung dysfunction tends to occur early and persists. Serious CNS dysfunction or liver function often occur hours to days after sepsis onset and persists for variable periods of time. Most organ failures resolve within a month in surviving patients.[173]

Treatment of multi-organ failure in sepsis is primarily supportive. It includes effective antibiotic therapy, goal-directed therapy (to reverse hypotension, anaemia, coagulopathy, bleeding, and shock), and standard supportive ICU care. This may include dialysis, ventilatory support, and sedation.

Hepatic encephalopathy | short term | low
**Complications**

<table>
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<th>Neurological sequelaes</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tr>
<td>Rarely, liver dysfunction may lead to hepatic encephalopathy. Hepatic encephalopathy results primarily from nitrogen absorption from the gut bypassing effective hepatic clearance, resulting in electrolyte abnormalities. The mainstay of therapy includes laxatives to empty the bowel, prevention of GI bleeding, and avoidance of nitrogen intake and sedative drugs, which further suppress consciousness.</td>
<td>long term</td>
<td>medium</td>
</tr>
<tr>
<td>DIC</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Occurs in sepsis when leukocytes and endothelial cells are activated or injured by toxic substances released during infection or shock. The injured cells generate tissue factor on the cell surface, activating the coagulation cascade. In acute DIC, an explosive generation of thrombin depletes clotting factors and platelets. This activates the fibrinolytic system. DIC leads to bleeding into the subcutaneous tissues, skin, and mucous membranes occurs, along with occlusion of blood vessels caused by fibrin in the microcirculation. Treatment of the underlying disease is the mainstay of management of either acute or chronic DIC, with blood products to control bleeding.</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>death</td>
<td>variable</td>
<td>high</td>
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<tr>
<td>The exact cause of death in sepsis is multi-factorial, exhibiting great individual variability. Death from septic shock typically occurs due to multi-organ failure, unresponsiveness to treatments, or secondary infection. Predictors of death include vasopressor use, development of ARDS, failure to improve with early critical care therapy, and severity of underlying illness. Patients with sepsis have an increased mortality risk for at least 1 year after the septic episode. Administration of early effective antibiotic therapy and fluid challenges are paramount to reduce mortality.</td>
<td>variable</td>
<td>high</td>
</tr>
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</table>

**Prognosis**

The prognosis in patients with sepsis and septic shock is guarded at best. The mortality rate from sepsis has been estimated in a number of studies to be between 28% and 50%. More recently, the SOAP...
study in Europe observed an overall hospital mortality of 36%,[35] and the Surviving Sepsis Campaign
reported mortality by the end of an improvement project to be 31%.[10]

ICU-specific mortality has been shown to be 27% to 32% in patients with sepsis, and 50% to 70% in patients
with septic shock, compared with 14% in ICU patients without sepsis.[4] [114]

Multi-organ compromise is common in advanced sepsis with variable residual morbidity.[4] [8]
## Diagnostic guidelines

### Europe

**Sepsis: recognition, diagnosis and early management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2016

**Sepsis - a clinical toolkit for emergency departments**

*Published by:* College of Emergency Medicine  
*Last published:* 2014

### Latin America

**Guidelines for the treatment of severe sepsis and septic shock: management of the infectious agent - diagnosis**

*Published by:* Brazilian Medical Association  
*Last published:* 2010

### Oceania

**Sepsis toolkit**

*Published by:* Clinical Excellence Commission  
*Last published:* 2014

## Treatment guidelines

### Europe

**Sepsis: recognition, diagnosis and early management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2016

**Sepsis - a clinical toolkit for emergency departments**

*Published by:* College of Emergency Medicine  
*Last published:* 2014

**British consensus guidelines on intravenous fluid therapy for adult surgical patients**

*Published by:* British Association for Parenteral and Enteral Nutrition; Association for Clinical Biochemistry; Association of Surgeons of Great Britain and Ireland; Society of Academic and Research Surgery; Renal Association; Intensive Care Society  
*Last published:* 2011


*Published by:* French Intensive Care Societies  
*Last published:* 2006
### International

**Surviving sepsis campaign guidelines for management of sepsis and septic shock - 2016**  
*Published by:* International Surviving Sepsis Campaign Guidelines  
*Last published:* 2016

### North America

**Standards of medical care in diabetes - 2017**  
*Published by:* American Diabetes Association  
*Last published:* 2017

**Management of patients with infections caused by methicillin-resistant Staphylococcus aureus**  
*Published by:* Infectious Diseases Society of America  
*Last published:* 2011

**Severe sepsis and septic shock: review of the literature and emergency department management guidelines**  
*Published by:* Emergency Department Sepsis Education Program and Strategies to Improve Survival (ED-SEPSIS) Working Group  
*Last published:* 2006
Online resources

1. Surviving Sepsis Campaign: evaluation for severe sepsis screening tool (external link)
Key articles


References


111. Gaiieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010;38:1045–1053. Abstract


Sepsis in adults


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<th>Title</th>
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Figure 1: Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) criteria

Figure 2: Severe purpura fulminans, most commonly associated with pneumococcal septicaemia

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission
Figure 3: Capillary refill time. Top image: normal skin tone; middle image: pressure applied for 5 seconds; bottom image: time to hyperaemia measured

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