Sepsis in adults

Straight to the point of care
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Summary

Suspect sepsis based on acute deterioration in a patient in whom there is clinical evidence or strong suspicion of infection. Have a low threshold for suspicion.

Think ‘Could this be sepsis?’ whenever an acutely unwell person presents with likely infection, even if their temperature is normal. Remember that sepsis represents the severe, life-threatening end of infection.

The key to improving outcomes is early recognition and prompt treatment, as appropriate, of patients with suspected or confirmed infection who are deteriorating and at risk of organ dysfunction. By the time the diagnosis becomes obvious, with multiple abnormal physiological parameters, risk of mortality is very high.

Your clinical judgement is crucial to how you approach the individual patient. Be aware that signs and symptoms are extremely variable and often non-specific.

Assess acute deterioration using your clinical judgement alongside a validated scoring system, such as the National Early Warning Score 2 (NEWS2); consult local guidelines for the recommended scoring system at your institution. Arrange urgent assessment by a senior clinical decision-maker for any patient with an aggregate NEWS2 score of 5 or more.

Within 1 hour of the risk being recognised: take two sets of blood cultures, measure serum lactate on a blood gas, and assess the patient’s hourly urine output.

Within 1 hour of the risk being recognised: give intravenous broad-spectrum antibiotics (after taking blood cultures), if there is evidence of a bacterial infection; intravenous fluids, if there is any sign of circulatory insufficiency; and oxygen, if needed.

Ensure any patient with suspected sepsis has frequent and ongoing monitoring (e.g., using an early warning score such as NEWS2).

Definition

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] This recommended that organ dysfunction should be defined using the Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) criteria or the ‘quick’ (q)SOFA criteria.

The 2016 consensus definitions marked a shift away from the previous systemic inflammatory response syndrome (SIRS) definition, which classified sepsis as two or more of the following in the context of infection: temperature >38.3°C (101°F) or <36.0°C (96.8°F); tachycardia >90 beats per minute; tachypnoea >20 breaths/minute or arterial carbon dioxide level (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 (white blood cell [WBC] count >12×10⁹/L [12,000/microlitre]); leukopenia (WBC count <4×10⁹/L [4000/microlitre]); or a normal WBC count with >10% immature forms.[2]

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.[2]
However, the 2016 Third International Consensus Group (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 there is co-existence of: persistent hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg; and serum lactate >2 mmol/L (>18 mg/dL).\[1\]

Septic shock indicates profound circulatory, cellular, and metabolic deterioration, and is associated with a greater risk of mortality than with sepsis alone.\[1\]
Epidemiology

There are a lack of reliable sepsis incidence and prevalence data. This is due to the absence of a consistent definition for sepsis and differences in coding practice between professionals and organisations.[4] [5]

In 2017/18, 186,000 hospital admissions in the UK were for people with a primary diagnosis of sepsis.[6]

Sepsis is present in many hospitalisations that culminate in death. In 2015, 23,135 people in the UK died from sepsis, where sepsis was an underlying or contributory cause of death. [NHS England: Sepsis] The true contribution of sepsis to these deaths is unknown. Most underlying causes of death in people with sepsis are thought to relate to severe chronic comorbidities and frailty.[5] [7] [8]

Most epidemiological studies find sepsis to be more common in men than in women. People over 65 years old are particularly susceptible, with one study finding almost two-thirds of people with sepsis to be in this age group.[9]

Risk factors

Strong

age >65 years

Associated with an increased risk of sepsis (relative risk 7.0, 95% CI 5.6 to 8.7).[36]

Risk of sepsis is particularly high in people aged >75 years or those who are frail.[3]

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).[3] [37]

indwelling lines or catheters

Risk of sepsis is high in people with indwelling lines or catheters.[3]

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.[3]

Risk of sepsis is particularly high following oesophageal, pancreatic, or elective gastric surgery.[38]

haemodialysis

Associated with an increased risk of sepsis (relative risk 208.7, 95% CI 142.9 to 296.3).[36]

diabetes mellitus

Decreased resistance to infections, complications of diabetes, and increased surgical complications play a role (relative risk 5.9, 95% CI 4.4 to 7.8).[36]
intravenous drug misuse
Risk of sepsis is high in people who misuse drugs intravenously.[3]

alcohol dependency
Associated with an increased risk of sepsis (relative risk 5.6, 95% CI 3.8 to 8.0).[36]

pregnancy
Pregnancy or recent pregnancy is a risk factor for the development of sepsis.[3] In the UK, the estimated incidence of sepsis in pregnancy has been reported to be 47 cases per 100,000 maternities per year,[39] 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.[9]

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.[3]

breached skin integrity
Risk of sepsis is high in people with any breach of skin integrity (e.g., cuts, burns, blisters, or skin infection).[3]

Weak
urban residence
May predispose to increased exposure to infections and drug-resistant pathogens (relative risk 2.4, 95% CI 1.2 to 5.6).[36]

lung disease
Weakly associated with sepsis (relative risk 3.8, 95% CI 2.6 to 5.4).[36]

male sex
May be at greater risk (odds ratio 1.28, 95% CI 1.24 to 1.32).[40]

non-white ancestry
May be at increased risk (odds ratio 1.90, 95% CI 1.80 to 2.00).[40]

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.[16]

Aetiology
Causative agents vary significantly, depending on several factors including the region, hospital size, season, and type of unit (neonatal, transplantation, oncology, or haemodialysis; if acquired in hospital).[10] [11] [12] [13] [14] [15] [16] [17] [18] [19]

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The Extended Prevalence of Infection in Intensive Care (EPIC II) study provides the best recent evidence on the infectious causes of sepsis in an intensive care setting.[20] The prospective study gathered extensive data from more than 14,000 adult patients in 1265 intensive care units from 75 countries on a single day in May 2007. Of the 7087 patients classified as ‘infected’, the sites of infection were the:

- Lungs: 64%
- Abdomen: 20%
- Bloodstream: 15%
- Renal or genitourinary tract: 14%.

Of the 70% of infected patients with positive microbiology:

- 47% of isolates were gram-positive (Staphylococcus aureus alone accounted for 20%)
- 62% were gram-negative (20% Pseudomonas species and 16% Escherichia coli)
- 19% were fungal.

Other studies tend to broadly concur on the relative frequencies of sources of infection. In people over 65, the most common site is the genitourinary tract.[21] [22] A definite source of infection cannot be found in 20% to 30% of people with sepsis.[9]

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).[23]
- The innate immune system is activated by bacterial cell wall products, such as lipopolysaccharide, binding to host receptors, including Toll-like receptors (TLRs).[24] [25] These are widely found on leukocytes and macrophages, and some types are found on endothelial cells.[26] At least 10 TLRs have been described in humans. These have specificity for different bacterial, fungal, or viral surface markers or products. Genetic polymorphisms are associated with a predisposition to shock with gram-negative organisms.[27]
- Activation of the innate immune system results in a complex series of cellular and humoral responses, each with amplification steps:[28]
  - Pro-inflammatory cytokines such as tumour necrosis factor-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.[29]
  - 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),
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**Theory**

‘remember’ it in case of future infection (memory cells, B lymphocytes), and cause the increased production and chemotaxis of more T helper cells.[30]

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 stimulated immune cells, but becomes porous to large molecules such as proteins, resulting in tissue oedema.
- Alterations in the coagulation systems include an increase in pro-coagulant 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, which also carry anti-inflammatory and modulatory roles.[31] [32]

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, leading to 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.[33] 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.[34]
- 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 anuria and hypotension, once the systemic inflammation resolves.[35]

**Classification**

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

- Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection.
- Septic shock is 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 ≥65 mmHg, and a lactate level >2 mmol/L (>18 mg/dL), despite adequate fluid resuscitation.
• Owing to revisions to the definition of sepsis, the term 'severe sepsis' (as previously defined in the 1991/2001 international consensus definitions) should no longer be used.

Case history

Case history #1

A 78-year-old woman presents to hospital for an elective right hemicolectomy. 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 per minute. She is tachycardic at 118 beats per minute, and her blood pressure 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.[3]
**Recommendations**

**Urgent**

Suspect sepsis based on **acute deterioration** in a patient in whom there is clinical evidence or strong suspicion of **infection**. [41]

Think ‘**Could this be sepsis?**’ whenever an acutely unwell person presents with likely infection, even if their temperature is normal.[3] [41] [42] Remember that sepsis represents the severe, life-threatening end of infection.[4]

- Have a **low threshold** for suspicion.
  - The key to improving outcomes is early recognition and prompt treatment, as appropriate, of patients with suspected or confirmed infection who are deteriorating and at risk of organ dysfunction.[3] [43]
  - By the time the diagnosis becomes obvious, with multiple abnormal physiological parameters, risk of mortality is very high.[41]
- Your **clinical judgement is crucial** to how you approach the individual patient.[41]
  - Be aware that signs and symptoms are extremely variable and often non-specific.[21] [41] [43]
  - No diagnostic test is available that can reliably confirm or exclude sepsis in the timeframe within which treatment should be started for suspected sepsis.[41]

Whenever an acutely ill patient presents with a known infection, presents with symptoms or signs of infection, or is at high risk of infection, **use a systematic approach to assess the risk of deterioration due to sepsis**. [42] [43] # [NHS England: Sepsis]

- Always assess and record temperature, heart rate, respiratory rate, blood pressure, level of consciousness, hourly fluid balance (including urine output), and oxygen saturations.[3]
- Use the findings to risk stratify patients so that immediate sepsis treatment can be prioritised for those at high risk of deterioration.[3] [43] Always use your clinical judgement.[41]

**Urgent: in hospital**

**Consult local guidelines** for the recommended approach for assessing acute deterioration. Use your clinical judgement alongside a validated **scoring system** such as the National Early Warning Score 2 (**NEWS2**) (see the Risk stratification subsection below for more information), which is recommended by NHS England.[3] [41] [43] [44]. **In a patient with a known or likely infection, a NEWS2 score of 5 or more is likely to indicate sepsis.** [42]

- Arrange **urgent** assessment by a senior clinical decision-maker (CT3/ST3 or higher in the UK, or a trained nurse with prescribing rights in acute care) for any patient with an aggregate NEWS2 score of 5 or more. [41]
  - The higher the resulting aggregate NEWS2 score, the higher the risk of clinical deterioration.[41] [42]
  - If necessary (e.g., NEWS2 score of 7 or more) arrange emergency assessment by a critical care specialist.

If the senior clinical decision-maker strongly suspects sepsis (i.e., new organ dysfunction related to severe infection) in an acutely unwell and rapidly deteriorating patient with a NEWS2 score of 5 or more, the team should act promptly to:[41] [43] [45] [46]
• Establish venous access early so you can proceed without delay to:[3] [41] [43] [45] [46]

  • Give within 1 hour of the risk being recognised:

    1. Broad-spectrum intravenous antibiotics (after taking blood cultures), if there is evidence of a bacterial infection
    2. Intravenous fluids, if there is any sign of circulatory insufficiency
    3. Oxygen, if needed[47]

• Take within 1 hour of the risk being recognised:

  1. Blood cultures: take two sets of blood cultures

    • Take bloods immediately, preferably before antibiotics are started (although sampling should not delay the administration of antibiotics)[3] [43] [48] [49]
    • Prioritise filling the aerobic bottle before filling the anaerobic one
    • If a line infection is suspected, it is good practice to remove the line and culture the tip

  2. Lactate level: measure serum lactate, on a blood gas, to determine the severity of sepsis and monitor the patient’s response to treatment

    • Lactate is a marker of stress and may be a marker of a worse prognosis (as a reflection of the degree of stress)
      • Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst
      • Lactate >4 mmol/L (>36 mg/dL) is associated with worse outcomes

    • Alert critical care immediately if the patient is acutely unwell and has persistent lactate >4 mmol/L (>36 mg/dL) [3] despite fluid resuscitation#

    • Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL])
      • This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their NEWS2 score

  3. Hourly urine output: assess the patient’s urine output

    • A low urine output may suggest intravascular volume depletion or renal failure
    • Consider catheterising the patient on presentation if they are shocked/confused/oliguric/critically unwell.

Beware septic shock, a subtype of sepsis with a much higher mortality.[1] [42]

• Characterised by profound circulatory and metabolic abnormalities.
Sepsis in adults

Diagnosis

• Presents with persistent hypotension and serum lactate >2 mmol/L (>18 mg/dL) despite adequate fluid resuscitation, with a need for vaspressors to maintain mean arterial pressure at 65 mmHg or above.[1]
• See our topic Shock.

Early and adequate source identification and control is critical. Undertake intensive efforts, including imaging, to attempt to identify the source of infection in all patients with sepsis. [3] [43]

• Consider the need for urgent source control as soon as the patient is stable.

Urgent: in the community

Use formal risk stratification (e.g., NEWS2), which is endorsed by NHS England and the Royal College of General Practitioners in the UK, or the UK National Institute for Health and Care Excellence high-risk criteria (see the Risk stratification subsection below for more information) to identify which patients are at high risk of deterioration due to sepsis.[3] [41] [43] [50]

• Refer for emergency medical care in hospital (usually by blue-light ambulance in the UK) any patient who is acutely ill with a suspected infection and is:[3]
  • Deemed to be at high risk of deterioration due to organ dysfunction (as measured by risk stratification)
  • At risk of neutropenic sepsis
    • See our topic Febrile neutropenia.

Key Recommendations

Sepsis is a medical emergency, [3] [43] #with reported high mortality.

• Sepsis is present in many hospitalisations that culminate in death. In 2015, 23,135 people in the UK died from sepsis, where sepsis was an underlying or contributory cause of death. [NHS England: Sepsis] The true contribution of sepsis to these deaths is unknown. Most underlying causes of death in people with sepsis are thought to relate to severe chronic comorbidities and frailty.[5] [7] [8]

Make all efforts to determine escalation status and appropriate potential limits of treatment; ensure any initiated treatments are appropriate for the individual patient.

Presentation

Have a high index of suspicion for sepsis as clinical presentation can be subtle.[3] [21]

• Your patient may present with non-specific or non-localised symptoms (e.g., acutely unwell with a normal temperature) or there may be severe signs with evidence of multi-organ dysfunction and shock.[3] [21]
• At-risk groups include those who:
  • Are aged older than 65 years (particularly patients older than 75 years or who are very frail)[3] [9] [21] [36] [51]
  • Are immunocompromised[3] [36] [37] [52] [53]
  • Have indwelling lines or catheters[3]
  • Have recently had surgery (in the previous 6 weeks)[3]
  • Are undergoing haemodialysis[36]
  • Have diabetes mellitus[36]
Sepsis in adults

Diagnosis

- Misuse drugs intravenously[3]
- Are alcohol-dependent[36] [54]
- Are pregnant, have given birth, or have had a termination or miscarriage in the past 6 weeks[3]
- Have a breach of skin integrity (e.g., cuts, burns, blisters, skin infections).[3]
  - Age younger than 1 year is also a strong risk factor.[3] See our topic Sepsis in children.
  - Sepsis may also be signalled by a deterioration in functional ability (e.g., a patient newly unable to stand from sitting).[3]

Be aware that any patient with known infection, with symptoms or signs of infection, or who is at high risk of infection might also have or develop sepsis, even with a NEWS2 score of less than 5. In this group, continue to be aware of the risk of sepsis and specifically look for indicators that suggest the possibility of underlying sepsis:[41]

- A single NEWS parameter of 3 or more
- Non-blanching rash/mottled/ashen/cyanotic skin
- Responds only to voice or pain, or unresponsive
- Not passed urine in last 18 hours or urine output <0.5 mL/kg/hour
- Lactate ≥2 mmol/L (≥18 mg/dL).

Protocolised approaches

Your institution may use a guideline-based care bundle as an aide-memoire to ensure key investigations, and subsequent interventions, are carried out in a timely way as appropriate for the individual patient. Check local guidelines for the recommended approach in your area. Examples include the following.

The Sepsis Six resuscitation bundle from the UK Sepsis Trust [46]

Sepsis Six is a practical checklist of interventions that must be completed within 1 hour of identifying suspected sepsis.[46] The original paper outlining this approach, published in 2011, remains the only published evidence on Sepsis Six,[55] and this has since been contested.[56] The six interventions are:[46]

- Ensure a senior clinician attends
- Give oxygen if required
- Obtain intravenous access/take blood cultures
- Give intravenous antibiotics
- Give intravenous fluids
- Monitor.

The 2018 1-hour care bundle from the Surviving Sepsis Campaign (SSC) [45]#

The latest guidelines from the SSC propose a novel 1-hour care bundle, based on the premise that the temporal nature of sepsis means benefit from even more rapid identification and intervention. The SSC identifies the start of the bundle as patient arrival at triage. It draws out five investigations and interventions to be completed within the first hour:[45]

- Measure lactate level and remeasure if the initial lactate level is greater than 2 mmol/L (18 mg/dL)
- Obtain blood cultures before administration of antibiotics
- Administer broad-spectrum antibiotics
- Begin rapid administration of crystalloid at 30 mL/kg for hypotension or lactate level greater than or equal to 4 mmol/L (36 mg/dL)
• Start vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure level greater than or equal to 65 mmHg.

Although early identification and prompt, tailored treatment are key to the successful management of sepsis, none of the published protocolised approaches is supported by evidence. Therefore, your clinical judgement is a key part of any approach.

### Oxygen saturation in suspected sepsis

**Difficulty obtaining peripheral oxygen saturations may be a red flag for shock.**

- Peripheral oxygen saturations can be difficult to measure in a patient with sepsis if the tissues are hypoperfused.
- You should have a high index of suspicion for shock if you are unable to measure oxygen saturations.

### Objective evidence of new altered mental state

Determine the patient's baseline mental state and establish whether there has been a change. Use a validated scale (e.g., the Glasgow Coma Scale or AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale). As well as checking response to cues, you should ask a relative or carer (if available) about the patient’s recent behaviour.

- Change in mental state can manifest in many ways, which makes it challenging to recognise as part of a short clinical consultation.
- This is even more challenging in older patients, who may also have dementia.
  - In people with dementia, change in mental state may present as irritability or aggression but equally could present with hypoactive delirium (e.g., with lethargy, apathy).

### Full Recommendations

#### Early recognition

Sepsis is present in many hospitalisations that culminate in death. In 2015, 23,135 people in the UK died from sepsis, where sepsis was an underlying or contributory cause of death. The true contribution of sepsis to these deaths is unknown. Most underlying causes of death in people with sepsis are thought to relate to severe chronic comorbidities and frailty.

- Sepsis is defined as life-threatening organ dysfunction that results from a systemic and dysregulated response to an infection. The presentation can range from non-specific or non-localised symptoms (e.g., feeling unwell with a normal temperature) through to multi-organ dysfunction and septic shock.
- Septic shock is a subtype of sepsis in which the patient has persistent hypotension and a serum lactate >2 mmol/L (>18 mg/dL) despite adequate fluid resuscitation, with a need for vasopressors to maintain mean arterial pressure ≥65 mmHg.
- See our topic Shock.

Early recognition of suspected sepsis is key to improving outcomes. By the time the diagnosis becomes obvious, with multiple abnormal physiological parameters, risk of mortality is very high.

Have a low threshold for suspecting sepsis: consider the possibility in any acutely unwell patient who meets both of the following criteria.
1. Has signs or symptoms suggesting infection. In practice, any signs of infection at presentation may be very subtle and non-specific, so easy to miss. **Your initial assessment is therefore key.**

   - The respiratory tract is the most common site of infection in most people with sepsis.[20] [60] In people over 65, the most common site is the genitourinary tract.[21] [22]
   - Look for any obvious infection source that might need urgent source control.

2. **Has vital observations that indicate a risk of deterioration due to organ dysfunction.**
   Use your clinical judgement alongside a validated early warning score or a structured risk stratification process to assess this.

   - **In hospital,** use the National Early Warning Score 2 (NEWS2) or an alternative early warning score.[41] [42] [44] NEWS2 is endorsed by NHS England.[41]
   - **In the community,** use an early warning score such as NEWS2, which is recommended by NHS England,[41] or the UK National Institute for Health and Care Excellence high-risk criteria.[3]
   - **Check local guidance** for your institution’s recommended approach.

   See the Risk stratification subsection below for more information.

**Practical tip**

Be aware that patients might not necessarily appear seriously ill at presentation, but their condition may **deteriorate rapidly.** The seriousness of a sepsis presentation can be easily underestimated in a busy environment, such as the emergency department.

**Clinical assessment**

Careful clinical assessment with a thorough history, examination, and investigations can help you identify sepsis early. You should consider the possibility of sepsis (i.e., new onset organ dysfunction) whenever an acutely ill patient presents with a suspected infection.[3]

**Presentation**

Always interpret signs and symptoms of sepsis in the context of the wider clinical picture as they are often non-specific and extremely variable. [21] [43] Your initial assessment should focus on:

   - Identifying abnormalities of behaviour, circulation, or respiration: in particular, any signs suggestive of septic shock or serious organ dysfunction
   
   and
   
   - Determining the most likely source of infection and any need for immediate source control.

Common non-specific signs and symptoms include:[21] [43]

   - Those associated with a specific source of infection. [Signs and symptoms of possible infection sources] The most common sources are:[60]

      - Respiratory tract (cough/pleuritic chest pain)
      - Urinary tract (flank pain/dysuria)
      - Abdominal/upper gastrointestinal tract (abdominal pain)
      - Skin/soft tissue (abscess/wound/catheter site)
      - Surgical site or line/drain site
      - Tachypnoea
      - High (>38°C [>100.4°F]) or low (<36°C [<96.8°F]) temperature, sometimes with rigors
      - Tachycardia
Sepsis in adults

Diagnosis

- Acutely altered mental status
- Low oxygen saturation
- Hypotension
- Decreased urine output
  - Ask the patient when they last passed urine
- Poor capillary refill, mottling of the skin, or ashen appearance
- Cyanosis
- Malaise/lethargy
- Nausea/vomiting/diarrhoea
- Purpura fulminans (a very late sign but may be seen on presentation)
- Ileus
- Jaundice.

Practical tip
Jaundice is a rare sign of sepsis unless it is associated with a specific source of infection (biliary sepsis).

Capillary refill time. Top image: normal skin tone; middle image: pressure applied for 5 seconds; bottom image: time to hyperaemia measured

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission
History

Take a detailed history, focusing on symptoms, recent surgery, underlying disease, history of recent antibiotic use, other medication history, and travel. Use the history to identify factors for acquiring infection and clues to infection sites to guide choice of antimicrobial therapy.[21]

• Ask specific questions, including:
  
  • When was the last time you passed urine?
    
    • And how often over the past 18 hours?[3]
  
  • Do you take any medication?
  
  • Have you recently taken antibiotics?
  
  • Have you recently been in hospital and/or had surgical procedures?
  
  • Have you travelled abroad recently?
  
  • Have you had contact with animals?
  
  • Have you had any contact with anyone infectious?

• Ask about the patient’s lifestyle, including:
  
  • Drug misuse
  
  • Alcohol intake
Sepsis in adults

Diagnosis

- Housing situation.

Practical tip

Check to see whether there are any microbiological samples already in the lab (e.g., urine sent by the GP) or other available test results (血液, x-rays, etc).

Have a higher index of suspicion for sepsis when a patient presents with signs of infection and acute illness and falls into an at-risk group:

- Age older than 65 years (and particularly older than 75 years)[3][9][36][51]
- Immunocompromised (e.g., chemotherapy, sickle cell disease, AIDS, splenectomy, long-term steroids)[3][36][37][52][53]
- Indwelling lines or catheters[3]
- Recent surgery (in the previous 6 weeks).[3] The risk of sepsis is particularly high following oesophageal, pancreatic, or elective gastric surgery[38]
- Haemodialysis[36]
- Diabetes mellitus[36]
- Intravenous drug misuse[3]
- Alcohol dependence[36][54]
- Pregnancy (and the 6 weeks after delivery/termination/miscarriage)[3]
- Breaches of skin integrity (e.g., burns, cuts, blisters, skin infections).[3]

Age younger than 1 year is also a strong risk factor.[3] See our topic Sepsis in children.

Practical tip

Pay particular attention to the patient’s family/carers when taking a history. They will know the patient well and might be able to offer insight into acute behavioural changes as well as changes to their respiration or circulation, compared with the norm. Consider how they may describe the result of changes in physiology that are likely to have affected the patient’s vital observations, for example:[61]

- Altered mental state – ‘confused’, ‘drowsy’, ‘not themselves’
- Fever – ‘warm to touch’, ‘shivery’, ‘burning up’
- Hypotension – ‘dizzy’, ‘faint’, ‘lightheaded’
- Tachypnoeic – ‘out of breath’, ‘breathless’
- Tachycardic – ‘heart is racing’, ‘heart is pounding’.

Be aware of the risk of sepsis in women who are pregnant, have given birth, or have had a termination or miscarriage in the past 6 weeks. Risk factors for the development of sepsis in these groups include:[3][62]

- Obesity
- Gestational diabetes or diabetes mellitus
- Impaired immune systems (due to illness or drugs)
- Anaemia
- History of pelvic infection
- History of group B streptococcal infection
- Amniocentesis and other invasive procedures (e.g., instrumental delivery, caesarean section, removal or retained products of conception)
- Cervical cerclage
- Prolonged rupture of membranes
- Vaginal trauma
- Wound haematoma
Sepsis in adults

Diagnosis

• Close contact with people with group A streptococcal infection (e.g., scarlet fever).

Practical tip

When weighing up whether a patient who is acutely ill with symptoms or signs of possible infection can be safely managed in the community, it is important to consider whether they fall into one or more of the at-risk groups.[3]

Examination

Follow the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) format to include assessment of the airway, respiratory, and circulatory sufficiency. Monitor:

• Oxygen saturation
  - May show signs of hypoxaemia.
• Respiratory rate
• Heart rate
• Blood pressure
• Temperature
• Hourly fluid balance (including urine output)
• Level of consciousness (Glasgow Coma Scale or AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale).

Practical tip

Difficulty obtaining peripheral oxygen saturations may be a red flag for possible shock.[3]

• Peripheral oxygen saturations can be difficult to measure in a patient with sepsis if the tissues are hypoperfused.
  - This may occur in the later stages of the condition, as earlier in the disease process the circulation is usually hyperdynamic.
  - Some conditions such as meningococcal sepsis can present early with poor peripheral perfusion. These patients often have profound myocardial depression on presentation. In others, there may be a hyperdynamic central circulation concurrent with poor peripheral perfusion and a subsequent uncoupling of blood flow.
  - You should have a high index of suspicion for shock if you are unable to measure oxygen saturations.
  - See our topic Shock.

Practical tip

Never rule out sepsis on the basis of a normal temperature reading. Fever is a common presenting sign but some patients are apyrexial or have hypothermia.[3]

• Always assess the patient’s temperature in the context of their wider clinical picture.
• Hypothermia at presentation is associated with a poorer prognosis than fever.[63]
• People who are older (>75 years) or very frail (regardless of age) are particularly prone to a blunted febrile response and may present with a normal temperature.[3] [64]
• Other groups that are less susceptible to temperature fluctuations and so may not develop a raised temperature with sepsis include:[3]
  - Infants or children
  - People with cancer receiving treatment
  - Severely ill patients.
Practical tip

Always interpret the vital signs that you take as part of the ABCDE assessment in relation to the patient’s known or likely baseline for that parameter; take account of the patient in front of you and the full clinical picture. For example:

- A fall in systolic blood pressure of ≥40 mmHg from the patient’s baseline is a cause for concern, regardless of the systolic blood pressure reading itself.[3]
- Although tachycardia can be an indicator of potential risk of sepsis developing, when assessing heart rate you should consider:[3]

  - Pregnancy
    - In pregnant people, heart rate is usually 10 to 15 bpm faster than normal
  - Older people
    - Older people may not develop tachycardia in response to infection and are more at risk of developing new arrhythmias (e.g., atrial fibrillation)
  - Medications
    - Some drugs, such as beta-blockers or rate-limiting calcium-channel blockers, may inhibit a tachycardic response to infection
  - Baseline
    - The baseline heart rate in young people or people who are very physically fit (e.g., athletes) may be lower than the norm. The rate of change of heart rate may therefore be more important (to reflect the severity of infection) than the actual rate.

Pay particular attention to common signs and symptoms :[3] [43]

- Of possible organ dysfunction
  - Cyanosis of the skin, lips, or tongue
  - Jaundice
  - Oliguria
  - Mental status changes
  - Airway compromise, dyspnoea, hypoxaemia, fever, or hypothermia
  - Purpura fulminans
  - Fever or hypothermia
  - Arrhythmia
  - Tachypnoea
- Of possible shock [65]
  - Hypotension
  - Arrhythmia
  - Skin changes (mottled, ashen, sweaty; cold or clammy peripheries)
  - Fever or hypothermia
  - Oliguria
- Of possible circulatory insufficiency
• Oliguria
• Mottled, ashen appearance; sweating
• Prolonged capillary refill times

• Of possible hypovolaemia [66]
• Reduced peripheral skin perfusion and skin temperature
• Reduced skin turgor and dry mucous membranes
• Postural hypotension
• Thirst

• Indicating potential infection/source of infection. [Signs and symptoms of possible infection sources] Most commonly:[20] [60]

• Respiratory tract (cough/pleuritic chest pain/tachypnoea/dyspnoea)
• Urinary tract (suprapubic tenderness, loin tenderness, dysuria)
• Abdominal/upper gastrointestinal tract (abdominal pain or guarding/decreased bowel sounds/diarrhoea/vomiting)
• Skin/soft tissue (breakdown of abscess/wound with redness, swelling, or discharge)
• Post-operative (redness/swelling/discharge/pain at surgical site or line/drain site).

**Practical tip**

Change in mental state is a commonly missed sign of sepsis, particularly in older patients in whom dementia may co-exist. Change in mental state is often due to non-infectious causes (e.g., electrolyte disturbances). It can manifest in many ways, which makes it challenging to recognise as part of a short clinical consultation.

• The term ‘confusion’ can be unhelpful and instead you should attempt to identify any change from the patient's normal behaviour or cognitive state .[3]
• A collateral history – if friends, family members, or carers are available – is key. They might describe the patient as ‘not themselves’.
• In people with dementia, change in mental state may present as irritability or aggression ,[3] but equally could present with hypoactive delirium (e.g., with lethargy, apathy) .[59]
• In addition, sepsis may be signalled by a deterioration in functional ability (e.g., a patient newly unable to stand from sitting).[3]

Ensure any patient with suspected sepsis has frequent and ongoing monitoring (e.g., using an early warning score such as the National Early Warning Score 2 [NEWS2]). See our Management recommendations section for advice on when to consult a senior colleague or escalate to critical care.

**Risk stratification**

Early identification of sepsis relies on systematic assessment of any acutely ill patient who presents with presumed infection to identify their risk of deterioration due to sepsis. By the time sepsis is at an advanced stage, with multiple abnormal physiological parameters, the risk of mortality is very high. [41]

In any patient in whom sepsis is a possibility, use a systematic process to check vital observations and assess and record the risk of deterioration .[41] [42] [43] Remember that no risk stratification process is 100% sensitive or 100% specific; therefore, you must use your clinical judgement .

Consult local guidelines for the recommended approach for assessing acute deterioration.

1. In hospital: use the National Early Warning Score 2 ( NEWS2 ) or an alternative early warning score .[41] [42] [44] NEWS2 is endorsed by NHS England for use in this setting.[41]
2. In the **community**: use an early warning score such as NEWS2, which is recommended by NHS England[41] and the Royal College of General Practitioners in the UK,[50] or the **UK National Institute for Health and Care Excellence (NICE) high-risk criteria**.[3]

* **None is validated** in primary care.[50]

NEWS2 is the most widely used early warning score in the UK National Health Service and is endorsed by NHS England.[41] [NHS England: Sepsis] In a patient with a known or likely infection, a NEWS2 score of 5 or more is likely to indicate sepsis.[42]

**In hospital: use the NEWS2 early warning score together with your clinical judgement**

Early warning scores are often used in hospitals to **triage patients** and to **detect clinical deterioration or improvement over time**.[67] [68] NEWS2 is the latest version of the National Early Warning Score (NEWS), first developed by the UK Royal College of Physicians in 2012 and updated in 2017.[41] [42] [44]

* NEWS has been tested and validated in many different healthcare settings, including emergency departments and pre-hospital care, and has performed well.[42]
* NHS England recommends NEWS2 for risk stratification and early identification of sepsis in any acutely ill patient who has symptoms or signs of infection.[41]

NEWS2 is based on the assessment of **six individual parameters, which are each assigned a score of between 0 and 3**.[41] [42] [44]

* **Respiratory rate**
* **Oxygen saturations**

  * There are different scales for oxygen saturation levels based on a patient’s physiological target; use scale 2 for patients at risk of hypercapnic respiratory failure

* **Temperature**
* **Blood pressure**
* **Heart rate**
* **Level of consciousness**.

Assess each parameter individually and then add up the final score.
**National Early Warning Score 2 (NEWS2)** is an early warning score produced by the Royal College of Physicians in the UK. It is based on the assessment of six individual parameters, which are assigned a score of between 0 and 3: respiratory rate, oxygen saturations, temperature, blood pressure, heart rate, and level of consciousness. There are different scales for oxygen saturation levels based on a patient’s physiological target (with scale 2 being used for patients at risk of hypercapnic respiratory failure). The score is then aggregated to give a final total score; the higher the score, the higher the risk of clinical deterioration.


In an acutely ill patient with symptoms or signs of infection, the NEWS2 score can be an indicator of the likelihood of sepsis. The higher the resulting aggregate score, the higher the risk of clinical deterioration. [41] [42] #Use the following approach as a guide alongside your clinical judgement, based on the individual patient, their history, and their prognosis.#

<table>
<thead>
<tr>
<th>Physiological parameter</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>Score 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration rate (per minute)</td>
<td>≤8</td>
<td>9–11</td>
<td>12–20</td>
<td>21–24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ Scale 1 (%)</td>
<td>≤91</td>
<td>92–93</td>
<td>94–95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ Scale 2 (%)</td>
<td>≤83</td>
<td>84–85</td>
<td>86–87</td>
<td>88–92</td>
<td>93–94 on oxygen</td>
<td>95–96 on oxygen</td>
<td>≥97 on oxygen</td>
</tr>
<tr>
<td>Air or oxygen?</td>
<td>Oxygen</td>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>≤90</td>
<td>91–100</td>
<td>101–110</td>
<td>111–219</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse (per minute)</td>
<td>≤40</td>
<td>41–50</td>
<td>51–90</td>
<td>91–110</td>
<td>111–130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>Alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>≤35.0</td>
<td>35.1–36.0</td>
<td>36.1–38.0</td>
<td>38.1–39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEWS2 aggregate score in a patient with known or likely infection</td>
<td>What to do? [41] [42]</td>
<td>Why?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>≥7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|  | • Arrange emergency assessment by critical care  
• Consider transfer to a high-dependency setting for continuous monitoring of vital signs  
• Consider immediately starting investigation for and, if appropriate, treatment of sepsis | Very likely to be sepsis; significant risk of mortality |
| ≥5 |  |  |
|  | • Arrange urgent review by a senior clinical decision-maker (CT3/ST3 or higher in the UK, or a trained nurse with prescribing rights in acute care), who should assess whether escalation to the critical care team is needed  
• Consider immediately initiating investigation for and, if appropriate, treatment of sepsis | Likely to be sepsis |
| <5 |  |  |
|  | • Continue to be aware of the risk of sepsis  
• Look for indicators that suggest the possibility of underlying infection and sepsis:  
  • A single NEWS2 parameter of 3 or more  
  • Non-blanching rash/mottled/ashen/cyanotic skin  
  • Responds only to voice or pain, or unresponsive  
  • Not passed urine in last 18 hours | May be sepsis |
Debate: Role of the qSOFA score

*Although the sequential organ failure assessment score (SOFA) and quick-SOFA (qSOFA) are accepted as useful tools for prognostication, they are not recommended by national UK guidelines as a tool for early identification of sepsis.*

- NHS England recommends the use of NEWS2 scores, while NICE acknowledges a role for NEWS2 but has based its formal recommendations on its own risk stratification criteria.[3] [41] [69] [NHS England: Sepsis]

While the qSOFA score is not a bedside scoring tool, it can be used as an alternative to NEWS to identify any patient at high risk of an adverse outcome in healthcare systems that don’t use NEWS. qSOFA shares 3 of the 7 NEWS2 criteria; using qSOFA, an acutely ill patient with suspected or confirmed infection is considered to be at high risk of an adverse outcome (from sepsis) if at least two of the following three criteria are present:[1]

- Altered mental state (Glasgow Coma Scale score <15)
- Systolic blood pressure ≤100 mmHg
- Respiratory rate ≥22 breaths/minute.

**Evidence suggests that early warning scores such as NEWS2 have better sensitivity and specificity than the qSOFA score for predicting deterioration and mortality among patients presenting to the emergency department with suspected infection.** [68]

Evidence: NEWS

*Although not specifically intended to be used for identifying suspected sepsis, several studies have highlighted how the National Early Warning Score (NEWS) may support earlier identification of patients with sepsis and septic shock. [68] [70] [71] These data relate specifically to NEWS, a previous iteration of NEWS2.*

- An analysis of audit data from 20 emergency departments in the UK, which included a total of 2003 patients, found a single NEWS score calculated from the patient's initial observations to be strongly predictive of adverse outcomes in sepsis.[71]
  - Total NEWS scores were grouped into four categories: 0-4, 5-6, 7-8, and 9-20.
  - Each rise in NEWS score category was associated with an increased risk of mortality when compared with the lowest category (0-4):[71]
    - 5-6: odds ratio (OR) 1.95 (95% CI 1.21 to 3.14)
    - 7-8: OR 2.26 (95% CI 1.42 to 3.61)
    - 9-20: OR 5.64 (95% CI 3.70 to 8.60).

- A further study of 30,677 adults admitted via emergency departments in the US with suspected infection found that the NEWS score performed better than either the Modified Early Warning Score (MEWS) or qSOFA scores in predicting the risk of death or need for an intensive care unit transfer. [68]

- In a retrospective observational study, an aggregate NEWS score of 3 or more at emergency department triage was found to have a **sensitivity of 92.6%** (95% CI 74.2% to 98.7%) and a
specification of 77% (95% CI 72.8% to 80.6%) for detecting patients at risk of sepsis and septic shock.[70]

### Practical tip

It is important to be aware that no scoring system has been validated for use in pregnant women; in practice, seek senior input to determine the best approach in a pregnant patient. Examples of scores that have been developed but are yet to be universally accepted include the following.

- A modified qSOFA has been proposed by the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) for use in pregnant women. The SOMANZ score includes systolic blood pressure 90 mmHg, respiratory rate >25 per minute, and altered mental status.[72]
- The Sepsis in Obstetrics Score uses a combination of maternal temperature, blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, white blood cell count, and lactic acid level as predictors of intensive care admission for sepsis.[73]

### In the community: use the NEWS2 early warning score or the NICE high-risk criteria, together with your clinical judgement

Primary care has a significant role to play in identifying suspected sepsis at an early stage and to promptly escalate care where appropriate. [50] A key aspect of this is the consistent use and recording of physiology as part of the assessment of infection and the deteriorating patient. The method selected for doing this in primary care is still open to challenge due to a lack of evidence in this setting; no one approach to risk stratification has been validated in primary care.[50] Therefore, using your clinical judgement in making a decision is paramount.[41]

To identify which acutely ill patients with suspected or confirmed infection are at high risk of deterioration due to sepsis in the community, use either:

- NEWS2 or an alternative early warning score [41] [42] [50] [NHS England: Sepsis]
  - NEWS2 is recommended by NHS England[41] and the Royal College of General Practitioners in the UK[50]
- The NICE sepsis high-risk criteria [3]
  - If an acutely ill patient presents with symptoms and signs of infection AND meets any one or more of these criteria, OR is deemed to be at risk of neutropenic sepsis, refer for emergency medical care in hospital (usually by blue-light ambulance in the UK):
    - Objective evidence of new altered mental state (e.g., new deterioration in Glasgow Coma Scale score/AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale)
    - Respiratory rate: 25 breaths per minute or more OR new need for oxygen (40% or more fraction of inspired oxygen [FiO₂]) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)
    - Heart rate: more than 130 beats per minute
    - Systolic blood pressure 90 mmHg or less or systolic blood pressure more than 40 mmHg below normal
    - Not passed urine in previous 18 hours, or for catheterised patients passed less than 0.5 mL/kg of urine per hour
    - Mottled or ashen appearance
    - Cyanosis of skin, lips, or tongue
Sepsis in adults

Diagnosis

• Non-blanching rash on skin.

Historically, respiratory rate, blood pressure/perfusion, and cognition are among the least well recorded values by general practitioners in the UK when assessing patients with sepsis. [60]

Practical tip

A systematic approach is key to earlier identification of patients at risk of sepsis. The Royal College of General Practitioners in the UK highlights the importance of ensuring you have the right equipment available in every consultation room, including: a thermometer (tympanic and axillary), a pulse oximeter suitable for use in all age groups, and a sphygmomanometer.[74]

Take a cautious approach when deciding whether it is safe to treat an acutely unwell patient in the community.

• For more details on managing patients in the community, see our Management recommendations section.

Practical tip

If you need to refer a patient for emergency medical care in hospital, it is important to inform the hospital clinical team that the patient is on the way. This will enable the hospital to prepare to start appropriate management as soon as the patient arrives.

Debate: NICE risk stratification versus NEWS2 scoring in community settings

Following the introduction of the NICE risk stratification criteria, there has been ongoing debate around their advantages and drawbacks. There is significant overlap between the NEWS2 scoring system and the NICE risk stratification criteria, with many of the same clinical observations used in both. A key difference is that the risk category a patient falls into under NEWS2 generally depends on an aggregate score across all the vital observations, whereas under the approach recommended by NICE this risk categorisation depends on a score on a single parameter.

• The decision as to whether to use the NEWS2 or NICE approach for recognition of suspected sepsis may be made at individual institution, clinical commissioning group, or regional level. What is important is that implementation of either approach should lead to more systematic assessment and recording of the vital observations that can help identify patients at risk of deterioration whose care needs escalating immediately.
• Whichever tool you use, it should only ever be in addition to (and never a replacement for) your clinical judgement.
• For example, NHS England has concluded that the complexity of the NICE risk stratification criteria makes them difficult to translate into practice and has recommended the alternative NEWS2 approach as more pragmatic for frontline clinicians, both in hospital and community settings.[41]
• Concern has also been raised about the low threshold for suspecting sepsis using the NICE criteria, which could lead to so many patients being referred to hospitals as emergencies that assessment and treatment could be delayed for those at the very highest risk. One small study that retrospectively reviewed admissions to an acute medical unit found the NICE criteria identified 69% of adult patients as requiring a review within 1 hour by a senior clinician.[75]
• It is important to remember that none of these criteria negates clinical judgement and they should only be assessed in patients with suspected infections.[3]
Identifying the infection source

Make intensive efforts to identify the most likely anatomical source of infection as soon as possible. Consider the need for urgent source control as soon as the patient is stable.

- Start with a thorough and focused clinical history and examination, as well as initial investigations including imaging.
- Early and adequate source control is critical, particularly for:
  - Gastrointestinal sources (such as visceral abscesses, cholangitis, or peritonitis secondary to perforation)
  - Severe skin infections (e.g., necrotising fasciitis)
  - Infection involving an indwelling device, where a procedure or surgery is likely to be required.

Consider all lines, including Hickman and peripherally inserted central catheter (PICC), and catheters as potential sources. If you suspect a line infection, is it good practice to remove the line and culture the tip.

- Assume that any intravenous route is likely to either be the source of the infection, or will seed infections in the bloodstream, making eradication particularly difficult. Therefore, the priority for source control is often to remove any intravenous devices after vascular access has been obtained.

If you suspect an abdominal or pelvic source, involve the relevant surgical team early, particularly if surgery is likely.

- In practice, this may mean early transfer of the patient to a surgical centre if there are no facilities at your hospital.

Sites of infection

The respiratory tract is the most common site of infection in people with sepsis, followed by the abdomen, urinary tract, soft tissues, and joints, and – rarely – the central nervous system.

- Beware necrotising fasciitis and septic arthritis, which require immediate surgical intervention.

Practical tip

Necrotising fasciitis is notoriously difficult to diagnose. The initial symptoms are non-specific and the clinical course is often slower than might be expected. Typically, the first sign is pain disproportionate to the clinical findings, followed or accompanied by fever.

Evidence: Infectious causes of sepsis

The Extended Prevalence of Infection in Intensive Care (EPIC II) study provides the best recent evidence on the infectious causes of sepsis in an intensive care setting. The study gathered extensive data from more than 14,000 adult patients in 1265 intensive care units from 75 countries on a single day in May 2007.
• Of the 7000 patients classified as ‘infected’, the sites of infection were the:
  • Lungs: 64%
  • Abdomen: 20%
  • Bloodstream: 15%
  • Renal or genitourinary tract: 14%.

• Of the 70% of infected patients with positive microbiology:
  • 47% of isolates were gram-positive (Staphylococcus aureus alone accounted for 20%)
  • 62% were gram-negative (20% Pseudomonas species and 16% Escherichia coli)
  • 19% were fungal.

Other studies tend to broadly concur on the relative frequencies of sources of infection. The graph below shows the results of the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2015.[60]

![Graph showing the relative frequencies of sources of infection in sepsis](image)

Evidence from studies in people over age 65 years shows the genitourinary tract is the biggest source of infection.[21] [22]

Investigations

No diagnostic test is available that can reliably confirm or exclude sepsis in the timeframe within which treatment should be started for suspected sepsis.[41] Start treatment promptly and before test results are available if the patient is acutely ill.[41]
Within 1 hour

Above all else, complete these three investigations:[3] [43] [46]

- Take two sets of blood cultures
- Measure serum lactate
- Start monitoring hourly urine output.

Take bloods immediately, before antibiotics are started (although sampling should not delay the administration of antibiotics).[3] [43] [48] [49]

Practical tip
Take blood cultures and measure serum lactate at the same time.

Blood cultures (within 1 hour)

Ideally, take peripheral blood cultures (aerobic and anaerobic) from at least two different sites.[43]

- Prioritise filling the aerobic bottle before filling the anaerobic one.
- To improve yield, ensure these samples are incubated as soon as possible.

If you suspect a line infection, remove the line and culture the tip.

Practical tip
Take cultures of blood and other fluids at the first opportunity as they may take up to 48 to 72 hours to yield sensitivities of causative organisms (if identified). It is usually possible to take cultures first without this causing any delay to administration of antibiotics. This is important as cultures are far less likely to be positive if delayed until after giving antimicrobials.

Lactate (within 1 hour)

Measure serum lactate, on a blood gas, to determine the severity of the sepsis and monitor response to treatment.[3] [43] [46]

- Lactate is a marker of stress and may be a marker of a worse prognosis (as a reflection of the degree of stress). Raised serum lactate highlights the possibility of tissue hypoperfusion and may be present in many conditions.[77] [78]
- Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst.
- Lactate >4 mmol/L (>36 mg/dL) is associated with worse outcomes.

  - One study found in-hospital mortality rates as follows:[79]
    - Lactate <2 mmol/L (<18 mg/dL): 15%
    - Lactate 2.1 to 3.9 mmol/L (19 to 35mg/dL): 25%
    - Lactate >4 mmol/L (>36 mg/dL): 38%.

Sepsis guidelines from the UK National Institute for Health and Care Excellence (NICE) and NHS England recommend escalating treatment depending on lactate level.[3] [41] #Alert critical care immediately if the patient is acutely unwell and has persistent lactate >4 mmol/L (>36 mg/dL) [3] #despite fluid resuscitation.

Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL]).
Sepsis in adults

Diagnosis

- This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their National Early Warning Score 2 (NEWS2) score.

Practical tip

Lactate is typically measured using a blood gas analyser, although laboratory analysis can also be performed. Traditionally, arterial blood gas has been recommended as the ideal means of measuring lactate accurately. However, in practice, in the emergency department setting it may be more practical and quicker to use venous blood gas, which is recommended by NICE although this recommendation is not supported by strong evidence. Evidence suggests good agreement at lactate levels <2 mmol/L (<18 mg/dL) with small disparities at higher lactate levels.

Be aware that persisting raised lactate may not be recognised until after initial resuscitation has been given. In the patient with persisting raised lactate, ensure:

- Adequate source control; remove any suspected septic or necrotic focus
- The patient is adequately filled (their central venous pressure ‘goes up and stays up’)
- The patient’s cardiac output and blood pressure are adequate for their tissue needs (a low central venous oxygen saturation, \(\text{ScVO}_2\), serves as a good indicator of impaired tissue oxygenation).

Practical tip

Persistent raised lactate should incite efforts to identify other hidden causes including thiamine deficiency, adrenaline or other drugs, and liver failure.

Urine output (start monitoring within 1 hour)

Assess the patient’s urine output. Ask the patient or their carer about urine output over the previous 12 to 18 hours. Consider catheterising the patient on presentation if they are shocked, confused, oliguric, or critically unwell. Ensure arrangements are in place for urine output to be monitored once an hour.

A low urine output may suggest intravascular volume depletion and/or acute kidney injury and is therefore a marker of sepsis severity.

- The NICE sepsis guideline categorises any patient who has not passed urine in the previous 18 hours (or for catheterised patients passed less than 0.5 mL/kg of urine per hour) as being at high risk of severe illness or death from sepsis.

Care bundles

Your institution may use a guideline-based care bundle as an aide-memoire to ensure key investigations, and subsequent interventions, are carried out in a timely way as appropriate for the individual patient. Check local guidelines for the recommended approach in your area. Examples include the following.

The Sepsis Six resuscitation bundle from the UK Sepsis Trust

Sepsis Six is a practical checklist of interventions that must be completed within 1 hour of identifying suspected sepsis. The original paper outlining this approach, published in 2011, remains the only published evidence on Sepsis Six and this has since been contested. The six interventions are:
Sepsis in adults

• Ensure a senior clinician attends
• Give oxygen if required
• Obtain intravenous access/take blood cultures
• Give intravenous antibiotics
• Give intravenous fluids
• Monitor.

The 2018 1-hour bundle from the Surviving Sepsis Campaign (SSC) [45]

The latest guidelines from the SSC propose a novel 1-hour care bundle, based on the premise that the temporal nature of sepsis means benefit from even more rapid identification and intervention. The SSC identifies the start of the bundle as patient arrival at triage. It draws out five investigations and interventions to be completed within the first hour:[45]

• Measure lactate level and remeasure if the initial lactate level is greater than 2 mmol/L (18 mg/dL)
• Obtain blood cultures before administration of antibiotics
• Administer broad-spectrum intravenous antibiotics
• Begin rapid administration of crystalloid at 30 mL/kg for hypotension or lactate level greater than or equal to 4 mmol/L (36 mg/dL)
• Start vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure level greater than or equal to 65 mmHg.

Although early identification and prompt, tailored treatment are key to the successful management of sepsis, none of the published protocolised approaches is supported by evidence.[57] [58] Therefore, your clinical judgement is a key part of any approach.

Controversy: Protocolised care bundles

Robust evidence to support the use of care bundles, such as Sepsis Six or the SSC 1-hour bundle (2018), to improve outcomes in people with sepsis is lacking. [57] [58] Available data are from observational studies only, [55] [83] [84] [85] [86] [87] [88] which come with methodological limitations; in particular, they cannot resolve questions of causality. Some organised medical societies have declined to support 1-hour target-based approaches to the management of sepsis, [57] [58] [89] [90] while other current guidelines mandate the importance of 1-hour care bundles. [3] [43] There is agreement across the board that appropriate and timely recognition and subsequent resuscitation are important for any severely ill patient presenting with sepsis. [3] [43] [57] [58] [89] [90]

• Sepsis Six was specifically designed to facilitate early intervention in busy hospital and prehospital settings. [91] [92] The original paper outlining the approach, published in 2011, was a prospective observational cohort study that looked at data from 567 patients. [55] Statistical analysis of the data did not take into account the differences between the cohorts: most importantly, age and infection source. The study reported that delivery of the bundle is associated with a 55% relative risk reduction in mortality. [55] Further evidence has since emerged to contest the delivery of Sepsis Six translating to any improvement in mortality. [56]
• Other datasets report clinical improvements associated with earlier completion of sepsis bundles, [83] [84] [85] [86] [87] [88] some citing an increased mortality for every hour’s delay. [85]

• Commentators have challenged the methodology of these studies, which were all observational cohorts that separated patients by the time to intervention and usually after a clear start signal, such as shock or an elevated lactate level – in particular, their inability to:[57] [58]

  • Define causation, only association
  • Detect the granular differences that 1 hour versus 2 or 3 hours to complete makes on overall care (for patients with and without sepsis alike).
Blood tests

Full blood count

Carry out a venous blood test to determine the patient’s full blood count.[3]

Thrombocytopenia of non-haemorrhagic origin may occur in patients who are severely ill with sepsis.[94]

- Persistent thrombocytopenia is associated with an increased risk of mortality.[94]

Lymphocytopenia is increasingly recognised as a useful sign in a patient with sepsis.

The white blood cell (WBC) count is neither sensitive nor specific for sepsis.[95]

- WBC count was one of the diagnostic criteria for sepsis under the old systemic inflammatory response syndrome (SIRS) definition but this has been superseded by the 2016 Sepsis-3 diagnostic criteria, which rely on demonstrating organ dysfunction.[1]

Practical tip

Non-infectious (e.g., crush) injury, surgery, cancer, and immunosuppressive agents can also lead to either increased or decreased WBC counts.

Urea and electrolytes (including creatinine)

Request urea and electrolyte tests;[3] use to:

- Evaluate the patient for renal dysfunction
  - Patients with acute kidney injury due to sepsis have a worse prognosis than those with non-septic acute kidney injury[96]
  - Determine whether the patient would benefit from haemofiltration or intermittent haemodialysis[43]
  - Identify sodium, potassium, calcium, magnesium, and chloride abnormalities.
Sepsis in adults

### Diagnosis

**Serum glucose**

Measure serum glucose on a blood gas, venous blood through venepuncture, or via capillary blood with bedside testing.#

- Depending on the patient’s baseline glucose level, hyperglycaemia may be associated with increased morbidity and mortality in patients with sepsis.[97]
  - Bear in mind that studies of people with diabetes show no clear association between hyperglycaemia during intensive care unit stay and mortality and markedly lower odds ratios of death at all levels of hyperglycaemia.[98]
  - Glucose levels may be elevated, with or without a known history of diabetes mellitus, due to the stress response and altered glucose metabolism.[97] [99] Drug therapy (e.g., with corticosteroids and catecholamines) may also lead to elevated glucose.

**Practical tip**

Spontaneous or iatrogenic hypoglycaemia also poses significant dangers.[100] [101] Persisting hypoglycaemia may suggest acute liver failure.[102]

**C- reactive protein**

Carry out a venous blood test to determine the patient’s level of C-reactive protein.[3]

*Reasonably sensitive*, but not specific, for sepsis.[3] [103] [104]

**Serum procalcitonin**

Baseline serum procalcitonin is increasingly being used in critical care settings to guide decisions on how long to continue antibiotic therapy.[43] [105] [106] [107]

- Procalcitonin is a peptide precursor of calcitonin, which is responsible for calcium homeostasis.
- It is currently excluded from key guidelines, but increasingly used in practice.

**Clotting screen**

Include prothrombin time, partial thromboplastin time, and fibrinogen. [3]

- Use to determine whether the patient has established coagulopathy in the presence of sepsis. This is associated with a worse prognosis.[108]

**Liver function tests**

Use liver function tests, notably bilirubin, to evaluate for organ dysfunction.[109] [110] Liver dysfunction may also be a cause of a coagulopathy.

**Blood gas**

Request blood gas tests. [3]

Use either arterial blood gas (ABG) or venous blood gas evaluation. Use ABG to optimise oxygenation and assess metabolic status (acid-base balance), particularly with regard to the arterial carbon dioxide level (PaCO₂).

- In ventilated patients, this may help to determine the positive end-expiratory pressure (PEEP), while minimising adverse levels of inspiratory pressure and unnecessarily high fraction of inspired oxygen (FiO₂).

**Practical tip**

Spontaneous or iatrogenic hypoglycaemia also poses significant dangers. Persisting hypoglycaemia may suggest acute liver failure.
VBG is increasingly being used in preference to ABG in the emergency department, particularly if a respiratory cause seems unlikely. VBG is less invasive and less painful than ABG and evidence shows there is good concordance between venous and arterial values for pH, bicarbonate ion concentration, base excess, and lactate.[78] ABG will be used instead of VBG if the patient is escalated to critical care as an arterial line is usually inserted for ease of access. Be aware that venous PCO₂ may be artificially high if taken from a tourniqueted limb.

**Investigations to identify source of infection**

Tailor investigations to the patient’s history and examination findings. [3]

**Urinary analysis**

Consider a [dipstick test](#) in any patient who has suspected sepsis to help add weight to a suspected urinary source of infection.[3]

Always interpret urine analysis in the context of the wider clinical assessment.

- Bear in mind that this does not definitively confirm a urinary source, particularly as urine analysis has a low specificity.[111]

**Chest x-ray**

Consider a [chest x-ray (CXR)](#) in any patient with suspected sepsis to help add weight to a suspected respiratory source (the most common source) of infection.[3]

**Practical tip**

A CXR is always indicated after central venous catheterisation (jugular or subclavian position) and/or endotracheal tube placement to rule out malposition and complications.[112] [113]

**Cultures from multiple sources**

Consider taking cultures from multiple sources to determine the site and/or organism responsible for the infection.[43] including:

- Urine
- Sputum (if accepted by the laboratory)
- Stool
- Cerebrospinal fluid
- Pleural fluid
- Ascitic fluid
- Joint fluid
- Abscess aspirate
- Swabs from open wounds or ulcers.

**Lumbar puncture**

Perform a [lumbar puncture](#) if you suspect meningitis or encephalitis, provided there is no suspicion of raised intracranial pressure (a computed tomography scan should be performed prior to lumbar puncture if you suspect raised intracranial pressure) or other risk to performing the procedure.[3] [43]

- This should never delay treatment, particularly the administration of antibiotics.
Computed tomography

A computed tomography (CT) scan of the chest and/or abdomen and pelvis provides cross sectional imaging of the body to attempt to identify the source of sepsis.\[3\] Consider early CT if you suspect gastrointestinal infection in particular as, in practice, outcomes tend to be worse with gastrointestinal sepsis compared with other sites of infection.

- A CT scan can help to identify a hidden collection (e.g., an intra-peritoneal abscess or effusion) in a patient presenting with ‘acute abdomen’, which may not be readily apparent on ultrasound or chest x-ray.
- CT can also be used to identify free air (perforation).
- If you suspect intra-abdominal or pelvic infection, involve the surgical or gynaecological teams early in case the patient needs surgical intervention.\[3\]

Ultrasound

Consider ultrasound scanning to help locate the source of the infection, particularly if you suspect an abdominal source or where the source of infection is not clear after the initial clinical examination and tests.\[43\]

- In particular, use ultrasound to identify:
  - Abscesses in the liver or skin
  - Free fluid (peritonitis)
  - Hydronephrosis (pyelonephritis).
- Ultrasound has a reasonable false negative rate; absence of positive findings on ultrasound does not rule out any given infection source.

Urine antigen testing

Carry out legionella and pneumococcal urine antigen testing in all patients with suspected or confirmed community-acquired pneumonia.\[120\]

Viral swabs

Consider rapid respiratory viral polymerase chain reaction in people with suspected respiratory aetiology.\[121\]

Other investigations for all patients

ECG

Request a baseline ECG for any patient with suspected sepsis, as you would for all acutely ill presentations, to:

- Rule out differential diagnoses: for example, myocardial infarction, pericarditis, or myocarditis
- Detect arrhythmias (e.g., atrial fibrillation); commonly seen in older people with sepsis.\[3\]

Other investigations to consider for some patients

HIV screen

Consider performing a screen for HIV infection, particularly in patients presenting with recurrent infections or atypical infections and those considered to be in high-risk groups.\[122\]
• Key risk factors for contracting HIV infection include intravenous drug use and unprotected sexual intercourse (heterosexual and homosexual).

Echocardiogram (echo)
Consider echo for a more detailed assessment of the **causes of the haemodynamic issues**.[43]
Use echo to assess (left and/or right) ventricular dysfunction, which may be caused by sepsis, and to detect endocarditis. Echo can also be used to assess inferior vena cava collapsibility, which is a marker of hypovolaemia.

Procedural videos

History and exam

Key diagnostic factors

risk factors (common)

Have a higher index of suspicion for sepsis when a patient presents with signs of infection and acute illness and falls into an at-risk group:

- Age older than 65 years (and particularly older than 75 years)[3] [9] [36] [51]
- Immunocompromised (e.g., chemotherapy, sickle cell disease, AIDS, splenectomy, long-term steroids)[3] [36] [37] [52] [53]
- Indwelling lines or catheters[3]
- Recent surgery (in previous 6 weeks).[3] The risk of sepsis is particularly high following oesophageal, pancreatic, or elective gastric surgery[38]
- Haemodialysis[36]
- Diabetes mellitus[36]
- Intravenous drug misuse[3]
- Alcohol dependence[36] [54]
- Pregnancy (and the 6 weeks after delivery/termination/miscarriage)[3]
- Breaches of skin integrity (e.g., burns, cuts, blisters, skin infections).[3]

Age younger than 1 year is also a strong risk factor.[3] See our topic **Sepsis in children**.

Be aware of the risk of sepsis in **women who are pregnant, have given birth, or have had a termination or miscarriage in the past 6 weeks**. Risk factors for the development of sepsis in these groups include:[3] [62]

- Obesity
- Gestational diabetes or diabetes mellitus
- Impaired immune systems (due to illness or drugs)
- Anaemia
- History of pelvic infection
- History of group B streptococcal infection
- Amniocentesis and other invasive procedures (e.g., instrumental delivery, caesarean section, removal or retained products of conception)
Sepsis in adults

Diagnosis

- Cervical cerclage
- Prolonged rupture of membranes
- Vaginal trauma
- Wound haematoma
- Close contact with people with group A streptococcal infection (e.g., scarlet fever).

Practical tip

When weighing up whether a patient who is acutely ill with symptoms or signs of possible infection can be safely managed in the community, it is important to consider whether they fall into one or more of the at-risk groups.[3]

Practical tip

Pay particular attention to the patient’s family/carers when taking a history. They will know the patient well and might be able to offer insight into acute behavioural changes as well as changes to their respiration or circulation, compared with the norm. Consider how they may describe the result of changes in physiology that are likely to have affected the patient’s vital observations, for example:[61]

- Altered mental state – ‘confused’, ‘drowsy’, ‘not themselves’
- Fever – ‘warm to touch’, ‘shivery’, ‘burning up’
- Hypotension – ‘dizzy’, ‘faint’, ‘lightheaded’
- Tachypnoeic – ‘out of breath’, ‘breathless’
- Tachycardic – ‘heart is racing’, ‘heart is pounding’.

Signs associated with specific source of infection (common)

The most common sources of infection are:[60]

- Respiratory tract (cough/pleuritic chest pain)
- Urinary tract (flank pain/dysuria)
- Abdominal/upper gastrointestinal tract (abdominal pain)
- Skin/soft tissue (abscess/wound/catheter site)
- Surgical site or line/drain site.

[Signs and symptoms of possible infection sources]

Use the history to identify factors for acquiring infection and clues to infection sites to guide choice of antimicrobial therapy.[21]

- Ask specific questions, including:
  - When was the last time you passed urine?
    - And how often over the past 18 hours?[3]
  - Do you take any medication?
  - Have you recently taken antibiotics?
  - Have you recently been in hospital and/or had surgical procedures?
  - Have you travelled abroad recently?
  - Have you had contact with animals?
Sepsis in adults

Diagnosis

• Have you had any contact with anyone infectious?

• Ask about the patient’s lifestyle, including:
  • Drug misuse
  • Alcohol intake
  • Housing situation.

Practical tip

Pay particular attention to the patient’s family/carers when taking a history. They will know the patient well and might be able to offer insight into acute behavioural changes as well as changes to their respiration or circulation, compared with the norm. Consider how they may describe the result of changes in physiology that are likely to have affected the patient’s vital observations, for example:[61]
  • Altered mental state – ‘confused’, ‘drowsy’, ‘not themselves’
  • Fever – ‘warm to touch’, ‘shivery’, ‘burning up’
  • Hypotension – ‘dizzy’, ‘faint’, ‘lightheaded’
  • Tachypnoeic – ‘out of breath’, ‘breathless’
  • Tachycardic – ‘heart is racing’, ‘heart is pounding’.

Practical tip

Check to see whether there are any microbiological samples already in the lab (e.g., urine sent by the GP) or other available test results (bloods, x-rays etc).

Evidence: Infectious causes of sepsis

The Extended Prevalence of Infection in Intensive Care (EPIC II) study provides the best recent evidence on the infectious causes of sepsis in an intensive care setting. [20]

The study gathered extensive data from more than 14,000 adult patients in 1265 intensive care units from 75 countries on a single day in May 2007.

Of the 7000 patients classified as ‘infected’, the sites of infection were the:
  • Lungs: 64%
  • Abdomen: 20%
  • Bloodstream: 15%
  • Renal or genitourinary tract: 14%.

Of the 70% of infected patients with positive microbiology:
  • 47% of isolates were gram-positive (Staphylococcus aureus alone accounted for 20%)
  • 62% were gram-negative (20% Pseudomonas species and 16% Escherichia coli)
  • 19% were fungal.

Other studies tend to broadly concur on the relative frequencies of sources of infection. The graph below shows the results of the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2015.[60]
Sepsis in adults

Diagnosis

The relative frequencies of sources of infection in sepsis

Evidence from studies in people over age 65 years shows the genitourinary tract is the biggest source of infection.[21] [22]

high early warning score (e.g., NEWS2 5 or more) (common)

Early identification of sepsis relies on systematic assessment of any acutely ill patient who presents with presumed infection to identify their risk of deterioration due to sepsis. By the time sepsis is at an advanced stage, with multiple abnormal physiological parameters, the risk of mortality is very high. [41]

In any patient in whom sepsis is a possibility, use a systematic process to check vital observations and assess and record the risk of deterioration .[41] [42] [43] Remember that no risk stratification process is 100% sensitive or 100% specific; therefore, you must use your clinical judgement.

Consult local guidelines for the recommended approach for assessing acute deterioration.

1. In hospital : use the National Early Warning Score 2 ( NEWS2 ) or an alternative early warning score .[41] [42] [44] NEWS2 is endorsed by NHS England for use in this setting.[41]

2. In the community : use an early warning score such as NEWS2 , which is recommended by NHS England[41] and the Royal College of General Practitioners in the UK,[50] or the UK National Institute for Health and Care Excellence (NICE) high-risk criteria .[3]

- None are validated in primary care.[50]
NEWS2 is the most widely used early warning score in the UK National Health Service and is endorsed by NHS England. In a patient with a known or likely infection, a NEWS2 score of 5 or more is likely to indicate sepsis.

Arrange urgent assessment by a senior clinical decision-maker (CT3/ST3 or higher in the UK, or a trained nurse with prescribing rights in acute care) for any patient with an aggregate NEWS2 score of 5 or more.

- The higher the resulting aggregate NEWS2 score, the higher the risk of clinical deterioration.
- If necessary (e.g., NEWS2 score of 7 or more) arrange emergency assessment by a critical care specialist.

Debate: NICE risk stratification versus NEWS2 scoring in community settings

Following the introduction of the NICE risk stratification criteria, there has been ongoing debate around their advantages and drawbacks. There is significant overlap between the NEWS2 scoring system and the NICE risk stratification criteria, with many of the same clinical observations used in both. A key difference is that the risk category a patient falls into under NEWS2 generally depends on an aggregate score across all the vital observations, whereas under the approach recommended by NICE this risk categorisation depends on a score on a single parameter.

- The decision as to whether to use the NEWS2 or NICE approach for recognition of suspected sepsis may be made at individual institution, clinical commissioning group, or regional level. What is important is that implementation of either approach should lead to more systematic assessment and recording of the vital observations that can help identify patients at risk of deterioration whose care needs escalating immediately.
- Whichever tool you use, it should only ever be in addition to (and never a replacement for) your clinical judgement.
- For example, NHS England has concluded that the complexity of the NICE risk stratification criteria make them difficult to translate into practice and has recommended the alternative NEWS2 approach as more pragmatic for frontline clinicians, both in hospital and community settings.
- Concern has also been raised about the low threshold for suspecting sepsis using the NICE criteria, which could lead to so many patients being referred to hospitals as emergencies that assessment and treatment could be delayed for those at the very highest risk. One small study that retrospectively reviewed admissions to an acute medical unit found the NICE criteria identified 69% of adult patients as requiring a review within 1 hour by a senior clinician.
- It is important to remember that none of these criteria negate clinical judgement and they should only be assessed in patients with suspected infections.
- The National Quality Board and NICE have recommended further evaluation of the use of NEWS2 in primary care and recognise the value of a 'common language' to communicate the severity of a patient's acute illness.
Although not specifically intended to be used for identifying suspected sepsis, several studies have highlighted how the National Early Warning Score (NEWS) may support earlier identification of patients with sepsis and septic shock. \[68\] \[70\] \[71\] These data relate specifically to NEWS, a previous iteration of NEWS2.

- An analysis of audit data from 20 emergency departments in the UK, which included a total of 2003 patients, found a single NEWS score calculated from the patient’s initial observations to be strongly predictive of adverse outcomes in sepsis.\[71\]
  - Total NEWS scores were grouped into four categories: 0-4, 5-6, 7-8, and 9-20.
  - Each rise in NEWS score category was associated with an increased risk of mortality when compared with the lowest category (0-4):\[71\]
    - 5-6: odds ratio (OR) 1.95 (95% CI 1.21 to 3.14)
    - 7-8: OR 2.26 (95% CI 1.42 to 3.61)
    - 9-20: OR 5.64 (95% CI 3.70 to 8.60).

- A further study of 30,677 adults admitted via emergency departments in the US with suspected infection found that the NEWS score performed better than either the Modified Early Warning Score (MEWS) or qSOFA scores in predicting the risk of death or need for an intensive care unit transfer.\[68\]
  - In a retrospective observational study, an aggregate NEWS score of 3 or more at emergency department triage was found to have a sensitivity of 92.6% (95% CI 74.2% to 98.7%) and a specificity of 77% (95% CI 72.8% to 80.6%) for detecting patients at risk of severe sepsis and septic shock.\[70\]

**Practical tip**

It is important to be aware that no scoring system has been validated for use in pregnant women; in practice, seek senior input to determine the best approach in a pregnant patient. Examples of scores that have been developed but are yet to be universally accepted include the following.

- A modified qSOFA has been proposed by the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) for use in pregnant women. The SOMANZ score includes systolic blood pressure 90 mmHg, respiratory rate >25 per minute, and altered mental status.\[72\]
- The Sepsis in Obstetrics Score uses a combination of maternal temperature, blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, white blood cell count, and lactic acid level as predictors of intensive care admission for sepsis.\[73\]

tachypnoea (NEWS2) (common)

A common non-specific sign of sepsis;\[3\] \[21\] \[43\] typically, respiratory rate >20 breaths/minute.

high or low temperature, sometimes with rigors (NEWS2) (common)

Although changes in body temperature are often seen in people with sepsis, temperature should not be used as the sole predictor of sepsis and should not be used to rule sepsis either in or out. Be aware that some people with sepsis will present with a normal temperature.\[3\] \[41\] \[42\]
**Practical tip**

Never rule out sepsis on the basis of a normal temperature reading. Fever is a common presenting sign but some patients are apyrexial or have hypothermia.[3]

- Always assess the patient’s temperature in the context of their wider clinical picture.
- Hypothermia at presentation is associated with a poorer prognosis than fever.[63]
- People who are older (>75 years) or very frail (regardless of age) are particularly prone to a blunted febrile response and may present with a normal temperature.[3] [64]
- Other groups that are less susceptible to temperature fluctuations and so may not develop a raised temperature with sepsis include:[3]
  - Infants or children
  - People with cancer receiving treatment
  - Severely ill patients.

**tachycardia (NEWS2) (common)**

A common feature of sepsis:[21] [43] typically heart rate >90 beats per minute (bpm).

**Practical tip**

Always interpret the vital signs that you take as part of the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) assessment in relation to the patient’s known or likely baseline for that parameter; take account of the patient in front of you and the full clinical picture. For example:

- A fall in systolic blood pressure of ≥40 mmHg from the patient's baseline is a cause for concern, regardless of the systolic blood pressure reading itself.[3]
- Although tachycardia can be an indicator of potential risk of sepsis developing, when assessing heart rate you should consider:[3]

  - Pregnancy
    - In pregnant people, heart rate is usually 10 to 15 bpm faster than normal
  - Older people
    - Older people may not develop tachycardia in response to infection and are more at risk of developing new arrhythmias (e.g., atrial fibrillation)
  - Medications
    - Some drugs, such as beta-blockers or rate-limiting calcium-channel blockers, may inhibit a tachycardic response to infection
  - Baseline
    - The baseline heart rate in young people or people who are very physically fit (e.g., athletes) may be lower than the norm. The rate of change of heart
rate may therefore be more important (to reflect the severity of infection) than the actual rate.

**acutely altered mental status (NEWS2) (common)**

Determine the patient’s baseline mental state and establish whether there has been a change. [3] Use a validated scale (e.g., the Glasgow Coma Scale or AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale). [3] As well as checking response to cues, you should ask a relative or carer (if available) about the patient’s recent behaviour.[3]

**Practical tip**

Change in mental state is a commonly missed sign of sepsis, particularly in older patients in whom dementia may co-exist. Change in mental state is often due to non-infectious causes (e.g., electrolyte disturbances). It can manifest in many ways, which makes it challenging to recognise as part of a short clinical consultation.

- The term ‘confusion’ can be unhelpful and instead you should attempt to identify any change from the patient’s normal behaviour or cognitive state .[3]
- A collateral history – if friends, family members, or carers are available – is key. They might describe the patient as ‘not themselves’.
- In people with dementia, change in mental state may present as irritability or aggression .[3] but equally could present with hypoactive delirium (e.g., with lethargy, apathy). [59]
- In addition, sepsis may be signalled by a deterioration in functional ability (e.g., a patient newly unable to stand from sitting).[3]

**low oxygen saturation (NEWS2) (common)**

Low oxygen saturation is often seen in people with sepsis:[21] [43] systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, or reduction in systolic blood pressure >40 mmHg from baseline.

**Practical tip**

Difficulty obtaining peripheral oxygen saturations may be a red flag for possible shock. [3]

- Peripheral oxygen saturations can be difficult to measure in a patient with sepsis if the tissues are hypoperfused .
  - This may occur in the later stages of the condition , as earlier in the disease process the circulation is usually hyperdynamic.
  - Some conditions such as meningococcal sepsis can present early with poor peripheral perfusion . These patients often have profound myocardial depression on presentation. In others, there may be a hyperdynamic central circulation concurrent with poor peripheral perfusion and a subsequent uncoupling of blood flow.
- You should have a high index of suspicion for shock if you are unable to measure oxygen saturations .
- See our topic Shock .

**hypotension (NEWS2) (common)**
Hypotension is commonly seen in people with sepsis.\cite{21} \cite{43}

**Beware septic shock, a subtype of sepsis with a much higher mortality.** \cite{1} \cite{42}

- Characterised by profound circulatory and metabolic abnormalities.
- Presents with **persistent hypotension** and serum lactate \(>2\) mmol/L (\(>18\) mg/dL) despite adequate fluid resuscitation, with a need for vasopressors to maintain mean arterial pressure \(\geq 65\) mmHg.\cite{1}

**oliguria (common)**

**Assess the patient’s urine output.** \cite{3} \cite{43} \cite{46}

- Ask the patient or their carer about urine output over the previous 12 to 18 hours
- Consider catheterising the patient on presentation if they are shocked, confused, oliguric, or critically unwell
- Ensure arrangements are in place for urine output to be monitored once an hour.

**A low urine output may suggest intravascular volume depletion and/or acute kidney injury and is therefore a marker of sepsis severity.**

- The UK National Institute for Health and Care Excellence sepsis guideline categorises any patient who has not passed urine in the previous 18 hours (or for catheterised patients passed less than 0.5 mL/kg of urine per hour) as being at high risk of severe illness or death from sepsis.\cite{3}

**poor capillary refill, mottling of the skin, or ashen appearance (common)**

Signs of circulatory insufficiency are thought to indicate peripheral perfusion, with a longer capillary refill time suggesting reduced capillary perfusion.\cite{125}
Sepsis in adults

Diagnosis

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

cyanosis (common)
A common non-specific sign of sepsis.[21] [43]

Other diagnostic factors

malaise/lethargy (common)
Commonly seen in people with sepsis.[21] [43]

nausea/vomiting/diarrhoea (common)
Commonly seen in people with sepsis.[21] [43]

purpura fulminans (uncommon)
A very late sign of possible organ dysfunction; may be seen on presentation.

*Severe purpura fulminans; classically associated with meningococcal sepsis but can occur with pneumococcal sepsis*

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission

**ileus (uncommon)**

A sign of possible organ dysfunction.

**jaundice (uncommon)**

A rare sign of organ dysfunction unless it is associated with a specific source of infection (biliary sepsis).
## Investigations

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood cultures</td>
<td>may be positive for infection-causing organism</td>
</tr>
<tr>
<td>Take bloods immediately, before antibiotics are started (although sampling should not delay the administration of antibiotics).</td>
<td></td>
</tr>
<tr>
<td>Ideally, take peripheral blood cultures (aerobic and anaerobic) from at least two different sites.</td>
<td></td>
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<tr>
<td>• Prioritise filling the aerobic bottle before filling the anaerobic one.</td>
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</tr>
<tr>
<td>• To improve yield, ensure these samples are incubated as soon as possible.</td>
<td></td>
</tr>
<tr>
<td>If you suspect a line infection, remove the line and culture the tip.</td>
<td></td>
</tr>
<tr>
<td><strong>Practical tip</strong></td>
<td></td>
</tr>
<tr>
<td>Take blood cultures and measure serum lactate at the same time.</td>
<td></td>
</tr>
<tr>
<td>Take cultures of blood and other fluids at the first opportunity as they may take up to 48 to 72 hours to yield sensitivities of causative organisms (if identified). It is usually possible to take cultures first without this causing any delay to administration of antibiotics. This is important as cultures are far less likely to be positive if delayed until after giving antimicrobials.</td>
<td></td>
</tr>
<tr>
<td>serum lactate</td>
<td>may be elevated; persistent levels &gt;2 mmol/L (&gt;18 mg/dL) associated with adverse prognosis; even worse prognosis with persistent levels &gt;4 mmol/L (&gt;36 mg/dL)</td>
</tr>
<tr>
<td>Measure serum lactate, on a blood gas, to determine the severity of the sepsis and monitor response to treatment.</td>
<td></td>
</tr>
<tr>
<td>• Lactate is a marker of stress and may be a marker of a worse prognosis (as a reflection of the degree of stress). Raised serum lactate highlights the possibility of tissue hypoperfusion and may be present in many conditions.</td>
<td></td>
</tr>
<tr>
<td>• Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst.</td>
<td></td>
</tr>
<tr>
<td>• Lactate &gt;4 mmol/L (&gt;36 mg/dL) is associated with worse outcomes.</td>
<td></td>
</tr>
<tr>
<td>• One study found in-hospital mortality rates as follows:[79]</td>
<td></td>
</tr>
<tr>
<td>• Lactate &lt;2 mmol/L (&lt;18 mg/dL): 15%</td>
<td></td>
</tr>
<tr>
<td>• Lactate 2.1 to 3.9 mmol/L (19 to 35 mg/dL): 25%</td>
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</tbody>
</table>
### Sepsis in adults

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>• Lactate &gt;4 mmol/L (&gt;36 mg/dL): 38%.</td>
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</tr>
</tbody>
</table>

**Practical tip**

Take blood cultures and measure serum lactate at the same time.

**Sepsis guidelines from the National Institute for Health and Care Excellence (NICE) in the UK and NHS England recommend escalating treatment depending on lactate level.**

[3] [41] #Alert critical care immediately if the patient is acutely unwell and has persistent lactate >4 mmol/L (>36 mg/dL) [3] #despite fluid resuscitation.

Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL]).

• This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their NEWS2 score.

**Practical tip**

Lactate is typically measured using a blood gas analyser, although laboratory analysis can also be performed. Traditionally, arterial blood gas has been recommended as the ideal means of measuring lactate accurately. However, in practice, in the emergency department setting it may be more practical and quicker to use venous blood gas, which is recommended by NICE although this recommendation is not supported by strong evidence.[3] Evidence suggests good agreement at lactate levels <2 mmol/L (<18 mg/dL) with small disparities at higher lactate levels.[80] [81] [82]

Be aware that persisting raised lactate may not be recognised until after initial resuscitation has been given. In the patient with persisting raised lactate, ensure:

• Adequate source control; remove any suspected septic or necrotic focus
• The patient is adequately filled (their central venous pressure ‘goes up and stays up’)  
• The patient’s cardiac output and blood pressure are adequate for their tissue needs (a low central venous oxygen saturation, ScvO$_2$, serves as a good indicator of impaired tissue oxygenation).

**Practical tip**
## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent raised lactate should incite efforts to identify other hidden causes including thiamine deficiency, adrenaline or other drugs, and liver failure.</td>
<td></td>
</tr>
<tr>
<td><strong>hourly urine output</strong></td>
<td>may be markedly decreased</td>
</tr>
<tr>
<td>Assess the patient’s urine output. [3] [43] [46]</td>
<td></td>
</tr>
<tr>
<td>• Ask the patient or their carer about urine output over the previous 12 to 18 hours</td>
<td></td>
</tr>
<tr>
<td>• Consider catheterising the patient on presentation if they are shocked, confused, oliguric, or critically unwell</td>
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</tr>
<tr>
<td>• Ensure arrangements are in place for urine output to be monitored once an hour.</td>
<td></td>
</tr>
<tr>
<td>A low urine output may suggest intravascular volume depletion and/or acute kidney injury and is therefore a marker of sepsis severity.</td>
<td></td>
</tr>
<tr>
<td>• The UK National Institute for Health and Care Excellence sepsis guideline categorises any patient who has not passed urine in the previous 18 hours (or for catheterised patients passed less than 0.5 mL/kg of urine per hour) as being at high risk of severe illness or death from sepsis.[3]</td>
<td></td>
</tr>
<tr>
<td><strong>full blood count</strong></td>
<td></td>
</tr>
<tr>
<td>Carry out a venous blood test to determine the patient’s full blood count.[3]</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia of non-haemorrhagic origin may occur in patients who are severely ill with sepsis.[94]</td>
<td></td>
</tr>
<tr>
<td>• Persistent thrombocytopenia is associated with an increased risk of mortality.[94]</td>
<td></td>
</tr>
<tr>
<td>Lymphocytopenia is increasingly recognised as a useful sign in a patient with sepsis.</td>
<td></td>
</tr>
<tr>
<td>The <strong>WBC count</strong> is neither sensitive nor specific for sepsis.[95]</td>
<td></td>
</tr>
<tr>
<td>• WBC count was one of the diagnostic criteria for sepsis under the old systemic inflammatory response syndrome (SIRS) definition but this has been superseded by the 2016 Sepsis-3 diagnostic criteria, which rely on demonstrating organ dysfunction.[1]</td>
<td></td>
</tr>
<tr>
<td><strong>Practical tip</strong></td>
<td></td>
</tr>
<tr>
<td>Non-infectious (e.g., crush) injury, surgery, cancer, and immunosuppressive agents can also lead to either increased or decreased WBC counts.</td>
<td></td>
</tr>
<tr>
<td><strong>urea and electrolytes (including creatinine)</strong></td>
<td></td>
</tr>
<tr>
<td>Request urea and electrolyte tests;[3] use to:</td>
<td></td>
</tr>
<tr>
<td>• Evaluate the patient for renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Serum electrolytes frequently deranged; blood urea may be</td>
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</tbody>
</table>
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td><strong>serum glucose</strong>&lt;br&gt;Measure serum glucose on blood gas, [3] in venous blood through venepuncture, or via capillary blood with bedside testing.</td>
<td>elevated or, more rarely, low&lt;br&gt;May be elevated or, more rarely, low</td>
</tr>
<tr>
<td>• Depending on the patient’s baseline glucose level, hyperglycaemia may be associated with increased morbidity and mortality in patients with sepsis.[97]</td>
<td></td>
</tr>
<tr>
<td>• Bear in mind that studies have shown that people with diabetes show no clear association between hyperglycaemia during intensive care unit stay and mortality and markedly lower odds ratios of death at all levels of hyperglycaemia.[98]&lt;br&gt;Glucose levels may be elevated, with or without a known history of diabetes mellitus, due to the stress response and altered glucose metabolism.[97] [99] Drug therapy (e.g., with corticosteroids and catecholamines) may also lead to elevated glucose.</td>
<td></td>
</tr>
<tr>
<td><strong>Practical tip</strong>&lt;br&gt;Spontaneous or iatrogenic hypoglycaemia also poses significant dangers.[100] [101] Persisting hypoglycaemia may suggest acute liver failure.[102]</td>
<td></td>
</tr>
<tr>
<td><strong>C-reactive protein</strong>&lt;br&gt;Carry out a venous blood test to determine the patient’s level of C-reactive protein.[3]&lt;br&gt;Reasonably sensitive, but not specific, for sepsis.[3] [103] [104]</td>
<td>elevated&lt;br&gt;May be elevated</td>
</tr>
<tr>
<td><strong>serum procalcitonin</strong>&lt;br&gt;Baseline serum procalcitonin is increasingly being used in critical care settings to guide decisions on how long to continue antibiotic therapy.[43] [105] [106] [107]&lt;br&gt;Procalcitonin is a peptide precursor of calcitonin, which is responsible for calcium homeostasis.&lt;br&gt;It is currently excluded from key guidelines, but increasingly used in practice.</td>
<td></td>
</tr>
</tbody>
</table>
### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>clotting screen</strong></td>
<td>elevated PT; elevated PTT; elevated D-dimer; elevated fibrinogen</td>
</tr>
<tr>
<td>Include prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. [3]</td>
<td></td>
</tr>
<tr>
<td>• Use to determine whether the patient has established coagulopathy in the presence of sepsis. This is associated with a worse prognosis.[108]</td>
<td></td>
</tr>
<tr>
<td><strong>liver function tests</strong></td>
<td>elevated bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma glutamyl transpeptidase</td>
</tr>
<tr>
<td>Use liver function tests, notably <strong>bilirubin</strong>, to evaluate for <strong>organ dysfunction</strong>.[109] [110] Liver dysfunction may also be a cause of a coagulopathy.</td>
<td></td>
</tr>
<tr>
<td><strong>blood gas</strong></td>
<td>PaCO$_2$ &lt;4.3 kPa (32 mmHg) is one of the diagnostic criteria for systemic inflammatory response syndrome; may be hypoxaemia, hypercapnia</td>
</tr>
<tr>
<td>Use either arterial blood gas (ABG) or venous blood gas (VBG) evaluation. [3] #Use ABG to optimise oxygenation and assess metabolic status (acid-base balance), particularly with regard to the arterial carbon dioxide level (PaCO$_2$ ).</td>
<td></td>
</tr>
<tr>
<td>• In ventilated patients, this may help to determine the positive end-expiratory pressure (PEEP), while minimising adverse levels of inspiratory pressure and unnecessarily high fraction of inspired oxygen (FiO$_2$ ).</td>
<td></td>
</tr>
<tr>
<td><strong>Practical tip</strong></td>
<td>VBG is increasingly being used in preference to ABG in the emergency department, particularly if a respiratory cause seems unlikely. VBG is less invasive and less painful than ABG and evidence shows there is good concordance between venous and arterial values for pH, bicarbonate ion concentration, base excess, and lactate.[78] ABG will be used instead of VBG if the patient is escalated to critical care as an arterial line is usually inserted for ease of access. Be aware that venous PCO$_2$ may be artificially high if taken from a tourniqueted limb.</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>may show evidence of ischaemia, atrial fibrillation, or other arrhythmia</td>
</tr>
<tr>
<td>Request a baseline ECG for any patient with suspected sepsis, as you would for all acutely ill presentations, to:</td>
<td></td>
</tr>
<tr>
<td>• <strong>Rule out differential diagnoses</strong>: for example, myocardial infarction, pericarditis, or myocarditis</td>
<td></td>
</tr>
<tr>
<td>• <strong>Detect arrhythmias</strong> (e.g., atrial fibrillation); commonly seen in older people with sepsis.[3]</td>
<td></td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>urine analysis</strong></td>
<td>may show evidence of infection (nitrates; leucocytes; blood/protein)</td>
</tr>
<tr>
<td></td>
<td>Consider a dipstick test in any patient who has suspected sepsis to</td>
</tr>
<tr>
<td></td>
<td>help <strong>add weight to a suspected urinary source</strong> of infection.[3]</td>
</tr>
<tr>
<td></td>
<td>Always interpret urine analysis in the context of the wider clinical</td>
</tr>
<tr>
<td></td>
<td>assessment.</td>
</tr>
<tr>
<td></td>
<td>• Bear in mind that this does not definitively confirm a urinary</td>
</tr>
<tr>
<td></td>
<td>source, particularly as urine analysis has a low specificity.[111]</td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td>may show evidence of infection, such as consolidation or pleural</td>
</tr>
<tr>
<td></td>
<td>effusion, cardiac abnormalities, or a pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Consider a chest x-ray (CXR) in any patient with suspected sepsis</td>
</tr>
<tr>
<td></td>
<td>to help <strong>add weight to a suspected respiratory source</strong> (the most</td>
</tr>
<tr>
<td></td>
<td>common source) of infection.[3]</td>
</tr>
<tr>
<td><strong>Practical tip</strong></td>
<td>A CXR is always indicated after central venous catheterisation</td>
</tr>
<tr>
<td></td>
<td>(jugular or subclavian position) and/or endotracheal tube placement</td>
</tr>
<tr>
<td></td>
<td>to rule out malposition and complications.[112]</td>
</tr>
<tr>
<td></td>
<td>[113]</td>
</tr>
<tr>
<td><strong>cultures from multiple sources</strong></td>
<td>may be positive for infection-causing organism</td>
</tr>
<tr>
<td></td>
<td>Consider taking cultures from multiple sources to determine the site</td>
</tr>
<tr>
<td></td>
<td>and/or organism responsible for the infection,[43] including:</td>
</tr>
<tr>
<td></td>
<td>• Urine</td>
</tr>
<tr>
<td></td>
<td>• Sputum (if accepted by the laboratory)</td>
</tr>
<tr>
<td></td>
<td>• Stool</td>
</tr>
<tr>
<td></td>
<td>• Cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>• Pleural fluid</td>
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<tr>
<td></td>
<td>• Ascitic fluid</td>
</tr>
<tr>
<td></td>
<td>• Joint fluid</td>
</tr>
<tr>
<td></td>
<td>• Abscess aspirate</td>
</tr>
<tr>
<td></td>
<td>• Swabs from open wounds or ulcers.</td>
</tr>
<tr>
<td><strong>lumbar puncture</strong></td>
<td>elevated WBC count, presence of organism on microscopy, and positive</td>
</tr>
<tr>
<td></td>
<td>Perform a lumbar puncture if you suspect meningitis or encephalitis,</td>
</tr>
<tr>
<td></td>
<td>provided there is no suspicion of raised intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>(a computed tomography scan should be performed prior to lumbar</td>
</tr>
<tr>
<td></td>
<td>puncture if you suspect raised intracranial pressure) or other risk</td>
</tr>
<tr>
<td></td>
<td>to performing the procedure.[3] [43]</td>
</tr>
<tr>
<td></td>
<td>• This should never delay treatment, particularly the administration</td>
</tr>
<tr>
<td></td>
<td>of antibiotics.</td>
</tr>
<tr>
<td><strong>computed tomography</strong></td>
<td>findings vary depending on systems affected but may include: a hidden</td>
</tr>
<tr>
<td></td>
<td>Perform a computed tomography (CT) scan of the chest and/or abdomen</td>
</tr>
<tr>
<td></td>
<td>and pelvis provides cross-sectional imaging of the body to attempt</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>to identify the source of sepsis.[3]</td>
<td>(e.g., a visceral abscess or effusion); free air (perforation)</td>
</tr>
<tr>
<td>Consider early CT if you suspect</td>
<td></td>
</tr>
<tr>
<td>gastrointestinal (GI) infection in</td>
<td></td>
</tr>
<tr>
<td>particular as, in practice, outcomes</td>
<td></td>
</tr>
<tr>
<td>tend to be worse with GI sepsis</td>
<td></td>
</tr>
<tr>
<td>compared with other sites of infection.</td>
<td></td>
</tr>
<tr>
<td>• A CT scan can help to identify a</td>
<td></td>
</tr>
<tr>
<td>hidden collection (e.g., an intra-</td>
<td></td>
</tr>
<tr>
<td>peritoneal abscess or effusion) in a</td>
<td></td>
</tr>
<tr>
<td>patient presenting with 'acute abdomen',</td>
<td></td>
</tr>
<tr>
<td>which may not be readily apparent on</td>
<td></td>
</tr>
<tr>
<td>ultrasound or chest x-ray.</td>
<td></td>
</tr>
<tr>
<td>• CT can also be used to identify free</td>
<td></td>
</tr>
<tr>
<td>air (perforation).</td>
<td></td>
</tr>
<tr>
<td>• If you suspect intra-abdominal or pelvic</td>
<td></td>
</tr>
<tr>
<td>infection, involve the surgical or</td>
<td></td>
</tr>
<tr>
<td>gynaecological teams early in case the</td>
<td></td>
</tr>
<tr>
<td>patient needs surgical intervention.[3]</td>
<td></td>
</tr>
<tr>
<td>ultrasound</td>
<td></td>
</tr>
<tr>
<td>Consider ultrasound scanning to help</td>
<td></td>
</tr>
<tr>
<td>locate the source of the infection,</td>
<td></td>
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<tr>
<td>particularly if you suspect an</td>
<td></td>
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<tr>
<td>abdominal source or where the source of</td>
<td></td>
</tr>
<tr>
<td>infection is not clear after the initial</td>
<td></td>
</tr>
<tr>
<td>clinical examination and tests.[43]</td>
<td></td>
</tr>
<tr>
<td>• In particular, use ultrasound to</td>
<td></td>
</tr>
<tr>
<td>identify:</td>
<td></td>
</tr>
<tr>
<td>• Abscesses in the liver or skin</td>
<td></td>
</tr>
<tr>
<td>• Free fluid (peritonitis)</td>
<td></td>
</tr>
<tr>
<td>• Hydronephrosis (pyelonephritis).</td>
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<tr>
<td>• Ultrasound has a reasonable false</td>
<td></td>
</tr>
<tr>
<td>negative rate; absence of positive</td>
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<tr>
<td>findings on ultrasound does not rule out</td>
<td></td>
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<tr>
<td>any given infection source.</td>
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<tr>
<td>urine antigen testing</td>
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</tr>
<tr>
<td>Carry out legionella and pneumococcal</td>
<td>may show evidence of infection</td>
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<tr>
<td>urine antigen testing in all patients</td>
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<tr>
<td>with suspected or confirmed community-</td>
<td></td>
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<tr>
<td>acquired pneumonia.[120]</td>
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</tr>
<tr>
<td>viral swabs</td>
<td>may show evidence of respiratory infection</td>
</tr>
<tr>
<td>Consider rapid respiratory viral</td>
<td></td>
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<tr>
<td>polymerase chain reaction in people with</td>
<td></td>
</tr>
<tr>
<td>suspected respiratory aetiology.[121]</td>
<td></td>
</tr>
<tr>
<td>HIV screen</td>
<td>may be positive for HIV</td>
</tr>
<tr>
<td>Consider performing a screen for HIV</td>
<td></td>
</tr>
<tr>
<td>infection, particularly in patients</td>
<td></td>
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<tr>
<td>presenting with recurrent infections or</td>
<td></td>
</tr>
<tr>
<td>atypical infections and those</td>
<td></td>
</tr>
<tr>
<td>considered to be in high-risk groups.[122]</td>
<td></td>
</tr>
<tr>
<td>• Key risk factors for contracting HIV</td>
<td></td>
</tr>
<tr>
<td>infection include intravenous drug use</td>
<td></td>
</tr>
<tr>
<td>and unprotected sexual intercourse</td>
<td></td>
</tr>
<tr>
<td>(heterosexual and homosexual).</td>
<td></td>
</tr>
<tr>
<td>echocardiogram</td>
<td>inadequate left ventricular filling suggests hypovolaemia;</td>
</tr>
<tr>
<td>Consider echocardiogram (echo) for a</td>
<td></td>
</tr>
<tr>
<td>more detailed assessment of the causes of</td>
<td></td>
</tr>
<tr>
<td>the haemodynamic issues.[43] Use echo to</td>
<td></td>
</tr>
<tr>
<td>assess (left and/or right) ventricular</td>
<td></td>
</tr>
<tr>
<td>dysfunction, which may be caused by</td>
<td></td>
</tr>
<tr>
<td>sepsis, and to detect endocarditis.</td>
<td></td>
</tr>
<tr>
<td>Echo can also be</td>
<td></td>
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<tr>
<td>Test</td>
<td>Result</td>
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</tr>
<tr>
<td>used to assess inferior vena cava collapsibility, which is a marker of hypovolaemia.</td>
<td>vegetations, if endocarditis is cause of sepsis</td>
</tr>
</tbody>
</table>
## Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-infectious causes of systemic inflammatory response syndrome (SIRS)</strong></td>
<td>• SIRS can result as a non-specific finding from a host of other disease states, including post-operative recovery, trauma, burns, transplant rejection, hyperthyroidism, Addisonian crisis, blood product transfusion reactions, serum sickness, immunisations, and central nervous system infarction or haemorrhages.</td>
<td>• Specific tests are directed by clinical suspicion of underlying cause. • 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><strong>Myocardial infarction (MI)</strong></td>
<td>• Symptoms suggesting MI are central, squeezing chest pain or pressure radiating down the left arm or into the jaw. Pain may be felt in the epigastric region. • Patients may present in cardiogenic shock with breathlessness and hypotension. A low-grade fever and raised C-reactive protein may also be present.</td>
<td>• Ischaemic changes on ECG. Elevated creatine kinase-MB and troponin.</td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td>• Patients present with sharp, stabbing, pleuritic chest pain (typically better on sitting up and leaning forward, and worse with lying down) and sometimes a low-grade fever.</td>
<td>• ECG may have upward concave ST-segment elevation globally and PR-segment depression. • Echo may demonstrate a pericardial effusion; absence of left ventricular wall motion abnormalities.</td>
</tr>
<tr>
<td><strong>Myocarditis</strong></td>
<td>• Patients typically present with a viral prodrome (which may include a low-grade fever), dyspnoea, or underlying autoimmune condition, such as systemic lupus erythematosus. • Medications such as antibiotics, thiazide diuretics, antiepileptics, digoxin, lithium, amitriptyline, and dobutamine may be suggestive of drug aetiology.</td>
<td>• ECG may show non-specific ST-segment and T-wave abnormalities. • Inflammatory markers may be elevated. • Two-dimensional echo demonstrates global and regional left ventricular motion abnormalities and dilatation.</td>
</tr>
<tr>
<td><strong>Acute pancreatitis</strong></td>
<td>• May present with abdominal pain radiating through to the</td>
<td>• Elevated serum amylase, lipase, glucose; low calcium.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sepsis in adults</td>
<td>back, low-grade fever, and hypovolaemia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• There may be a history of gallstones, alcohol use, or viral infections (e.g., mumps).</td>
<td></td>
</tr>
<tr>
<td>Massive pulmonary embolism</td>
<td>• Typically presents with acute dyspnoea and hypotension. Symptoms may also include fever, decreased consciousness, syncope or pre-syncope, and pleuritic chest pain. Risk factors for thromboembolic disease may be evident.</td>
<td>• CT pulmonary angiogram shows a filling defect in the pulmonary arteries.</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>• 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.</td>
<td>• 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.</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>• This is a rare condition characterised by severe hyperthermia (&gt;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.[126] Malignant hyperthermia is an inherited disorder (autosomal dominant) and a high index of suspicion is necessary if there is a positive family history.[126]</td>
<td>• 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.[127] • 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.</td>
</tr>
<tr>
<td>Drug-induced fever and coma</td>
<td>• This includes neuroleptic malignant syndrome, serotonergic syndrome, delirium tremens, and metformin lactic acidosis.</td>
<td>• Clinical diagnosis. Specific tests are not readily available.</td>
</tr>
</tbody>
</table>
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.

In February 2016, new definitions of sepsis and septic shock were published by the Third International Consensus group; the so-called ‘Sepsis-3’ definitions.[43] Sepsis was redefined by Sepsis-3 as “life-threatening organ dysfunction caused by a dysregulated host response to infection”. [43]

Organ dysfunction is defined as a change of 2 or more points in the Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) score.[43]

Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) criteria

The shift away from the previous definitions (which described sepsis as a systemic inflammatory response syndrome [SIRS] arising due to a new infection) aimed to facilitate earlier diagnosis as well as greater consistency for research outcomes.[43]

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...
Sepsis in adults

Diagnosis

hypotension despite adequate fluid replacement.[3] However, the 2016 Third International Consensus Group (Sepsis-3) definitions state that the term 'severe sepsis' should be made redundant in light of the revisions to the definition of sepsis.[43]

Acute Physiology and Chronic Health Evaluation II score (APACHE II)[128]

The APACHE score is commonly used to establish illness severity in the intensive care unit (ICU) and predict the risk of death. 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.[129] [130] [131]

Patient group-specific scoring systems have also been developed. For example, the Predisposition Insult Response and Organ failure and Mortality in Emergency Department Sepsis scores have been developed to risk stratify patients with sepsis or septic shock who are admitted to the accident and emergency department;[132] the Sepsis in Obstetrics Score has been developed to risk stratify pregnant or postnatal women with sepsis.[73] These scoring systems can assist in the identification and management of sepsis in specific patient groups.[133]

There are numerous ongoing studies investigating techniques for 'staging' the severity of sepsis using a variety of blood-borne markers.[134] [135] Although some techniques have shown initial promise, the evidence base remains weak, and they have an unclear role in future clinical practice.

Risk stratification

In any patient in whom sepsis is a possibility, use a systematic process to check vital observations and assess and record the risk of deterioration.[41] [42] [43] Remember that no risk stratification process is 100% sensitive or 100% specific; therefore, you must use your clinical judgement.

Consult local guidelines for the recommended approach for assessing acute deterioration.

1. In hospital: use the National Early Warning Score 2 (NEWS2) or an alternative early warning score.[41] [42] [44] NEWS2 is endorsed by NHS England for use in this setting.[41]

2. In the community: use an early warning score such as NEWS2, which is recommended by NHS England[41] and the Royal College of General Practitioners in the UK,[50] or the UK National Institute for Health and Care Excellence high-risk criteria.[3]

   • None is validated in primary care.[50]

NEWS2 is the most widely used early warning score in the UK National Health Service and is endorsed by NHS England.[41] [NHS England: Sepsis] In a patient with a known or likely infection, a NEWS2 score of 5 or more is likely to indicate sepsis.[42]

See the Risk stratification subsection of Diagnosis recommendations for more information.
Recommendations

Urgent

Start treatment **immediately** if a senior clinical decision-maker makes a diagnosis of suspected sepsis.\[41\] [42] [NHS England: Sepsis]

- Sepsis is suspected based on acute deterioration (e.g., National Early Warning Score 2 [NEWS2] score of 5 or more, or a similar trigger using another validated scoring system) in a patient with known or likely infection.\[41\] [42] #For more detail on when to suspect sepsis, see Diagnosis recommendations.
- In the UK, a senior clinical decision-maker is CT3/ST3 or higher, or a trained nurse with prescribing rights in acute care.\[41\]

Treat suspected sepsis (i.e., new organ dysfunction related to severe infection) promptly. **Establish venous access early so you can proceed without delay to** \[3\] [41] [43] [46]

- Give within 1 hour of the risk being recognised:
  1. Intravenous antibiotics: where there is evidence of a bacterial infection, administer broad-spectrum empirical intravenous antibiotics before a pathogen is identified
    - Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice; use a ‘start smart then focus’ approach\[41\] [136]
    - Target the presumed site of infection if known
    - Take bloods immediately, preferably before antibiotics are started (although sampling should not delay the administration of antibiotics)\[3\] [43] [48] [49]
    - Narrow the choice of antibiotic as soon as a pathogen has been identified and sensitivities are available\[43\] [137]
  2. Intravenous fluids: 500 mL of crystalloid, with sodium in the range 130 to 154 mmol/L (130 to 154 mEq/L), over less than 15 minutes, if there is any sign of circulatory insufficiency
    - Repeat if clinically indicated
    - Do not exceed 30 mL/kg
  3. Oxygen: as needed, to maintain target oxygen saturations >94%\[3\] [43] [46] [47]
    - Latest evidence suggests that liberal use of supplemental oxygen (target SpO\textsubscript{2} >96%) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy.\[138\] Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia
    - Target saturation of 88% to 92% in people at risk of hypercapnic respiratory failure (e.g., those with COPD)
    - Take within 1 hour of the risk being recognised:
1. Blood cultures
2. Lactate level
3. Hourly urine output.

**Consult local protocols for specific routes of escalation.** In general, in hospital:

• Discuss with the admitting consultant,[3] and consider alerting critical care immediately if the patient is acutely unwell and:

  • Has a NEWS2 score of 7 or more, persisting high lactate (more than 4 mmol/L [36 mg/dL]) despite fluid resuscitation, or a systolic blood pressure of less than 90 mmHg[3]

    • Discuss with the admitting consultant[3]
  
  • Has hypotension that doesn’t respond to initial fluid resuscitation
  
  • Is likely to require central venous access and the initiation of inotropes or vasopressors[3]
  
  • Has any feature of septic shock

    • See our topic Shock
  
  • Has neutropenia
  
  • Is immunodeficient.

• **Urgently** discuss with a consultant or call them to attend if the patient:[41]

  • Is treated with intravenous antibiotics and/or a fluid bolus for sepsis
  
  • Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour.[3] [41] Failure to respond to treatment is defined as:[3]

    • Systolic blood pressure remains less than 90 mmHg
    • Persistent reduced level of consciousness
    • Respiratory rate more than 25 breaths per minute or the new need for mechanical ventilation
    • Lactate has not reduced by more than 20%.

Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

**Urgent: in the community**

**Refer for emergency medical care in hospital (usually by blue-light ambulance in the UK)** any patient who is acutely ill with a suspected infection and is:[3]

• Deemed to be at high risk of deterioration due to organ dysfunction, as measured by a formal risk stratification process such as NEWS2, which is recommended by NHS England, or the UK National Institute for Health and Care Excellence high-risk criteria[3] [41] [43]

• At risk of neutropenic sepsis.
Start oxygen therapy, if indicated, while awaiting the ambulance if resources are available to do so.[139][140]

Ensure you have a mechanism in place to administer antibiotics, if needed, to any high-risk patient (either at your practice or via the ambulance service) if the transfer to hospital is likely to be delayed.

Key Recommendations

Sepsis is a medical emergency. [3] [43] The key to improving outcomes is early recognition and prompt treatment, as appropriate, of patients with suspected or confirmed infection who are deteriorating and at risk of organ dysfunction.[3] [43]

- Always use your clinical judgement. [41]
- Take into account the full clinical picture of the individual patient in front of you including their NEWS2 score.

Identify and treat underlying source

Early and adequate source identification and control is critical. Undertake intensive efforts, including imaging, to attempt to identify the source of infection in all patients with sepsis. [3] [43]

- Consider the need for urgent source control as soon as the patient is stable.
- The respiratory tract is the most common site of infection in most people with sepsis.[20] [60] However, in people over age 65 years, the most common site is the genitourinary tract.[21] [22]
- Where organisms are identified, bacteria (gram-positive and gram-negative) are the causative organism in the majority of people with sepsis, with gram-positive bacterial and fungal infections increasing in frequency.[141]

Protocolised approaches

Your institution may use a guideline-based care bundle as an aide-memoire to ensure key interventions are carried out in a timely way as appropriate for the individual patient. Check local protocols for the recommended approach in your area. Examples include the following.

The Sepsis Six resuscitation bundle from the UK Sepsis Trust [46]

Sepsis Six is a practical checklist of interventions that must be completed within 1 hour of identifying suspected sepsis.[46] The original paper outlining this approach, published in 2011, remains the only published evidence on Sepsis Six.[55] The six interventions are:[46]

- Ensure a senior clinician attends
- Give oxygen if required
- Obtain intravenous access/take blood cultures
- Give intravenous antibiotics
- Give intravenous fluids
- Monitor.
The 2018 1-hour care bundle from the Surviving Sepsis Campaign (SSC) [45]

The latest guidelines from the SSC propose a novel 1-hour care bundle, based on the premise that the temporal nature of sepsis means benefit from even more rapid identification and intervention. The SSC identifies the start of the bundle as patient arrival at triage. It draws out five investigations and interventions to be completed within the first hour:[45]

- Measure lactate level and remeasure if the initial lactate level is greater than 2 mmol/L (18 mg/dL)
- Obtain blood cultures before administration of antibiotics
- Administer broad-spectrum intravenous antibiotics
- Begin rapid administration of crystalloid at 30 mL/kg for hypotension or lactate level greater than or equal to 4 mmol/L (36 mg/dL)
- Start vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure level greater than or equal to 65 mmHg.

Although early identification and prompt, tailored treatment are key to the successful management of sepsis, none of the published protocolised approaches are supported by evidence.[57] [58] Therefore, your clinical judgement is a key part of any approach. [41]

Reassess and monitor

Ensure frequent reassessment of the patient’s haemodynamic status throughout the initial resuscitation period. Make sure any patient with suspected sepsis has frequent and ongoing monitoring (e.g., using an early warning score such as NEWS2).

- Depending on the facilities available, consider continuous monitoring, or a minimum of once every 30 minutes.[3]
- Include:
  - Oxygen saturation
  - Respiratory rate
  - Heart rate
  - Blood pressure
  - Temperature
  - Hourly fluid balance (including urine output)
  - Lactate level.

Consider using a validated scale such as the Glasgow Coma Scale or the AVPU (‘Alert, responds to Voice, responds to Pain, Unresponsive’) scale to monitor the mental state of a patient with suspected sepsis. [3]

Be aware that a patient with a NEWS2 score of less than 5 might also have or develop sepsis. In this group, continue to be aware of the risk of sepsis and specifically look for indicators that suggest the possibility of underlying infection and sepsis:[41]

- A single NEWS parameter of 3 or more
- Non-blanching rash/mottled/ashen/cyanotic skin
- Responds only to voice or pain, or unresponsive
- Not passed urine in last 18 hours or urine output <0.5 mL/kg/hour
• Lactate ≥2 mmol/L (≥18 mg/dL).

**Full Recommendations**

**Treatment goals**

The overarching goals are to:

• **Resuscitate** the patient and restore haemodynamic stability using supportive measures to correct hypoxaemia, hypotension, and impaired tissue oxygenation (hypoperfusion)
• Rapidly **identify the source** of infection; contain and treat
• Where there is evidence of a bacterial infection, start effective broad-spectrum **intravenous antibiotics within an hour of the risk being recognised**.[41] switch to a targeted antibiotic once the pathogen has been confirmed[3]
• Maintain **organ system function**, guided by cardiovascular monitoring, and interrupt the progression of organ failure.

**When to start treatment for sepsis**

Early recognition of sepsis is critically important, but this can be challenging as patients often present with subtle and/or non-specific signs.[142]

In practice, you should make a diagnosis of suspected sepsis and start immediate treatment if the patient is acutely unwell and meets **both** of the following criteria:[3] [41]

1. Signs or symptoms suggestive of **infection** are present
   AND
2. Your clinical assessment of the patient indicates a **risk of deterioration** due to organ dysfunction.

Always use your **clinical judgement** when assessing the risk of deterioration due to sepsis, alongside a systematic approach to assessing vital observations.[3] [41] Consult local guidelines for the recommended approach.

• The National Early Warning Score 2 (NEWS2) is the most widely used early warning score in the UK National Health Service. [NHS England: Sepsis]

  • In **hospital**: use NEWS2 or an alternative **early warning score**.[41] [42] [44] NEWS2 is endorsed by NHS England for use in this setting.[41]
  • In the **community**: use an early warning score such as NEWS2, which is recommended by NHS England[41] and the Royal College of General Practitioners in the UK,[50] or the **UK National Institute for Health and Care Excellence high-risk criteria**.[3]

    • **None is validated** in primary care.[50]

• NHS England and the Royal College of Physicians in the UK set the **threshold for starting immediate sepsis treatment as a NEWS2 score of 5 or more**.[41] [42]
• You should strongly suspect sepsis and consider the need to start immediate treatment if the patient:
Has any single NEWS2 parameter score of 3 or more OR
Has a non-blanching rash or has mottled/ashen/cyanotic skin OR
Is unresponsive or only responds to voice or pain OR
Has not passed urine for 18 or more hours (or urine output <0.5 mL/kg/hour if catheterised) OR
Has a lactate level ≥2 mmol/L (≥18 mg/dL).

See Diagnosis recommendations for full details of risk stratification.

**Prompt management for all patients with suspected sepsis**

Start treatment **immediately** if a senior clinical decision-maker makes a diagnosis of suspected sepsis, based on acute deterioration (e.g., National Early Warning Score 2 [NEWS2] score of 5 or more, or a similar trigger using another validated scoring system) in a patient with known or likely infection.[41] [42]

- In the UK, a senior clinical decision-maker is CT3/ST3 or higher, or a trained nurse with prescribing rights in acute care.[41]

**The first hour**

For any acutely ill and deteriorating patient with a suspected or known bacterial infection and suspected sepsis, above all else prioritise (if needed):[3] [43] [45] [46]

- Securing their airway
- Correcting hypoxaemia
- Establishing venous access for the early administration of antibiotics and fluids.

**Early and adequate source identification and control is critical.** If your examination of the patient identifies a clear source of infection, consider the need for urgent source control, as soon as the patient is stable, particularly for:[43]

- Gastrointestinal sources (such as visceral abscesses, cholangitis, or peritonitis secondary to perforation)
- Severe skin infections (e.g., necrotising fasciitis)
- Infection involving an indwelling device, where a procedure or surgery is likely to be required.

**Give immediate, targeted intravenous antibiotics in people with sepsis thought to arise from a central nervous system source** (e.g., suspected meningitis or meningococcal sepsis).[3]

- Immediately give a third-generation cephalosporin such as ceftriaxone or cefotaxime.
- In community settings, pre-hospital administration of benzylpenicillin is recommended.
- **Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice; use a ‘start smart then focus’ approach.** [41] [136]

**Practical tip**
If intravenous access is not feasible or is likely to lead to a delay in starting antibiotics and fluids, use intra-osseous access as an interim measure.

**Intravenous antibiotics**

Where there is evidence of a bacterial infection and a strong suspicion of sepsis (based on acute deterioration [e.g., NEWS2 score of 5 or more, or a similar trigger using another validated scoring system]), give broad-spectrum intravenous antibiotics within 1 hour of the risk of sepsis being recognised. [3] [41] [43] [46] Do this before a pathogen is identified but after blood cultures have been taken. [3] [41] [43] [46]

- The Surviving Sepsis Campaign international guideline recommends empirical combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock. [43]

Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice.

- Use a ‘start smart then focus’ approach. [41] [136]

**More info: Antimicrobial resistance**

*NHS England recommends following a ‘start smart then focus’ approach for antibiotic use in people with sepsis.* [41] This is derived from Public Health England guidance, which outlines an evidence-based approach to improving antimicrobial prescribing and stewardship in hospital settings. [136] The prevalence of antimicrobial resistance (AMR) has risen alarmingly over the last 50 years and no new classes of antibiotics have been developed in decades. By 2050 it is estimated that AMR will kill 10 million people per year, more than cancer and diabetes combined. [143] The relationship between antibiotic exposure and antibiotic resistance is unambiguous not only at the population level but also in individual patients. [144] [145]

**Start smart** – in the context of sepsis:[136]

- Do not start antimicrobial therapy unless there is clear evidence of infection
- Take a thorough drug allergy history
- Initiate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients with sepsis or life-threatening infections. Avoid inappropriate use of broad-spectrum antibiotics
- Comply with local antimicrobial prescribing guidance
- Document clinical indication (and disease severity if appropriate), drug name, dose, and route on drug chart and in clinical notes. Include review/stop date or duration
- Obtain cultures prior to starting therapy where possible (but do not delay therapy).

**Then focus** – in the context of sepsis:[136]

- Review the clinical diagnosis and the continuing need for antibiotics at 48 to 72 hours* and document in a clear plan of action – the ‘antimicrobial prescribing decision
- The ‘antimicrobial prescribing decision’ options are:
  
  1. Stop antibiotics if there is no evidence of infection
2. Switch antibiotics from intravenous to oral
3. Change antibiotics – ideally to a narrower spectrum, or broader if required
4. Continue and document next review date or stop date
   - It is essential that the review and subsequent decision is clearly documented in the clinical notes and on the drug chart where possible (e.g., ‘stop antibiotic’).

*In clinical practice, daily prompting about de-escalation is encouraged.

Target the **presumed site** of infection.[3] [43]

If there is no clinical evidence to suggest a specific **site** of infection but a senior clinical decision-maker strongly suspects the presence of a bacterial infection, still give **empirical broad-spectrum intravenous antibiotics**.[3] [41] Choose an empirical antibiotic based on:[146] [147]

- Local antibiotic protocols and resistance patterns
  - Consult **microbiology/infectious disease colleagues** to determine the most appropriate choice
  - The likely causative organism
  - The patient’s immune function.

**Practical tip**

Check local policies regarding repeat cultures. These are indicated particularly if there are persistent or repeated fever spikes or if you identify a potential new site of infection. Observations from studies to date support taking as many as four blood culture sets over a 24-hour period for >99% test sensitivity.[148]

**Practical tip**

If a patient has a mild allergy (e.g., rash) to an unknown antibiotic, you should still give empirical broad-spectrum antibiotics if indicated to prevent delays in the treatment of sepsis, which is likely to worsen outcome. If the antibiotic is known and is part of the empirical protocol for your hospital, discuss potential alternatives with a microbiologist.

**Controversy: 1-hour antibiotic targets**

There is widespread agreement that appropriate and timely recognition of sepsis and subsequent resuscitation are key approaches to managing severely ill patients with sepsis. However, guideline-derived antibiotic delivery goals (as outlined by the UK National Institute for Health and Care Excellence [NICE], the Surviving Sepsis Campaign [SSC], and the UK Sepsis Trust) have been challenged owing to gaps in the evidence and concerns about over-treatment of individual patients and the subsequent effect on antimicrobial resistance. [57] [58]

The 1-hour antibiotic targets outlined by NICE,[3] the SSC,[43] and the UK Sepsis Trust (Sepsis Six)[46] are derived from data that appear to draw a direct correlation between each hour of delayed treatment of the patient with sepsis and an increased risk of further deterioration or death.[93] [149] [150] However, examining some of these data closely shows that 1-hour antibiotic targets may not be possible or necessarily advantageous for all patients with eventual sepsis diagnoses.[58]
Sepsis in adults

Management

• A retrospective cohort study of hypotensive inpatients with sepsis, published in 2006, first described a potential link between timing of antibiotics and outcomes.[149]

  • The authors noted 79.9% survival if septic patients received in vitro-active antibiotics within 1 hour of the onset of hypotension, with a subsequent 7.6% survival rate decrement with each additional hour to treatment.
  • Looking closely at the data, however, there was a lower survival rate (52%) among patients who received antibiotics before hypotension compared with those who received them within the first few hours of the onset of septic shock.
  • Commentators note that ascribing a biological effect to antibiotics for either the improvement or the decreased survival is endemic to observational or natural experiment designs, which are prone to confounding and bias in their interpretation of results.[58]
  • More recently, another retrospective cohort study of 3929 patients with sepsis described an 8% hourly incremental increased risk of progression to septic shock with longer time to antibiotics.[150]

  • There was little change in rate of worsening (progression to septic shock rate) until after 5 hours; by then, approximately 75% of patients had received antibiotics. The remaining 25% of the cohort (who were treated later than the first patient group) differed from those treated earlier. Notably, the later-treated group had more comorbidities.
  • As noted in a commentary on the study, this is in line with what is commonly seen in clinical practice: sepsis is harder to recognise in people with comorbidities, and patients with sepsis and comorbid illness have a worse prognosis in general.[58]
  • Another recent trial randomised 2672 patients with suspected sepsis (>95% without shock) to receive antibiotics in an ambulance or ‘quickly’ in an emergency department. The median 96-minute-earlier administration was not linked to improved outcomes, regardless of illness severity.[93]

In intensive care settings only, consider prolonged infusion when giving beta-lactam antibiotics to patients with sepsis (apart from those with kidney-related complications). [151] Note that prolonged infusion times are not licensed as most manufacturers advise infusion of beta-lactam antibiotics over 15 to 60 minutes.

Evidence: Prolonged antibiotic infusion

Intravenous antibiotics, administered over 3 hours, are linked to lower death rates in sepsis. [151]

Prolonged infusion should be easy to apply in the intensive care setting, without the need for additional training or equipment.

• A systematic review and meta-analysis pooled the results of 22 randomised controlled trials involving 1876 adults with sepsis. The trials compared prolonged versus short-term administration of any antipseudomonal beta-lactam. Carbapenems were studied in nine trials, penicillins in nine trials, and cephalosporins in eight trials.[151]

• Prolonged infusion was associated with lower all-cause mortality than short-term infusion, with 13.6% deaths compared with 19.8% (risk ratio [RR] 0.70, 95% CI 0.56 to 0.87; 17 studies, 1597 participants).
There was no significant difference between prolonged and short-term infusion for clinical cure or improvement (RR 1.06, 95% CI 0.96 to 1.17; 11 studies, 1219 participants).

There was no difference in reported adverse events between the groups (RR 0.88, 95% CI 0.71 to 1.09; 7 studies, 980 participants).

Two trials had no incidence of antibiotic resistance, and two trials had no difference in resistance between the two methods of antibiotic administration (RR 0.60, 95% CI 0.15 to 2.38).

Intravenous Fluids

Give 500 mL of crystalloid fluid, with a sodium content between 130 mmol/L and 154 mmol/L (130 to 154 mEq/L) (e.g., 0.9% sodium chloride or Hartmann’s solution), over less than 15 minutes to patients who need fluid resuscitation (if there is any sign of circulatory insufficiency). [3] [41] [66]

- Reassess the patient’s haemodynamic status after the first bolus to consider whether a second is required.[3] If there is no response to either the first or second bolus, seek senior support.[3]

Intravenous fluid resuscitation may be lifesaving in patients with hypotension. This is because in sepsis there is vasodilation and capillary leakage, which means that patients can rapidly become intravascularly deplete.[3]

- In patients with sepsis-induced hypoperfusion (as indicated by a systolic blood pressure <90 mmHg, a raised lactate level, or signs of organ dysfunction), the Surviving Sepsis Campaign international guideline recommends a total of at least 30 mL/kg of intravenous crystalloid over the first 3 hours.[43]

- If the patient’s initial lactate level is raised, the guideline recommends serial lactate measurements to guide the need for further intravenous fluids (with the goal of normalising lactate levels).[43]

Practical tip

The delivery of appropriate rapid fluid challenges is intended to restore the imbalance between oxygen supply and demand to the tissues. Patients who do not respond to rapid delivery of adequate volumes of intravenous fluids are in septic shock and need immediate referral to critical care. The immediate priority in this group of patients is to restore the circulation and oxygen delivery.

Practical tip

Monitor patients closely for signs of fluid overload such as pulmonary or systemic oedema before and after each additional fluid bolus, as they may require large volumes of fluid to support their circulating volume.[43] [152] [153]
Latest evidence suggests a balanced crystalloid may have marginal benefits over saline, but either option is a reasonable choice. [3] [154]

- Although early fluid resuscitation is a cornerstone of sepsis treatment that is given high priority by both Sepsis Six and NICE, choice of fluid has been the source of much discussion. In particular, there has been extensive debate over the choice between a balanced crystalloid (such as Hartmann’s solution, Ringer’s lactate, or PlasmaLyte) and normal saline (an unbalanced crystalloid). There have been very few high-quality studies, but latest evidence from critically ill patients points to marginal benefits from using a balanced crystalloid in preference to saline.[154]

- A 2018 US multicentre cluster-randomised trial among 15,802 critically ill adults receiving care in the intensive care unit found small benefits from balanced crystalloid compared with saline. The 30-day outcomes showed 10.3% mortality in the balanced crystalloid group compared with 11.1% in the saline group (P = 0.06), and a major adverse kidney event rate of 14.3% compared with 15.4% in the two groups, respectively (marginal odds ratio 0.91, 95% CI 0.84 to 0.99).[154]

- Colloids (e.g., starches, dextrans, gelatins, albumin, or fresh frozen plasma) are no longer used in emergency medicine in the UK.

Debate: Volume and rate of fluids

Studies have not shown benefits from early goal-directed therapy and your focus should instead be on adjusting treatment according to i) lactate level and ii) clinical assessment of the patient’s haemodynamic response to initial fluids. [43] [155] [156] [157] [158] [159] [160]

- Previous versions of the Surviving Sepsis Campaign (SSC) guidelines recommended a protocolled approach to resuscitation, otherwise known as early goal-directed therapy (EGDT).[161] [162] [163] EGDT involves the use of a series of ‘goals’ including central venous pressure and central venous oxygen saturation (ScvO₂). This recommendation was largely based on data from one study that showed a significant survival benefit for patients receiving EGDT.[155]

- This approach has since been challenged following the failure to show a mortality reduction in three subsequent large multicentre randomised controlled trials: PROCESS, ARISE, and PROMISE.[156] [157] [158]

- It is worth bearing in mind that these three trials included patients who were less severely ill (lower baseline lactate levels, ScvO₂ at or above the target value on admission, and lower mortality in the control group) than the patients in the original study that outlined EDGT as a recommended approach.

- Based on this latest evidence, the SSC no longer specifically recommends EDGT; it does, however, acknowledge the need for guidance on how to approach this group of patients who have significant mortality and morbidity.[43] The SSC therefore recommends that you:[43]

- View these patients as having a medical emergency that necessitates urgent assessment and treatment
• Begin initial fluid resuscitation with 30 mL/kg of crystalloid within the first 3 hours
  • This fixed volume of fluid enables initiation of resuscitation while giving an opportunity to ascertain more specific information about the patient and while awaiting more precise measurements of haemodynamic status
  • Although scant data are available to support this volume of fluid, interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice[159] [160]
  • The average volume of fluid pre-randomisation given was approximately 30 mL/kg in the PROCESS and ARISE trials, and approximately 2 L in the PROMISE trial.[156] [157] [158] The SSC acknowledges that many patients will need more fluid than this, and it advocates giving further fluid to this group in line with functional haemodynamic measurements.[43]
  • The UK National Institute for Health and Care Excellence guideline on sepsis focuses on initial management and treatment, and therefore makes no recommendations regarding intensive monitoring such as that used in EGDT.[3]

Practical tip

To guide the need for further intravenous fluids, it can sometimes be helpful to use bedside ultrasound to monitor changes in inferior vena cava (IVC) diameter during respiration.[164] [165]
  • In the spontaneously breathing patient: consider additional fluid resuscitation if there is a collapsed (or collapsing) IVC.
  • In the mechanically ventilated patient: an increase in IVC size >18% (or visible to the naked eye) with positive pressure ventilation suggests fluid-responsiveness.

Practical tip

Use the passive leg-raising test to predict fluid-responsiveness if adequate monitoring is available.[66] [166]
  • This is a useful indicator of fluid-responsiveness, which should be assessed using devices that can continuously monitor cardiac output in real time (e.g., Pulse index Continuous Cardiac Output [PICCO] monitor or oesophageal Doppler), usually in an intensive care unit rather than a general ward setting.
  • Sit the patient upright at 45° and tilt the entire bed through 45°.
  • Patients with a positive test have a >10% increase in cardiac output or stroke volume, indicating more fluids may be required.
  • The passive leg-raise response may be misleading in conscious patients who are uncomfortable or in pain when lying flat.

Oxygen

If indicated, give oxygen to maintain target oxygen saturations >94%.[3] [43] [46] [47] Latest evidence suggests that liberal use of supplemental oxygen (target \(\text{SpO}_2\) >96%) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy.[138] Therefore, a reasonable approach in
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practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia.

Target saturation of 88% to 92% if the patient is at risk of hypercapnic respiratory failure (e.g., those with COPD).[3] [43] [46] [47]

Evidence: Target oxygen saturation in acutely ill adults

Too much supplemental oxygen increases mortality.

Latest evidence supports a 96% upper limit for target oxygen saturation in non-hypercapnic acutely ill adults.

• Guidelines differ in their recommendations on target oxygen saturation in acutely unwell adults who are receiving supplemental oxygen. The 2017 British Thoracic Society guideline recommends a target SpO\textsubscript{2} range of 94% to 98% for patients not at risk of hypercapnia,[47] whereas the 2015 Thoracic Society of Australia and New Zealand guideline recommends 92% to 96%.[167]

• A 2018 systematic review including a meta-analysis of data from 25 randomised controlled trials found that in adults with acute illness, liberal oxygen therapy (broadly equivalent to a target saturation >96%) is associated with higher mortality than conservative oxygen therapy (broadly equivalent to a target saturation ≤96%).[138] In-hospital mortality was 11 per 1000 higher for the liberal oxygen therapy group versus the conservative therapy group (95% CI 2-22 per 1000 more). Mortality at 30 days was also higher in the group who had received liberal oxygen (risk ratio 1.14, 95% CI 1.01 to 1.29). The trials included adults with sepsis, critical illness, stroke, trauma, myocardial infarction, and cardiac arrest, and patients who had emergency surgery. Studies that were limited to people with chronic respiratory illness or psychiatric illness, patients on extracorporeal life support, patients receiving hyperbaric oxygen therapy, or those having elective surgery were all excluded from the review.

• An upper SpO\textsubscript{2} limit of 96% is therefore reasonable when administering supplemental oxygen to medical patients with acute illness who are not at risk of hypercapnia. However, a higher target may be appropriate for some specific conditions (e.g., pneumothorax, carbon monoxide poisoning, cluster headache, and sickle cell crisis).[168]

There is no specific evidence to show that giving oxygen improves clinical outcomes in sepsis. However, respiratory failure will lead to tissue hypoxia and anaerobic respiration. This is likely to lead to acidosis and consequently a poorer outcome.[169]

Reassess and monitor

Ensure frequent and ongoing monitoring. [3]

• Standard monitoring of vital signs, pulse oximetry, level of consciousness, and urinary output is important for any patient with suspected sepsis.

• The National Institute for Health and Care Excellence (NICE) in the UK recommends continuous or half-hourly monitoring (depending on setting) for any patient considered to be at high risk of deterioration (defined in the NICE guideline as meeting one or more of its high-risk criteria for severe illness or death from sepsis).[3]

• See the Risk stratification subsection of Diagnosis recommendations for more information.
Use a track-and-trigger scoring system such as the National Early Warning Score 2 (NEWS2) to identify any signs of deterioration. [3] Your monitoring should include:

- Vital signs: heart rate, blood pressure, oxygen saturations, respiratory rate, and temperature
- Measure blood pressure via an arterial line if the patient does not respond to initial treatment or needs vasoactive drugs. It provides precise, continuous monitoring, and access for arterial blood sampling
- Hourly urine output[3] [43] [46]
- The lactate level should decrease if the patient is clinically improving
- Frequency of repeat lactate measurement depends on cause of sepsis and treatment given.

In the UK, use physiological track-and-trigger systems to monitor all adult patients in acute hospital settings.[3]

Consider using a validated scale such as the Glasgow Coma Scale or AVPU (‘Alert, responds to Voice, responds to Pain, Unresponsive’) scale to monitor the mental state of a patient with suspected sepsis. [3]

**Practical tip**

AVPU should raise concerns if the assessment shows the patient is anything other than ‘alert’.

**When to escalate**

Any patient with sepsis may be at significant risk of severe illness or death so it is vital to consider escalation of care to senior colleagues and/or healthcare facilities where increased and more advanced monitoring can be given (e.g., high-dependency unit/intensive care unit). [7] [170] [171] #

- Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

Consult local protocols for specific escalation routes but in general:

- Ensure immediate review by a senior clinician (CT3/ST3 or higher in the UK) of any patient with a NEWS2 score of 5 or more, or who meets one or more of the UK National Institute for Health and Care Excellence sepsis high-risk criteria. Also ensure the patient is discussed with a consultant[3] [41]
- Discuss with the admitting consultant[3] and consider alerting critical care immediately if the patient is acutely unwell and:
  - Has a National Early Warning Score 2 (NEWS2) score of 7 or more, persisting high lactate (more than 4 mmol/L [36 mg/dL]) despite fluid resuscitation, or a systolic blood pressure of less than 90 mmHg [3]
    - Discuss with the admitting consultant[3]
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• Has hypotension that doesn’t respond to initial fluid resuscitation
• Is likely to require central venous access and the initiation of inotropes or vasopressors[3]
• Has any feature of septic shock
  • See our topic Shock
• Has neutropenia
  • See our topic Febrile neutropenia
• Is immunodeficient
• Urgently discuss with a consultant or call them to attend if the patient:[41]
  • Is treated with intravenous antibiotics and/or a fluid bolus for sepsis
  • Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour. [3] [41] Failure to respond to treatment is defined as:[3]
    • Systolic blood pressure remains less than 90 mmHg
    • Persistent reduced level of consciousness
    • Respiratory rate more than 25 breaths per minute or the new need for mechanical ventilation
    • Lactate has not reduced by more than 20%
• Refer to critical care any patient who is likely to require central venous access and initiation of inotropes or vasopressors[3]
  • This includes any patient with evidence of circulatory dysfunction or shock, or those who do not respond to initial therapy (as outlined above)
  • ECG can be used to determine which vasoactive drug(s) to proceed with in critical care.[43]

Practical tip

Ensure a clear escalation plan has been discussed and agreed with the clinical team; include specific points of contact for nursing staff if you are leaving a patient for later review. Involve a senior colleague and/or consider transferring to critical care sooner rather than later if the patient is not improving, or deemed high-risk. Examples include if the patient:
• Is not responding to fluids
• Needs inotropic support
• Has a low Glasgow Coma Scale score
• Needs ventilatory support.

Identify the infection source

Make intensive efforts to identify the anatomical source of infection as soon as possible. [3] [43] Consider the need for urgent source control as soon as the patient is stable.

• Start with a thorough and focused clinical history and examination, as well as initial investigations including imaging.[3]
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- Consider all lines and catheters as potential sources. Take cultures from the line tip. Remove lines where appropriate.[43]
  
  - Assume that any intravenous route is likely to either be the source of the infection, or will seed infections in the bloodstream, making eradication particularly difficult. Therefore, the priority for source control is often to remove any intravenous devices after vascular access has been obtained.[43]
  
  - If you suspect an abdominal or pelvic source, **involve the relevant surgical team early**, particularly if surgery is likely.[3]
  
  - In practice, this may mean early transfer of the patient to a surgical centre if there are no facilities at your hospital.

Switch to a targeted antibiotic as soon as culture and sensitivity results are available and a pathogen has been identified. [43] [137]

**Tailor antibiotics based on source**

Once a definitive source has been identified, if appropriate to continue treating the patient with antibiotics, choose a treatment regimen in line with local or national policy (which will take into account specialist knowledge of resistance patterns). [43] [137] Also consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice.

**Respiratory**

Ensure treatment regimens **cover common respiratory pathogens and atypical organisms** such as *Legionella pneumophila*.

  - The respiratory tract is the **most common** site of infection in people with sepsis.[20] [60]
  
  - See our topic **Overview of pneumonia**.

**Abdominal**

Ensure **gram-positive and gram-negative organisms including anaerobes** are covered.[172]

Arrange **urgent surgical drainage or percutaneous drainage** (where appropriate) for peritonitis or intra-peritoneal abscesses.[173]

**Urinary tract**

Ensure gram-negative coliforms and *Pseudomonas* are covered. Ensuring **patency of the urinary tract** is vital.

  - In people older than 65 years of age, genitourinary tract infections are the most common cause of sepsis.[21] [22]
Soft tissue and joint
Includes septic arthritis, wound infections, cellulitis, and acute super-infections arising from chronic ulceration. Most infections are polymicrobial. **Ensure gram-positive and gram-negative organisms including anaerobes** are covered.

- **Beware necrotising fasciitis**, which requires immediate surgical intervention (as does septic arthritis).

**Practical tip**
Necrotising fasciitis is **notoriously difficult to diagnose**. The initial symptoms are non-specific and the clinical course is often slower than might be expected. Typically, the first sign is pain disproportionate to the clinical findings, followed or accompanied by fever.[76]
See our topic Necrotising fasciitis.

Central nervous system
Relatively **uncommon but potentially devastating source** of sepsis. **Beware meningococcal sepsis**, which can be extremely rapidly fatal; if survived, can lead to greater morbidity than other forms of sepsis.

Give **immediate, targeted antibiotics in people with sepsis thought to arise from a central nervous system source**.[3]

- Immediately give a third-generation cephalosporin, such as ceftriaxone or cefotaxime, for suspected meningitis or meningococcal sepsis.[3]
- In community settings, give benzylpenicillin before referring to hospital.[3]

Unknown or unclear
Continue broad-spectrum coverage to include all common pathogens if the source is unknown or unclear.[3]

- Bear in mind that a definite source of infection cannot be found in 20% to 30% of people with sepsis.[9]

Further management by the critical care team
For any patient with suspected sepsis, consider the need for referral to a high-dependency unit for management by the critical care team.[155][174]

Refer to critical care as soon as possible any patient who does not respond to initial therapy, and in particular anyone:

- With **hypotension** that doesn’t respond to initial fluid resuscitation
- Who is likely to require **central venous access and initiation of inotropes or vasopressors**[3]
- With any feature of **septic shock**
  - See our topic Shock
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- **With neutropenia**
  - See our topic Febrile neutropenia
- **Who is immunodeficient**.

The following interventions should only be initiated by experienced members of the critical care team:

- Glycaemic control
- Vasoactive drugs (vasopressors/inotropes)
- Corticosteroids.

Additional intensive care measures that will be considered include:

- **Stress ulcer prophylaxis** (in people at risk of gastrointestinal bleeding)
  - With an H2 antagonist or proton-pump inhibitor
- **Deep venous thrombosis prophylaxis**
  - With heparin and compression stockings
- **Enteral or parenteral nutrition**
  - Administration of human albumin solution 4% to 5% in patients with sepsis and shock
  - With an H2 antagonist or proton-pump inhibitor
  - With heparin and compression stockings
- **Transfusion of packed cells**
  - Consult local protocols for recommended threshold
  - The Surviving Sepsis Campaign recommends using a threshold of 70 g/L (7 g/dL).

**Evidence: Threshold for transfusion of packed cells**

Studies in the general critical care population have shown no improvement with blood transfusions given at a higher haemoglobin threshold compared with a lower haemoglobin threshold and have shown potential harm associated with liberal transfusion.

- One multicentre parallel group randomised trial analysed data from 998 patients with septic shock, split into two intervention groups with similar baseline characteristics. In the intensive care unit, the group assigned to blood transfusion at a lower haemoglobin threshold received a median of 1 unit of blood (interquartile range, 0 to 3) and the group assigned to blood transfusion at a higher haemoglobin threshold received a median of 4 units (interquartile range, 2 to 7).

  - At 90 days after randomisation, 216 of 502 patients (43.0%) assigned to the lower-threshold group, compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died (relative risk 0.94, 95% CI 0.78 to 1.09; \(P = 0.44\)).
  - The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations.
  - The numbers of patients who had ischaemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.
A second multicentre randomised controlled trial compared the rates of death from all causes at 30 days and the severity of organ dysfunction in 838 critically ill patients receiving a restrictive strategy of red-cell transfusion compared with those receiving a liberal strategy.[179]

- Overall, 30-day mortality was similar in the two groups (18.7% vs. 23.3%, P = 0.11).
- However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill and in patients younger than 55 years of age (5.7% and 13.0%, respectively; P = 0.02), but not in those with clinically significant cardiac disease (20.5% and 22.9%, respectively; P = 0.69).
- The mortality rate during hospitalisation was significantly lower in the restrictive-strategy group (22.3% vs. 28.1%, P = 0.05).

There may be a case to consider giving transfusions at a higher haemoglobin level in people with myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis.[43]

In the initial resuscitative phase, transfusion to achieve a higher haematocrit of ≥30% may be appropriate.[155]

In patients requiring prolonged ventilatory support, give lung-protective ventilation using minimal peak inspiratory pressures (<30 cm H₂O) and permissive hypercapnia to specifically limit pulmonary compromise.[180]

- Titrate fraction of inspired oxygen (FiO₂) to lowest effective levels to prevent oxygen toxicity and maintain central venous oxygen tension.
- Place patients in a semi-recumbent position with the head elevated to 30° to 45°.[43]

### Glycaemic control

Although patients with sepsis are often hyperglycaemic, the optimal glucose target is unknown.

The Surviving Sepsis Campaign guideline recommends targeting a blood glucose level <10.0 mmol/L (<180 mg/dL).[43] The guideline also recommends a ‘sliding scale’ variable-rate intravenous insulin infusion.[43]

- The National Institute for Health and Care Excellence (NICE) in the UK makes no recommendations on glycaemic control in sepsis.[3]

### Evidence: Glycaemic control

Recent years have seen a shift in opinion and practice regarding glycaemic control in critically ill people. Since 2001, the use of tight glycaemic control has been advocated in people with sepsis. More recent evidence, however, suggests an increase in adverse events (e.g., severe hypoglycaemia) in patients managed with very tight glycaemic control (targeting a blood glucose below 6.1 mmol/L [110 mg/dL]).[181][182] The conflicting evidence has led to variations in recommendations in different countries and settings. Follow your local protocol.
Vasoactive drugs

Vasopressors for persistent haemodynamic instability

Vasopressors are used in a critical care setting to maintain a mean arterial pressure (MAP) ≥65 mmHg if the patient is unresponsive to fluid resuscitation. [3] [43] [175]

- Failure to respond to initial fluid resuscitation is a sign of septic shock. [1]
- Noradrenaline (norepinephrine) is the vasopressor of choice, mainly because it increases MAP. [43]
  - Noradrenaline is the vasopressor recommended by the Surviving Sepsis Campaign guideline. [43] NICE makes no recommendation on the choice of vasopressor. [3]
  - If further vasopressor therapy is required to maintain adequate blood pressure or the noradrenaline dose needs to be reduced, add vasopressin or adrenaline (epinephrine) to noradrenaline. [43] Dopamine is an option, but has been associated with higher mortality than noradrenaline. [186] [187] Therefore, it is only recommended in patients with a low risk of tachyarrhythmias and bradycardia. [43] It is rarely used in the UK. Do not use low-dose dopamine for renal protection. [43]

Practical tip

All infusions of vasoactive drugs to correct shock should be given via a secure catheter in a central vein with high flow, such as a central venous catheter. These patients should also have an arterial catheter inserted as soon as possible to ensure more accurate monitoring of arterial blood pressure. [43]

Evidence: Choice of vasopressor
**Inotropes**

Inotropes can be considered for patients with low cardiac output despite adequate fluid resuscitation and vasopressor therapy. [3][43]

- **Dobutamine** is recommended first line by the Surviving Sepsis Campaign guideline for people with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure.[43]
- **NICE** makes no specific recommendations on inotrope selection in patients with sepsis.[3]

**Practical tip**

Suspect **low cardiac output** if the clinical examination reveals **prolonged capillary refill times, low urine output, or poor peripheral perfusion**. Confirm with cardiac output monitoring or by sampling central venous or pulmonary arterial blood to measure oxygen saturations.

When using inotropes, keep the patient’s heart rate at less than 100 beats per minute to minimise myocardial ischaemia.[175]

**Corticosteroids**

The Surviving Sepsis Campaign guideline recommends **intravenous hydrocortisone** as an option to consider for patients who are **unresponsive to both fluid resuscitation and vasopressor therapy**.[43]

- **NICE** does not give any recommendations on the use of corticosteroids for managing sepsis in adults.[3]

**Evidence: Benefits and harms of corticosteroids**

Corticosteroids are a late critical-care intervention for patients in whom all other attempts to raise their blood pressure have failed. [3] In this critically ill group, corticosteroids may result in a small reduction in mortality. [189] [190] Possible harms include an increased risk of neuromuscular weakness, hyperglycaemia, and hypernatraemia with corticosteroids compared with no corticosteroids. [189]

- An international panel reviewing the inconsistent conclusions of large randomised controlled trials (RCTs) on the topic suggested in 2018 that the evidence for the use of corticosteroids was weak, but that “fully informed patients who value avoiding death over quality of life and function would likely choose corticosteroids”, although a no-corticosteroid approach remained reasonable.[189] This judgement was based on an assessment that corticosteroids may reduce mortality by around 2% (this effect was seen in sepsis with and without shock although the greatest benefit was among patients with septic shock), but can increase the risk of neuromuscular weakness and resulting functional deterioration. Most notably, the panel reviewed the following trials:
• ADRENAL: 3658 patients who had septic shock[191]
  • No statistically significant difference in 90-day mortality between the hydrocortisone and placebo groups
• APROCCHSS: 1241 patients who had septic shock[192]
  • Hydrocortisone plus fludrocortisone reduced 90-day mortality.

A more recent systematic review and meta-analysis (comprising 37 RCTs, incorporating both ADRENAL and APROCCHSS) included 9564 people with sepsis.[190] The review found corticosteroid use to be associated with significant improvement in healthcare outcomes as shown by:[190]

• Reduced 28-day mortality (risk ratio [RR] 0.90, 95% CI 0.82 to 0.88) compared with placebo or standard supportive care
Response to therapy

Antibiotics

Narrow choice of antibiotic as soon as a pathogen has been identified and sensitivities are available. [43] [137] #Assess the need to de-escalate antimicrobial therapy daily. [43]

- Studies have shown that daily prompting about antimicrobial de-escalation is effective and may be associated with improved outcomes. [193] [194]

Use the shortest effective course of antibiotics. [195]

- Unnecessarily prolonged antibiotic treatment is associated with resistance. See More info: Antimicrobial resistance in the section Prompt management for all patients with suspected sepsis above.

#Consult local microbiology guidance for other specific recommendations on de-escalation.

- Most protocols will recommend switching from intravenous to oral antibiotics as soon as possible.

According to the Surviving Sepsis Campaign (SSC), most serious infections associated with sepsis and septic shock will need 7 to 10 days of antibiotic treatment. [43] However, in practice, shorter courses of antibiotics are often appropriate. [196] The optimal duration of antibiotic treatment in patients with sepsis remains contentious, with concerns regarding not only under-treatment but also the potential encouragement of antibiotic resistance. Consider seeking advice from microbiology/infectious disease colleagues.

- The SSC guideline suggests considering shorter courses in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis. [43]

- Longer courses of treatment may be appropriate in patients who have:

  - A slow clinical response
  - Undrainable foci of infection
  - Bacteraemia with *Staphylococcus aureus*
  - Some fungal and viral infections
  - Immunological deficiencies, including neutropenia.

Baseline serum procalcitonin is increasingly being used in critical care settings to guide decisions on how long to continue antibiotic therapy. [43] [105] [106] [107]
Procalcitonin is a peptide precursor of calcitonin, which is responsible for calcium homeostasis. It is currently excluded from key guidelines, but increasingly used in practice.

**Serum lactate**

Measure serum lactate, on a blood gas, to monitor response to treatment. [3] [43] [46]

- Lactate is a **marker of stress** and may be a marker of a worse prognosis (as a reflection of the degree of stress).
- Raised serum lactate highlights the possibility of tissue **hypoperfusion** and may be present in many conditions.[77] [78]
- Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst.
- Lactate >4 mmol/L (>36 mg/dL) is associated with worse outcomes.
  - One study found in-hospital mortality rates as follows:[79]
    - Lactate <2 mmol/L (<18 mg/dL): 15%
    - Lactate 2.1 to 3.9 mmol/L (19 to 35 mg/dL): 25%
    - Lactate >4 mmol/L (>36 mg/dL): 38%.

**Sepsis guidelines from the UK National Institute for Health and Care Excellence (NICE) and NHS England recommend escalating treatment depending on lactate level.** [3] [41] Alert critical care immediately if the patient is acutely unwell and has persistent lactate >4 mmol/L (>36 mg/dL) [3] despite fluid resuscitation.

Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL]).

- This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their National Early Warning Score 2 (NEWS2) score.

**Practical tip**

Lactate is typically measured using a blood gas analyser, although laboratory analysis can also be performed. Traditionally, arterial blood gas has been recommended as the ideal means of measuring lactate accurately. However, in the emergency department setting it is more practical and quicker to use venous blood gas, which is recommended by NICE.[3] Evidence suggests good agreement at lactate levels <2 mmol/L (<18 mg/dL) with small disparities at higher lactate levels.[80] [81] [82]

**Evidence: Lactate clearance**

The best available evidence supports lactate clearance (the rate at which lactate is cleared over a period of 6 hours) as being as useful as more invasive tests, such as central venous oxygen saturation (ScvO₂), in determining a patient’s response to treatment. [197] [198] [199] [200] [201] [202]

- In one study that looked at patients with septic shock who were treated to normalise central venous and mean arterial pressure, additional management to normalise lactate clearance
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compared with additional management to normalise ScvO\textsubscript{2} did not result in significantly different in-hospital mortality.[198]

- Of 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographics, comorbidities, and physiological features. There were no differences in treatments administered during the initial 72 hours of hospitalisation.
- Thirty-four patients (23%) in the ScvO\textsubscript{2} group died while in the hospital (95% CI 17% to 30%) compared with 25 (17%, 95% CI 11% to 24%) in the lactate clearance group. This observed difference between mortality rates did not reach the predefined -10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, -3% to 15%). There were no differences in treatment-related adverse events between the groups.
- Several trials have assessed the diagnostic accuracy of percentage lactate clearance over 0 to 6 hours. It is worth noting that these studies provide very low-quality evidence, owing mainly to a presumed lack of blinding of treating physicians to the patient’s lactate status.

- The studies’ findings agree that lactate clearance early in the hospital course is associated with decreased mortality rate. Patients with higher lactate clearance after 6 hours of emergency department intervention had improved outcomes compared with those with lower lactate clearance.[197] [199] [200] [201] [202]

Treating sepsis in the community

Referring to hospital

Use your clinical judgement. Use National Early Warning Score 2 (NEWS2) scoring (encouraged by NHS England) to refer urgently to hospital any acutely unwell patient with suspected or confirmed infection according to the following triggers: [41] [NHS England: Sepsis]

- Score 7 or more
  - Make an emergency referral to hospital (via blue-light ambulance) for immediate critical care input
- Score 5-6 total, or 3 or more on any single parameter
  - Make an immediate referral to an acute care setting and ensure the patient is reviewed by an acute clinician within an hour.

[Track and trigger map developed by the West of England Academic Health Science Network National Early Warning Score project team]

Alternatively, refer for emergency medical care in hospital (usually by blue-light ambulance in the UK) any acutely unwell patient with suspected or confirmed infection who:[3]

- Meets one or more of the UK National Institute for Health and Care Excellence (NICE) high-risk criteria (red flags)
• Objective evidence of new altered mental state (e.g., new deterioration in Glasgow Coma Scale/AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale)
• Respiratory rate: ≥25 breaths per minute OR new need for oxygen (40% or more fraction of inspired oxygen [FiO₂]) to maintain saturation >92% (or >88% in known chronic obstructive pulmonary disease)
• Heart rate: >130 beats per minute
• Systolic blood pressure ≤90 mmHg or more than 40 mmHg below normal
• Not passed urine in previous 18 hours, or for catheterised patients passed <0.5 mL/kg of urine per hour
• Mottled or ashen appearance
• Cyanosis of skin, lips, or tongue
• Non-blanching rash of skin

• Is at risk of neutropenic sepsis and presents with symptoms and signs of infection

Carefully consider whether emergency medical care is required or whether the patient can be safely managed in the community with safety netting advice.[3] See box below on safety netting advice.

If you have decided to refer the patient for emergency medical care and have called for an emergency ambulance, the UK Sepsis Trust/NICE general practitioner toolkit recommends that, if indicated, you should start oxygen therapy while awaiting the ambulance if resources are available to do so.[139] [140]

• Give oxygen immediately to maintain target oxygen saturations >94%. [3] [43] [46] [47] Latest evidence suggests that liberal use of supplemental oxygen (target SpO₂ >96%) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy.[138] Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia.
• Target saturation of 88% to 92% in people at risk of hypercapnic respiratory failure (e.g., those with COPD).[3] [43] [46] [47]

Evidence: Target oxygen saturation in acutely ill adults

Too much supplemental oxygen increases mortality.

Latest evidence supports a 96% upper limit for target oxygen saturation in non-hypercapnic acutely ill adults.

• Guidelines differ in their recommendations on target oxygen saturation in acutely unwell adults who are receiving supplemental oxygen. The 2017 British Thoracic Society guideline recommends a target SpO₂ range of 94% to 98% for patients not at risk of hypercapnia,[47] whereas the 2015 Thoracic Society of Australia and New Zealand guideline recommends 92% to 96%.[167]
• A 2018 systematic review including a meta-analysis of data from 25 randomised controlled trials found that in adults with acute illness, liberal oxygen therapy (broadly equivalent to a target saturation >96%) is associated with higher mortality than conservative oxygen therapy (broadly equivalent to a target saturation ≤96%).[138] In-hospital mortality was 11 per 1000 higher for
the liberal oxygen therapy group versus the conservative therapy group (95% CI 2-22 per 1000 more). Mortality at 30 days was also higher in the group who had received liberal oxygen (risk ratio 1.14, 95% CI 1.01 to 1.29). The trials included adults with sepsis, critical illness, stroke, trauma, myocardial infarction, and cardiac arrest, and patients who had emergency surgery. Studies that were limited to people with chronic respiratory illness or psychiatric illness, patients on extracorporeal life support, patients receiving hyperbaric oxygen therapy, or those having elective surgery were all excluded from the review.

- An upper SpO₂ limit of 96% is therefore reasonable when administering supplemental oxygen to medical patients with acute illness who are not at risk of hypercapnia. However, a higher target may be appropriate for some specific conditions (e.g., pneumothorax, carbon monoxide poisoning, cluster headache, and sickle cell crisis).[168]

Ensure you have a mechanism in place to administer antibiotics to any high-risk patient (either at your practice or via the ambulance service) if the transfer time to hospital is likely to be more than 1 hour.

**Practical tip**

If you need to refer a patient for emergency medical care in hospital, it is important to inform the hospital clinical team that the patient is on the way. This will enable the hospital to initiate appropriate treatment as soon as the patient arrives.

**Management in the community**

In a patient with signs and symptoms of an infection and evidence of physiological deterioration, presume sepsis until it can safely be excluded. Take a cautious approach when deciding whether it is safe to treat the patient’s infection in the community. Using your clinical judgement in making a decision is paramount. In particular, carefully consider the need for hospital admission if:[50] [74] [140]

- The patient has one or more risk factors for sepsis (as listed above)
- The patient appears seriously unwell to you, based on experience and clinical judgement
- The patient lives alone with poor access to communication and/or transport
- A carer or parent expresses serious concern about the patient (e.g., “they’re just not right”).

See our section Diagnosis recommendations for details of the NICE risk criteria.

Treat the patient’s infection in line with local protocols and accepted practice. Antimicrobial prescribing guidelines from Public Health England and NICE are available for general practitioners in the UK.[203] [204]

**Practical tip**

If you decide that the patient is safe to treat in the community, written and verbal safety netting is vital.[50] Ensure the information is clear and specific rather than generalised advice; for example, do not say to “come back if you get worse” – instead specify key symptoms to watch out for (such as a non-blanching rash, change in behaviour or mental state, mottled skin, or ashen appearance) and explain where and how to access immediate medical care both in and out of hours.[50] If you give the patient any safety netting advice, ensure you document this clearly in their medical notes, along with the patient’s observations and whether you have offered them any antibiotics. The
2015 national confidential enquiry into sepsis deaths found recorded evidence that safety netting advice had been provided in fewer than one quarter of cases.[60]

The UK Sepsis Trust advises the following acronym:[140]

- **S** lurred speech or confusion
- **E** xtreme shivering or muscle pain
- **P** assing no urine (in a day)
- **S** evere breathlessness
- ‘I feel I might die’
- **S** kin mottled, ashen, blue, or very pale.

**Advise the patient to call the emergency services if any of these symptoms develop.**

If the patient has a change in condition or deterioration that is not covered by the acronym above, advise them to arrange another appointment to see their general practitioner or to call their out of hours service provider.

It is also good practice to consider arranging a next-day review appointment or telephone call; if you will be unable to review the patient yourself, provide a written handover for your colleagues.[139]

---

**Treatment algorithm overview**

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: [see disclaimer](https://bestpractice.bmj.com).
## Initial Management

<table>
<thead>
<tr>
<th>in hospital: sepsis highly suspected and unknown or unclear source of bacterial infection</th>
<th>(summary)</th>
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<tbody>
<tr>
<td>1st</td>
<td>broad-spectrum intravenous antibiotics</td>
</tr>
<tr>
<td>plus</td>
<td>reassess and monitor</td>
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<tr>
<td>plus</td>
<td>identify the infection source</td>
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<tr>
<td>consider</td>
<td>fluid resuscitation</td>
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<tr>
<td>consider</td>
<td>oxygen</td>
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<td>consider</td>
<td>standard intensive care unit supportive care</td>
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<tr>
<td>consider</td>
<td>vasopressor (should only be initiated by experienced members of the critical care team)</td>
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<tr>
<td>consider</td>
<td>inotrope (should only be initiated by experienced members of the critical care team)</td>
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<tr>
<td>consider</td>
<td>corticosteroid (should only be initiated by experienced members of the critical care team)</td>
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<table>
<thead>
<tr>
<th>in the community: sepsis highly suspected and bacterial infection confirmed or highly suspected</th>
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<tbody>
<tr>
<td>1st</td>
<td>refer for emergency medical care in hospital</td>
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<tr>
<td>consider</td>
<td>oxygen</td>
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<td>consider</td>
<td>broad-spectrum antibiotics</td>
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### Acute

<table>
<thead>
<tr>
<th>in hospital: sepsis highly suspected and clear source of bacterial infection identified</th>
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<tr>
<td>1st</td>
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<td>plus</td>
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<td>consider</td>
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</table>
Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Initial

in hospital: sepsis highly suspected and unknown or unclear source of bacterial infection

1st broad-spectrum intravenous antibiotics

» Start treatment immediately if a senior clinical decision-maker makes a diagnosis of suspected sepsis, based on acute deterioration (e.g., National Early Warning Score 2 [NEWS2] score of 5 or more, or a similar trigger using another validated scoring system) in a patient with known or likely infection. [41] [42]

• In the UK, a senior clinical decision-maker is CT3/ST3 or higher, or a trained nurse with prescribing rights in acute care. [41]

» For any acutely ill and deteriorating patient with a suspected or known bacterial infection and suspected sepsis, above all else prioritise (if needed): [3] [43] [45] [46]

• Securing their airway
• Correcting hypoxaemia
• Establishing venous access for the early administration of antibiotics and fluids.

» Where there is evidence of a bacterial infection and a strong suspicion of sepsis (based on acute deterioration [e.g., NEWS2 score of 5 or more, or a similar trigger using another validated scoring system]), give broad-spectrum intravenous antibiotics within 1 hour of the risk of sepsis being recognised. [3] [41] [43] [46]

Do this before a pathogen is identified but after blood cultures have been taken. [3] [41] [43] [46]

• The Surviving Sepsis Campaign international guideline recommends empirical combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock. [43]

» Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice.
Initial

- Use a 'start smart then focus' approach. [41][136]

More info: Antimicrobial resistance

NHS England recommends following a 'start smart then focus' approach for antibiotic use in people with sepsis. [41] This is derived from Public Health England guidance, which outlines an evidence-based approach to improving antimicrobial prescribing and stewardship in hospital settings. [136] The prevalence of antimicrobial resistance (AMR) has risen alarmingly over the last 50 years and no new classes of antibiotics have been developed in decades. By 2050 it is estimated that AMR will kill 10 million people per year, more than cancer and diabetes combined. [143] The relationship between antibiotic exposure and antibiotic resistance is unambiguous not only at the population level but also in individual patients. [144][145]

Start smart – in the context of sepsis:[136]

- Do not start antimicrobial therapy unless there is clear evidence of infection
- Take a thorough drug allergy history
- Initiate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients with sepsis or life-threatening infections. Avoid inappropriate use of broad-spectrum antibiotics
- Comply with local antimicrobial prescribing guidance
- Document clinical indication (and disease severity if appropriate), drug name, dose, and route on drug chart and in clinical notes
- Include review/stop date or duration
- Obtain cultures prior to starting therapy where possible (but do not delay therapy).

Then focus – in the context of sepsis:[136]

- Review the clinical diagnosis and the continuing need for antibiotics at 48 to 72 hours* and document in a
Initial clear plan of action – the ‘antimicrobial prescribing decision’

- The ‘antimicrobial prescribing decision’ options are:
  1. Stop antibiotics if there is no evidence of infection
  2. Switch antibiotics from intravenous to oral
  3. Change antibiotics – ideally to a narrower spectrum, or broader if required
  4. Continue and document next review date or stop date

- It is essential that the review and subsequent decision is clearly documented in the clinical notes and on the drug chart where possible (e.g., ‘stop antibiotic’).

*In clinical practice, daily prompting about de-escalation is encouraged.

» Target the presumed site of infection.[3] [43]

» If there is no clinical evidence to suggest a specific site of infection but a senior clinical decision-maker strongly suspects the presence of a bacterial infection, still give empirical broad-spectrum intravenous antibiotics.[3] [41] Choose an empirical antibiotic based on:
  - Local antibiotic protocols and resistance patterns
  - Consult microbiology/infectious disease colleagues to determine the most appropriate choice
  - The likely causative organism
  - The patient’s immune function.

Practical tip

Check local policies regarding repeat cultures, which are particularly indicated if there are persistent or repeated fever spikes or if you identify a potential new site of infection. Observations from studies to date support taking as many as four
Sepsis in adults

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blood culture sets over a 24-hour period for >99% test sensitivity.[148]

**Practical tip**

If a patient has a mild allergy (e.g., rash) to an unknown antibiotic, you should still give empirical broad-spectrum antibiotics if indicated to prevent delay in the treatment of sepsis, which is likely to worsen outcome. If the antibiotic is known and is part of the empirical protocol for your hospital, discuss with potential alternatives with a microbiologist.

**Controversy: 1-hour antibiotic targets**

There is widespread agreement that appropriate and timely recognition of sepsis and subsequent resuscitation are key approaches to the management of the severely ill patient with sepsis. However, guideline-derived antibiotic delivery goals (as outlined by the UK National Institute for Health and Care Excellence [NICE], the Surviving Sepsis Campaign [SSC], and the UK Sepsis Trust) have been challenged owing to gaps in the evidence and concerns about over-treatment of the individual patient and the subsequent effect on antimicrobial resistance. [57] [58]

The 1-hour antibiotic targets outlined by NICE, [3] the SSC, [43] and the UK Sepsis Trust (Sepsis Six) [46] are derived from data that appear to draw a direct correlation between each hour of delayed treatment of the patient with sepsis and an increased risk of further deterioration or death. [93] [149] [150] However, examining some of these data closely shows that 1-hour antibiotic targets may not be possible or necessarily advantageous for all patients with eventual sepsis diagnoses. [58]

- A retrospective cohort study of hypotensive inpatients with sepsis, published in 2006, first described a potential link between timing of antibiotics and outcomes. [149]
  - The authors noted 79.9% survival if septic patients received in vitro-active antibiotics within 1 hour of the
| **Initial**                                                                 | onset of hypotension, with a subsequent 7.6% survival rate decrement with each additional hour to treatment.  
- Looking closely at the data, however, there was a lower survival rate (52%) among patients who received antibiotics before hypotension compared with those who received them within the first few hours of the onset of septic shock.  
- Commentators note that ascribing a biological effect to antibiotics for either the improvement or the decreased survival is endemic to observational or natural experiment designs, which are prone to confounding and bias in their interpretation of results.[58]  
- More recently, another retrospective cohort study of 3929 patients with severe sepsis described an 8% hourly incremental increased risk of progression to septic shock with longer time to antibiotics.[150]  
- There was little change in rate of worsening (progression to septic shock rate) until after 5 hours; by then, approximately 75% of patients had received antibiotics. The remaining 25% of the cohort (who were treated later than the first patient group) differed from those treated earlier. Notably, the later-treated group had more comorbidities.  
- As noted in commentary on the study, this is in line with what’s commonly seen in clinical practice: sepsis is harder to recognise in people with comorbidities, and patients with sepsis and comorbid illness have a worse prognosis in general.[58]  
- Another recent trial randomised 2672 patients with suspected sepsis (>95% |
Initial

without shock) to receive antibiotics in ambulances or ‘quickly’ in an emergency department. The median 96-minute-earlier administration was not linked to improved outcomes, regardless of illness severity.[93]

» In intensive care settings only, consider prolonged infusion when giving beta-lactam antibiotics to patients with sepsis (apart from those with kidney-related complications).[151] Note that prolonged infusion times are not licensed, as most manufacturers advise infusion of beta-lactam antibiotics over 15 to 60 minutes.

Evidence: Prolonged antibiotic infusion

Intravenous antibiotics, administered over 3 hours, are linked to lower death rates in sepsis.[151] Prolonged infusion should be easy to apply in the intensive care setting, without the need for additional training or equipment.

• A systematic review and meta-analysis pooled the results of 22 randomised controlled trials involving 1876 adults with sepsis. The trials compared prolonged versus short-term administration of any antipseudomonal beta-lactam. Carbapenems were studied in nine trials, penicillins in nine trials, and cephalosporins in eight trials.[151]

• Prolonged infusion was associated with lower all-cause mortality than short-term infusion, with 13.6% deaths compared with 19.8% (risk ratio [RR] 0.70, 95% CI 0.56 to 0.87; 17 studies, 1597 participants).

• There was no significant difference between prolonged and short-term infusion for clinical cure or improvement (RR 1.06, 95% CI 0.96 to 1.17; 11 studies, 1219 participants).

• There was no difference in reported adverse events between the groups (RR 0.88, 95% CI 0.71 to 1.09; 7 studies, 980 participants).
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- Two trials had no incidence of antibiotic resistance, and two trials had no difference in resistance between the two methods of antibiotic administration (RR 0.60, 95% CI 0.15 to 2.38).

  » **Narrow choice of antibiotic as soon as a pathogen has been identified and sensitivities are available.** [43] [137]

  #Assess the need to de-escalate antimicrobial therapy daily. [43]

  - Studies have shown that daily prompting about antimicrobial de-escalation is effective and may be associated with improved outcomes. [193] [194]

  » **Continue broad-spectrum coverage to include all common pathogens if the source is unknown or unclear.** [3]

  - Bear in mind that a definite source of infection cannot be found in 20% to 30% of people with sepsis. [9]

  » **Use the shortest effective course of antibiotics.** [195]

  - Unnecessarily prolonged antibiotic treatment is associated with resistance. See More info: Antimicrobial resistance above.

  » **Consult local microbiology guidance for other specific recommendations on de-escalation.**

  - Most protocols will recommend switching from intravenous to oral antibiotics as soon as possible.

  » **According to the Surviving Sepsis Campaign (SSC), most serious infections associated with sepsis and septic shock will need 7 to 10 days of antibiotic treatment.** [43] [However, in practice, shorter courses of antibiotics are often appropriate. [196] The optimal duration of antibiotic treatment in patients with sepsis remains contentious, with concerns regarding not only under-treatment but also the potential encouragement of antibiotic resistance. Consider seeking advice**
Initial management from microbiology/infectious disease colleagues.

- The SSC guideline suggests considering shorter courses in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis.[43]
- Longer courses of treatment may be appropriate in patients who have:[43]
  - A slow clinical response
  - Undrainable foci of infection
  - Bacteraemia with *Staphylococcus aureus*
  - Some fungal and viral infections
  - Immunological deficiencies, including neutropenia.

**Baseline serum procalcitonin** is increasingly being used in critical care settings to guide decisions on **how long to continue antibiotic therapy**.[43][105][106][107]

- Procalcitonin is a peptide precursor of calcitonin, which is responsible for calcium homeostasis.
- It is currently excluded from key guidelines, but increasingly used in practice.

**plus** reassess and monitor

Treatment recommended for ALL patients in selected patient group

**Ensure frequent and ongoing monitoring.**[3]

- Standard monitoring of vital signs, pulse oximetry, level of consciousness, and urinary output is important for any patient with suspected sepsis.
- The UK National Institute for Health and Care Excellence (NICE) recommends continuous or half-hourly monitoring (depending on setting) for any patient considered to be at high risk of deterioration (defined in the NICE guideline as meeting one or more of its high-risk criteria for severe illness or death from sepsis).[3]
### Initial

- See the Risk stratification subsection of Diagnosis recommendations for more information.

» **Use a track-and-trigger scoring system such as the National Early Warning Score 2 (NEWS2) to identify any signs of deterioration.** [3] Your monitoring should include:

- Vital signs: heart rate, blood pressure, oxygen saturations, respiratory rate, and temperature
  - Measure blood pressure via an arterial line if the patient does not respond to initial treatment or needs vasoactive drugs. It provides precise, continuous monitoring, and access for arterial blood sampling
- Hourly urine output[3] [43] [46]
- Lactate
  - The lactate level should decrease if the patient is clinically improving
  - Frequency of repeat lactate measurement depends on the cause of sepsis and treatment given.

» **Measure serum lactate, on a blood gas, to monitor response to treatment.** [3] [43] [46]

- Lactate is a **marker of stress** and may be a marker of a worse prognosis (as a reflection of the degree of stress). Raised serum lactate highlights the possibility of tissue hypoperfusion and may be present in many conditions.[77] [78]
- Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst.
- Lactate >4 mmol/L (>36 mg/dL) is associated with worse outcomes.
  - One study found in-hospital mortality rates as follows:[79]
### Sepsis in adults

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>• Lactate &lt;2 mmol/L (&lt;18 mg/dL): 15%</td>
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<tr>
<td>• Lactate 2.1 to 3.9 mmol/L (19 to 35 mg/dL): 25%</td>
</tr>
<tr>
<td>• Lactate &gt;4 mmol/L (&gt;36 mg/dL): 38%.</td>
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» Sepsis guidelines from NICE and NHS England recommend escalating treatment depending on lactate level. [3] [4] [41] #Alert critical care immediately if the patient is acutely unwell and has persistent lactate >4 mmol/L (36 mg/dL) [3] despite fluid resuscitation.

» Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL]).

- This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their NEWS2 score.

### Practical tip

Lactate is typically measured using a blood gas analyser, although laboratory analysis can also be performed. Traditionally, arterial blood gas has been recommended as the ideal means of measuring lactate accurately. However, in the emergency department setting it is more practical and quicker to use venous blood gas, which is recommended by NICE. [3] Evidence suggests good agreement at lactate levels <2 mmol/L (<18 mg/dL) with small disparities at higher lactate levels. [80] [81] [82]

### Evidence: Lactate clearance

The best available evidence supports lactate clearance (the rate at which lactate is cleared over a period of 6 hours) as being as useful as more invasive tests, such as central venous oxygen saturation (ScvO₂), in determining a patient’s response to treatment. [197] [198] [199] [200] [201] [202]

- In one study that looked at patients with septic shock who were treated
Initial

<table>
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<th>Management</th>
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<tr>
<td>to normalise central venous and mean arterial pressure, additional management to normalise lactate clearance compared with additional management to normalise ScvO₂ did not result in significantly different in-hospital mortality. [198]</td>
</tr>
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</table>

- Of 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographics, comorbidities, and physiological features. There were no differences in treatments administered during the initial 72 hours of hospitalisation.
- Thirty-four patients (23%) in the ScvO₂ group died while in hospital (95% CI 17% to 30%) compared with 25 (17%, 95% CI 11% to 24%) in the lactate clearance group. This observed difference between mortality rates did not reach the predefined -10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, -3% to 15%). There were no differences in treatment-related adverse events between the groups.
- Several trials have assessed the diagnostic accuracy of percentage lactate clearance over 0 to 6 hours. It is worth noting that these studies provide very low-quality evidence, owing mainly to a presumed lack of blinding of treating physicians to the patient’s lactate status.
- The studies’ findings agree that lactate clearance early in the hospital course is associated with decreased mortality rate. Patients with higher lactate clearance after 6 hours of emergency department intervention had improved outcomes compared with those with lower lactate
Sepsis in adults

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Initial clearance.[197] [199] [200] [201] [202]

- In the UK, use physiological track-and-trigger systems to monitor all adult patients in acute hospital settings.[3]

- Consider using a validated scale such as the Glasgow Coma Scale or AVPU ('Alert, responds to Voice, responds to Pain, Unresponsive') scale to monitor the mental state of a patient with suspected sepsis. [3]

**Practical tip**

AVPU should raise concerns if the assessment shows the patient is anything other than 'alert'.

- Any patient with sepsis may be at significant risk of severe illness or death so it is vital to consider escalation of care to senior colleagues and/or healthcare facilities where increased and more advanced monitoring can be given (e.g., high-dependency unit/intensive care unit). [7] [170] [171]

  - Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

- Consult local protocols for specific escalation routes but in general:
  - Ensure immediate review by a senior clinician (CT3/ST3 or higher in the UK) of any patient with a NEWS2 score of 5 or more, or who meets one or more of the NICE sepsis high-risk criteria. Also ensure the patient is discussed with a consultant.[3] [41]
  - Discuss with the admitting consultant [3] and consider alerting critical care immediately if the patient is acutely unwell and:
    - Has a NEWS2 score of 7 or more, persisting high lactate (more...
Sepsis in adults

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- Systolic blood pressure of less than 90 mmHg [3]
  - Discuss with the admitting consultant [3]
  - Has hypotension that doesn’t respond to initial fluid resuscitation
  - Is likely to require central venous access and the initiation of inotropes or vasopressors [3]
  - Has any feature of septic shock
    - See our topic Shock
    - Has neutropenia
      - See our topic Febrile neutropenia
    - Is immunodeficient
  - Urgently discuss with a consultant or call them to attend if the patient [41]
    - Is treated with intravenous antibiotics and/or a fluid bolus for sepsis
    - Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour. [3] [41] Failure to respond to treatment is defined as:[3]
      - Systolic blood pressure remains less than 90 mmHg
      - Persistent reduced level of consciousness
      - Respiratory rate more than 25 breaths per minute or the new need for mechanical ventilation
      - Lactate has not reduced by more than 20%
  - Refer to critical care any patient who is likely to require central venous access and initiation of inotropes or vasopressors [3]
    - This includes any patient with evidence of circulatory dysfunction or shock, or those who do not
**Initial**

- respond to initial therapy (as outlined above)
  - ECG can be used to determine which vasoactive drug(s) to proceed with in critical care.[43]

**Practical tip**

Ensure a clear escalation plan has been discussed and agreed with the clinical team; include specific points of contact for nursing staff if you are leaving a patient for later review. Involve a senior colleague and/or consider transferring to critical care sooner rather than later if the patient is not improving, or deemed high-risk.# Examples include if the patient:
  - Is not responding to fluids
  - Needs inotropic support
  - Has a low Glasgow Coma Scale score
  - Needs ventilatory support.

**Plus**

**Identify the infection source**

Treatment recommended for ALL patients in selected patient group

- Make intensive efforts to identify the anatomical site of infection as soon as possible. [3] [43] #Consider the need for urgent source control as soon as the patient is stable.

  - Start with a thorough and focused clinical history and examination, as well as initial investigations including imaging.[3]
  - Consider all lines and catheters as potential sources. Take cultures from the line tip. Remove lines where appropriate.[43]
  - Assume that any intravenous route is likely to either be the source of the infection, or will seed infections in the bloodstream, making eradication particularly difficult. Therefore, the priority for source control is often to remove any intravenous devices after vascular access has been obtained.[43]
  - If you suspect an abdominal or pelvic source, involve the relevant surgical team early, particularly if surgery is likely.[3]
In practice, this may mean early transfer of the patient to a surgical centre if there are no facilities at your hospital.

- Common non-specific signs and symptoms include:[21] [43]
  - Those associated with a specific source of infection. [Signs and symptoms of possible infection sources] The most common sources are:[60]
    - Respiratory tract (cough/pleuritic chest pain)
    - Urinary tract (flank pain/dysuria)
    - Abdominal/upper gastrointestinal tract (abdominal pain)
    - Skin/soft tissue (abscess/wound/catheter site)
    - Surgical site or line/drain site
  - Tachypnoea
  - High (>38 °C [>100.4 °F]) or low (<36 °C [<96.8 °F]) temperature, sometimes with rigors
  - Tachycardia
  - Acutely altered mental status
  - Low oxygen saturation
  - Hypotension
  - Decreased urine output

  - Ask the patient when they last passed urine
  - Poor capillary refill, mottling of the skin, or ashen appearance
  - Cyanosis
  - Malaise/lethargy
  - Nausea/vomiting/diarrhoea
  - Purpura fulminans (a very late sign but may be seen on presentation)
  - Ileus
  - Jaundice.
Jaundice is a rare sign of sepsis unless it is associated with a specific source of infection (biliary sepsis).

Capillary refill time. Top image: normal skin tone; middle image: pressure applied for 5 seconds; bottom image: time to hyperaemia measured

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission
If your examination of the patient identifies a clear source of infection, consider the need for urgent source control, as soon as the patient is stable, particularly for:

- Gastrointestinal sources (such as visceral abscesses, cholangitis, or peritonitis secondary to perforation)
- Severe skin infections (e.g., necrotising fasciitis)
- Infection involving an indwelling device, where a procedure or surgery is likely to be required.

Give immediate, targeted antibiotics in people with sepsis thought to arise from a central nervous system source (e.g., suspected meningitis or meningococcal sepsis).

- Immediately give a third-generation cephalosporin such as ceftriaxone or cefotaxime.
- In community settings, pre-hospital administration of benzylpenicillin is recommended.
- Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice; use a 'start smart then focus' approach.
**Initial**

<table>
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<th>Practical tip</th>
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<tr>
<td>If intravenous access is not feasible or is likely to lead to a delay in starting antibiotics and fluids, use intra-osseous access as an interim measure.</td>
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</table>

**Practical tip**

**Consider fluid resuscitation**

Treatment recommended for SOME patients in selected patient group

» Give 500 mL of crystalloid fluid, with a sodium content between 130 mmol/L and 154 mmol/L (130 to 154 mEq/L) (e.g., 0.9% sodium chloride or Hartmann’s solution), over less than 15 minutes to patients who need fluid resuscitation (if there is any sign of circulatory insufficiency). [3] [41] [66]

- Reassess the patient’s haemodynamic status after the first bolus to consider whether a second is required. [3] If there is no response to either the first or second bolus, seek senior support. [3]

» Intravenous fluid resuscitation may be lifesaving in patients with hypotension. This is because in sepsis there is vasodilation and capillary leakage, which means that patients can rapidly become intravascularly deplete. [3]

- In patients with sepsis-induced hypoperfusion (as indicated by a systolic blood pressure <90 mmHg, a raised lactate level, or signs of organ dysfunction), the Surviving Sepsis Campaign international guideline recommends a total of at least 30 mL/kg of intravenous crystalloid over the first 3 hours. [43]

  - If the patient’s initial lactate level is raised, the guideline recommends serial lactate measurements to guide the need for further intravenous fluids (with the goal of normalising lactate levels). [43]

**Practical tip**

The delivery of appropriate rapid fluid challenges is intended to restore the imbalance between oxygen supply and demand to the tissues. Patients who do not respond to rapid delivery of
adequate volumes of intravenous fluids are in **septic shock and need immediate referral to critical care**. The immediate priority in this group of patients is to **restore the circulation and oxygen delivery**.

**Practical tip**

Monitor patients closely for **signs of fluid overload such as pulmonary or systemic oedema** before and after each additional fluid bolus, as they may require large volumes of fluid to support their circulating volume.[43] [152] [153]

**Evidence: Choice of fluid**

*Latest evidence suggests a balanced crystalloid may have marginal benefits over saline, but either option is a reasonable choice.* [3] [154]

- Although early fluid resuscitation is a cornerstone of sepsis treatment that is given high priority by both Sepsis Six and the UK National Institute for Health and Care Excellence, choice of fluid has been the source of much discussion. In particular, there has been extensive debate over the choice between a balanced crystalloid (such as Hartmann’s solution, Ringer’s lactate, or PlasmaLyte) and normal saline (an unbalanced crystalloid). There have been very few high-quality studies, but latest evidence from critically ill patients points to marginal benefits from using a balanced crystalloid in preference to saline.[154]

- A 2018 US multicentre cluster-randomised trial among 15,802 critically ill adults receiving care in the intensive care unit found small benefits from balanced crystalloid compared with saline. The 30-day outcomes showed 10.3% mortality in the balanced crystalloid group compared with 11.1% in the saline group (P = 0.06), and a major adverse kidney event rate of 14.3% compared with 15.4% in the two groups, respectively (marginal
### Management

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<tr>
<td><strong>odds ratio 0.91, 95% CI 0.84 to 0.99.</strong>[^154]</td>
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<tr>
<td>• Colloids (e.g., starches, dextrans, gelatins, albumin, or fresh frozen plasma) are no longer used in emergency medicine in the UK.</td>
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</table>

### Debate: Volume and rate of fluids

*Studies have not shown benefits from early goal-directed therapy and your focus should instead be on adjusting treatment according to i) lactate level and ii) clinical assessment of the patient’s haemodynamic response to initial fluids.*[^43] [^155] [^156] [^157] [^158] [^159] [^160]

- Previous versions of the Surviving Sepsis Campaign (SSC) guidelines recommended a protocolled approach to resuscitation, otherwise known as early goal-directed therapy (EGDT).[161] [^162] [^163] EGDT involves the use of a series of ‘goals’ including central venous pressure and central venous oxygen saturation ($\text{ScvO}_2$). This recommendation was largely based on data from one study that showed a significant survival benefit for patients receiving EGDT.[155]

- This approach has since been challenged following the **failure to show a mortality reduction** in three subsequent large multicentre randomised controlled trials: PROCESS, ARISE, and PROMISE.[156] [^157] [^158]

- It is worth bearing in mind that these three trials included patients who were less severely ill (lower baseline lactate levels, $\text{ScvO}_2$ at or above the target value on admission, and lower mortality in the control group) than the patients in the original study that outlined EDGT as a recommended approach.

- Based on this latest evidence, the **SSC no longer specifically recommends EDGT**; it does, however, acknowledge the need for guidance on how to approach this...
### Initial

<p>| | |</p>
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<tr>
<td></td>
<td>group of patients who have significant mortality and morbidity. The SSC therefore recommends that you:</td>
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<td></td>
<td>• View these patients as having a <strong>medical emergency</strong> that necessitates urgent assessment and treatment</td>
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<tr>
<td></td>
<td>• Begin initial fluid resuscitation with 30 mL/kg of crystalloid within the first 3 hours</td>
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<td></td>
<td>• This fixed volume of fluid enables initiation of resuscitation while giving an opportunity to ascertain more specific information about the patient and while awaiting more precise measurements of haemodynamic status</td>
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<tr>
<td></td>
<td>• Although scant data are available to support this volume of fluid, interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice</td>
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<td></td>
<td>• The average volume of fluid pre-randomisation given was approximately 30 mL/kg in the PROCESS and ARISE trials, and approximately 2 L in the PROMISE trial. The SSC acknowledges that many patients will need more fluid than this, and advocates giving further fluid to this group in line with functional haemodynamic measurements.</td>
</tr>
<tr>
<td></td>
<td>• The UK National Institute for Health and Care Excellence guideline on sepsis focuses on initial management and treatment, and therefore makes no</td>
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</table>

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### Initial

|   | recommendations regarding intensive monitoring such as that used in EGDT. [3] |

### Practical tip

**To guide the need for further intravenous fluids, it can sometimes be helpful to use bedside ultrasound to monitor changes in inferior vena cava (IVC) diameter during respiration.** [164] [165]

- In the spontaneously breathing patient: consider additional fluid resuscitation if there is a collapsed (or collapsing) IVC.
- In the mechanically ventilated patient: an increase in IVC size >18% (or visible to the naked eye) with positive pressure ventilation suggests fluid-responsiveness.

### Practical tip

Use the passive leg-raising test to predict fluid-responsiveness if adequate monitoring is available. [66] [166]

- This is a useful indicator of fluid-responsiveness, which should be assessed using devices that can continuously monitor cardiac output in real time (e.g., Pulse index Continuous Cardiac Output [PiCCO] monitor or oesophageal Doppler), usually in an intensive care unit rather than a general ward setting.
- Sit the patient upright at 45° and tilt the entire bed through 45°.
- Patients with a positive test have a >10% increase in cardiac output or stroke volume, indicating more fluids may be required.
- The passive leg-raise response may be misleading in conscious patients who are uncomfortable or in pain when lying flat.

### consider oxygen

Treatment recommended for SOME patients in selected patient group.
**MANAGEMENT**

<table>
<thead>
<tr>
<th>Initial</th>
</tr>
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<tbody>
<tr>
<td>- <strong>If indicated</strong>, give oxygen to maintain target oxygen saturations &gt;94%. [3] [43] [46] [47] Latest evidence suggests that liberal use of supplemental oxygen (target $\text{SpO}_2 &gt;96%$) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy. [138] Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia.</td>
</tr>
<tr>
<td>- Target saturation of 88% to 92% if the patient is at risk of hypercapnic respiratory failure (e.g., patients with COPD). [3] [43] [46] [47]</td>
</tr>
</tbody>
</table>

**Evidence: Target oxygen saturation in acutely ill adults**

*Too much supplemental oxygen increases mortality.*

Latest evidence supports a 96% upper limit for target oxygen saturation in non-hypercapnic acutely ill adults.

- Guidelines differ in their recommendations on target oxygen saturation in acutely unwell adults who are receiving supplemental oxygen. The 2017 British Thoracic Society guideline recommends a target $\text{SpO}_2$ range of 94% to 98% for patients not at risk of hypercapnia, [47] whereas the 2015 Thoracic Society of Australia and New Zealand guideline recommends 92% to 96%. [167]

- A 2018 systematic review including a meta-analysis of data from 25 randomised controlled trials found that in adults with acute illness, liberal oxygen therapy (broadly equivalent to a target saturation >96%) is associated with higher mortality than conservative oxygen therapy (broadly equivalent to a target saturation ≤96%). [138] In-hospital mortality was 11 per 1000 higher for the liberal oxygen therapy group versus the conservative therapy group (95% CI 2.22 per 1000 more). Mortality at 30 days was also higher in the group who had received liberal oxygen (risk ratio 1.14, 95% CI 1.01 to 1.29). The trials included adults with sepsis, critical illness, stroke, trauma, myocardial infarction, and cardiac arrest, and patients who had emergency surgery. Studies that...
**Initial**

were limited to people with chronic respiratory illness or psychiatric illness, patients on extracorporeal life support, patients receiving hyperbaric oxygen therapy, or those having elective surgery were all excluded from the review.

- An upper SpO₂ limit of 96% is therefore reasonable when administering supplemental oxygen to medical patients with acute illness who are not at risk of hypercapnia. However, a higher target may be appropriate for some specific conditions (e.g., pneumothorax, carbon monoxide poisoning, cluster headache, and sickle cell crisis).[168]

» There is no specific evidence to show that giving oxygen improves clinical outcomes in sepsis. However, **respiratory failure will lead to tissue hypoxia and anaerobic respiration**. This is likely to lead to acidosis and consequently a poorer outcome.[169]

**Management**

Consider **standard intensive care unit supportive care**

Treatment recommended for SOME patients in selected patient group

» **Any patient with sepsis may be at significant risk of severe illness or death** so it is vital to consider escalation of care to senior colleagues and/or healthcare facilities where increased and more advanced monitoring can be given (e.g., high-dependency unit/intensive care unit).

[7] [170] [171]

- Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

» **Consult local protocols for specific escalation routes but in general**:

- Ensure immediate review by a senior clinician (CT3/ST3 or higher in the UK) of any patient with a National Early Warning Score 2 (NEWS2) score of 5 or more, or who meets one or more of the
### Initial

<table>
<thead>
<tr>
<th>UK National Institute for Health and Care Excellence sepsis high-risk criteria. Also ensure the patient is discussed with a consultant[^3] <a href="%5B%5E3%5D">[^41]</a></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discussion with the admitting consultant</strong> <a href="%5B%5E3%5D">[^3]</a> <strong>and consider alerting critical care immediately</strong> if the patient is acutely unwell and:</td>
</tr>
<tr>
<td>• Has a <strong>NEWS2 score of 7 or more</strong>, persisting <strong>high lactate</strong> (more than 4 mmol/L [36 mg/dL]) despite fluid resuscitation, or a <strong>systolic blood pressure of less than 90 mmHg</strong> <a href="%5B%5E3%5D">[^3]</a></td>
</tr>
<tr>
<td>• Discuss with the admitting consultant <a href="%5B%5E3%5D">[^3]</a></td>
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<tr>
<td>• Has hypotension that doesn’t respond to initial fluid resuscitation</td>
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<tr>
<td>• Is likely to require central venous access and the initiation of inotropes or vasopressors</td>
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<tr>
<td>• Has any feature of <strong>septic shock</strong></td>
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<tr>
<td>• See our topic Shock</td>
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<tr>
<td>• Has <strong>neutropenia</strong></td>
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<tr>
<td>• See our topic Febrile neutropenia</td>
</tr>
<tr>
<td>• Is immunodeficient</td>
</tr>
<tr>
<td><strong>Urgently discuss with a consultant or call them to attend</strong> if the patient: <a href="%5B%5E41%5D">[^41]</a></td>
</tr>
<tr>
<td>• Is treated with intravenous antibiotics and/or a fluid bolus for sepsis</td>
</tr>
<tr>
<td>• Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour. <a href="%5B%5E3%5D">[^3]</a> <a href="%5B%5E41%5D">[^41]</a> Failure to respond to treatment is defined as: <a href="%5B%5E3%5D">[^3]</a></td>
</tr>
<tr>
<td>• Systolic blood pressure remains less than 90 mmHg</td>
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<tr>
<td>• Persistent reduced level of consciousness</td>
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<tr>
<td>• Respiratory rate more than 25 breaths per minute or the</td>
</tr>
</tbody>
</table>
## Initial

- **new need for mechanical ventilation**
  - Lactate has not reduced by more than 20%

- **Refer to critical care** any patient who is likely to require central venous access and initiation of inotropes or vasopressors[3]

  - This includes any patient with evidence of circulatory dysfunction or shock, or those who do not respond to initial therapy (as outlined above)
  - ECG can be used to determine which vasoactive drugs(s) to proceed with in critical care.[43]

### Practical tip

Ensure a clear escalation plan has been discussed and agreed with the clinical team; include specific points of contact for nursing staff if you are leaving a patient for later review.

**Involve a senior colleague and/or consider transferring to critical care sooner rather than later if the patient is not improving, or deemed high-risk.**

Examples include if the patient:

- Is not responding to fluids
- Needs inotropic support
- Has a low Glasgow Coma Scale score
- Needs ventilatory support.

»

» **For any patient with suspected sepsis, consider the need for referral to a high-dependency unit for management by the critical care team.**[155][174]

» **The following interventions should only be initiated by experienced members of the critical care team:**[3][43][175]

  - Glycaemic control
  - Vasoactive drugs (vasopressors/inotropes)
  - Corticosteroids.

» **Additional intensive care measures that will be considered include:**[43][176][177]
Initial

- **Stress ulcer prophylaxis** (in people at risk of gastrointestinal bleeding)
  - With an H2 antagonist or proton-pump inhibitor

- **Deep venous thrombosis prophylaxis**
  - With heparin and compression stockings

- **Enteral or parenteral nutrition**
  - Administration of human albumin solution 4% to 5% in patients with sepsis and shock who have not responded to substantial volumes of crystalloids
  - Transfusion of packed cells
  - Consult local protocols for recommended threshold
  - The Surviving Sepsis Campaign recommends using a threshold of 70 g/L (7 g/dL).

**Evidence: Threshold for transfusion of packed cells**

*Studies in the general critical care population have shown no improvement with blood transfusions given at a higher haemoglobin threshold compared with a lower haemoglobin threshold* [178] and *have shown potential harm associated with liberal transfusion.* [179]

- One multicentre parallel group randomised trial analysed data from 998 patients with septic shock, split into two intervention groups with similar baseline characteristics. In the intensive care unit, the group assigned to blood transfusion at a lower haemoglobin threshold received a median of 1 unit of blood (interquartile range, 0 to 3) and the group assigned to blood transfusion at a higher haemoglobin threshold received a median of 4 units (interquartile range, 2 to 7).[178]

  - At 90 days after randomisation, 216 of 502 patients (43.0%) assigned to the lower-threshold group, compared with 223 of
496 (45.0%) assigned to the higher-threshold group, had died (relative risk 0.94, 95% CI 0.78 to 1.09; P = 0.44).

- The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations.
- The numbers of patients who had ischaemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.
- A second multicentre randomised controlled trial compared the rates of death from all causes at 30 days and the severity of organ dysfunction in 838 critically ill patients receiving a restrictive strategy of red-cell transfusion compared with those receiving a liberal strategy.[179]

- Overall, 30-day mortality was similar in the two groups (18.7% vs. 23.3%, P = 0.11).
- However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill and in patients younger than 55 years of age (5.7% and 13.0%, respectively; P = 0.02), but not in those with clinically significant cardiac disease (20.5% and 22.9%, respectively; P = 0.69).
- The mortality rate during hospitalisation was significantly lower in the restrictive-strategy group (22.3% vs. 28.1%, P = 0.05).

» There may be a case to consider giving transfusions at a higher haemoglobin level in people with myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis.[43]
### Initial

- In the initial resuscitative phase, transfusion to achieve a higher haematocrit of ≥30% may be appropriate. [155]

- In patients requiring prolonged ventilatory support, give **lung-protective ventilation using minimal peak inspiratory pressures (<30 cm H₂O) and permissive hypercapnia to specifically limit pulmonary compromise**. [180]
  
  - Titrate fraction of inspired oxygen (FiO₂) to lowest effective levels to prevent oxygen toxicity and maintain central venous oxygen tension.
  - Place patients in a semi-recumbent position with the head elevated to 30° to 45°. [43]

### Glycaemic control

Although patients with sepsis are often hyperglycaemic, the optimal glucose target is unknown.

The Surviving Sepsis Campaign guideline recommends targeting a **blood glucose level <10.0 mmol/L (<180 mg/dL)**. [43] The guideline also recommends a ‘sliding scale’ variable-rate intravenous insulin infusion. [43]

- The UK National Institute for Health and Care Excellence makes no recommendations on glycaemic control in sepsis. [3]

### Evidence: Glycaemic control

*Recent years have seen a shift in opinion and practice regarding glycaemic control in critically ill people. Since 2001, the use of tight glycaemic control has been advocated in people with sepsis. More recent evidence, however, suggests an increase in adverse events (e.g., severe hypoglycaemia) in patients managed with very tight glycaemic control (targeting a blood glucose below 6.1 mmol/L [110 mg/dL]). [181] [182] The conflicting evidence has led to variations in recommendations in different countries and settings. Follow your local protocol.*

- An international randomised controlled trial (RCT) of 6104 critically ill medical and surgical patients found increased 90-day mortality (odds ratio 1.14, 95%
Sepsis in adults

### Management

**Initial**

<table>
<thead>
<tr>
<th>CI 1.02 to 1.28) with tighter glucose control, possibly due to more frequent episodes of hypoglycaemia.[183]</th>
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<tbody>
<tr>
<td>• A 2010 systematic review of 6 RCTs and a meta-analysis investigating tight glucose control (4.4 to 6.1 mmol/L [80-110 mg/dL]) versus less strict glucose control in critically ill patients in the intensive care unit setting found no significant improvement in mortality with tight glucose control, but it was associated with significantly more hypoglycaemic episodes compared with less strict glucose control.[184]</td>
</tr>
<tr>
<td>• An RCT of critically ill patients in a primarily surgical intensive care setting found lower patient mortality with tight glucose control, 4.4 to 6.1 mmol/L (80-110 mg/dL), compared with ‘conventional’ more liberal glucose control.[185]</td>
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**Consider**

vasopressor (should only be initiated by experienced members of the critical care team)

Treatment recommended for SOME patients in selected patient group

**Primary options**

- noradrenaline (norepinephrine): 0.4 to 0.8 mg/hour intravenous infusion initially, adjust dose according to response
  
  Dose refers to noradrenaline base.

**Secondary options**

- noradrenaline (norepinephrine): 0.4 to 0.8 mg/hour intravenous infusion initially, adjust dose according to response
  
  Dose refers to noradrenaline base.

---AND---

- vasopressin: 0.01 units/minute intravenous infusion initially, adjust dose according to response, maximum 0.03 units/minute
  
  -OR-

- adrenaline (epinephrine): 2-10 micrograms/minute intravenous infusion initially, adjust dose according to response

**OR**

- dopamine: 2-5 micrograms/kg/minute intravenous infusion initially, adjust dose according to response
**Initial**

» **Vasopressors** are used in a critical care setting to maintain a mean arterial pressure (MAP) ≥65 mmHg if the patient is unresponsive to fluid resuscitation. [3] [43] [175]

- Failure to respond to initial fluid resuscitation is a sign of **septic shock** [1].
- **Noradrenaline (norepinephrine)** is the vasopressor of choice, mainly because it increases MAP. [43]
  - Noradrenaline is the vasopressor recommended by the Surviving Sepsis Campaign guideline. [43] The UK National Institute for Health and Care Excellence makes no recommendation on the choice of vasopressor. [3]
  - If further vasopressor therapy is required to maintain adequate blood pressure or the noradrenaline dose needs to be reduced, add vasopressin or adrenaline (epinephrine) to noradrenaline. [43]
  - Dopamine is an option, but has been associated with higher mortality than noradrenaline. [186] [187] Therefore, it is **only recommended in patients with a low risk of tachyarrhythmias and bradycardia**. [43] It is rarely used in the UK. Do not use low-dose dopamine for renal protection. [43]

**Practical tip**

All infusions of vasoactive drugs to correct shock should be given **via a secure catheter in a central vein with high flow**, such as a central venous catheter. These patients should also have an **arterial catheter** inserted as soon as possible to ensure more accurate monitoring of arterial blood pressure. [43]

**Evidence: Choice of vasopressor**

*Although a systematic review of 23 randomised trials of patients with shock found no convincing evidence for the superiority of one vasopressor over another [188] more recent meta-analyses reported a higher...*
Management

Sepsis in adults

<table>
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<tr>
<th>Initial</th>
<th>Consider</th>
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<tr>
<td>mortality associated with dopamine than with noradrenaline. [186]</td>
<td>inotrope (should only be initiated by experienced members of the critical care team)</td>
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<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
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</table>

**Primary options**

» dobutamine: 2.5 to 10 micrograms/kg/minute intravenous infusion initially, adjust dose according to response, maximum 40 micrograms/kg/minute

» Inotropes can be considered for patients with low cardiac output despite adequate fluid resuscitation and vasopressor therapy. [3] [43]

- Dobutamine is recommended first line by the Surviving Sepsis Campaign guideline for people with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure.[43]
- The UK National Institute for Health and Care Excellence makes no specific recommendations on inotrope selection in patients with sepsis.[3]

**Practical tip**

Suspect low cardiac output if the clinical examination reveals prolonged capillary refill times, low urine output, or poor peripheral perfusion. Confirm with cardiac output monitoring or by sampling central venous or pulmonary arterial blood to measure oxygen saturations. When using inotropes, keep the patient’s heart rate at less than 100 beats per minute to minimise myocardial ischaemia.[175]

Consider corticosteroid (should only be initiated by experienced members of the critical care team)

Treatment recommended for SOME patients in selected patient group

**Primary options**

» hydrocortisone sodium succinate: 200 mg/day intravenously
The Surviving Sepsis Campaign guideline recommends intravenous hydrocortisone as an option to consider for patients who are unresponsive to both fluid resuscitation and vasopressor therapy.\[43\]

The UK National Institute for Health and Care Excellence does not give any recommendations on the use of corticosteroids for managing sepsis in adults.\[3\]

Evidence: Benefits and harms of corticosteroids

Corticosteroids are a late critical-care intervention for patients in whom all other attempts to raise their blood pressure have failed.\[3\] In this critically ill group, corticosteroids may result in a small reduction in mortality.\[189\] Possible harms include an increased risk of neuromuscular weakness, hyperglycaemia, and hypernatraemia with corticosteroids compared with no corticosteroids.\[189\]

An international panel reviewing the inconsistent conclusions of large randomised controlled trials (RCTs) on the topic suggested in 2018 that the evidence for the use of corticosteroids was weak, but that “fully informed patients who value avoiding death over quality of life and function would likely choose corticosteroids”, although a no-corticosteroid approach remained reasonable.\[189\] This judgement was based on an assessment that corticosteroids may reduce mortality by around 2% (this effect was seen in sepsis with and without shock although the greatest benefit was among patients with septic shock), but can increase the risk of neuromuscular weakness and resulting functional deterioration. Most notably, the panel reviewed the following trials:

- **ADRENAL**: 3658 patients who had septic shock\[191\]
  - No statistically significant difference in 90-day mortality between the
Sepsis in adults

**Management**

<table>
<thead>
<tr>
<th>Initial</th>
<th>hydrocortisone and placebo groups</th>
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<tr>
<td>- APROCCHSS: 1241 patients who had septic shock [192]</td>
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<tr>
<td>- Hydrocortisone plus fludrocortisone reduced 90-day mortality.</td>
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**BMJ Rapid Recommendations:**
intravenous corticosteroids plus usual care versus usual care only

- A more recent systematic review and meta-analysis (comprising 37 RCTs, incorporating both ADRENAL and APROCCHSS) included 9564 people with sepsis [190]. The review found corticosteroid use to be associated with significant improvement in healthcare outcomes as shown by:

  - Reduced 28-day mortality (risk ratio [RR] 0.90, 95% CI 0.82 to 0.88) compared with placebo or standard supportive care
  - Reduced intensive care unit mortality (RR 0.85, 95% CI 0.77 to 0.94; $I^2 = 0\%$) compared with placebo or standard supportive care
  - Reduced in-hospital mortality (RR 0.88, 95% CI 0.79 to 0.99; $I^2 = 38\%$) compared with placebo or standard supportive care.

- However, corticosteroid use was also associated with increased risk of hyperglycaemia (RR 1.19, 95% CI 1.08 to 1.31).
Sepsis in adults

**Management**

**Initial**

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<th>1.08 to 1.30) and hypernatraemia (RR 1.57, 95% CI 1.24 to 1.99) compared with placebo or standard supportive care.[190]</th>
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</table>

in the community: sepsis highly suspected and bacterial infection confirmed or highly suspected

1st refer for emergency medical care in hospital

» Use your clinical judgement. Use National Early Warning Score 2 (NEWS2) scoring (encouraged by NHS England) to refer urgently to hospital any acutely unwell patient with suspected or confirmed infection according to the following triggers: [41] [NHS England: Sepsis]

- Score 7 or more
  - Make an emergency referral to hospital (via blue-light ambulance) for immediate critical care input.

- Score 5-6 total, or 3 or more on any single parameter
  - Make an immediate referral to an acute care setting and ensure the patient is reviewed by an acute clinician within an hour.

» [Track and trigger map developed by the West of England Academic Health Science Network National Early Warning Score project team]

» Alternatively, refer for emergency medical care in hospital (usually by blue-light ambulance in the UK) any acutely unwell patient with suspected or confirmed infection who:[3]

- Meets one or more of the **UK National Institute for Health and Care Excellence (NICE) high-risk criteria (red flags)**
  - Objective evidence of new altered mental state (e.g., new deterioration in Glasgow Coma Scale score/
### Initial

AVPU ['Alert, responds to Voice, responds to Pain, Unresponsive'] scale)

- Respiratory rate: ≥25 breaths per minute OR new need for oxygen (40% or more fraction of inspired oxygen [FiO₂]) to maintain saturation >92% (or >88% in known chronic obstructive pulmonary disease)
- Heart rate: >130 beats per minute
- Systolic blood pressure ≤90 mmHg or more than 40 mmHg below normal
- Not passed urine in previous 18 hours, or for catheterised patients passed <0.5 mL/kg of urine per hour
- Mottled or ashen appearance
- Cyanosis of skin, lips, or tongue
- Non-blanching rash of skin

- Is at risk of neutropenic sepsis and presents with symptoms and signs of infection

  - See our topic Febrile neutropenia.

» Carefully consider whether emergency medical care is required or whether the patient can be safely managed in the community with safety netting advice.[3] See box below on safety netting advice.

### Practical tip

If you need to refer a patient for emergency medical care in hospital, it is important to inform the hospital clinical team that the patient is on the way. This will enable the hospital to initiate appropriate treatment as soon as the patient arrives.

» In a patient with signs and symptoms of an infection and evidence of physiological deterioration, presume sepsis until it can safely be excluded. Take a cautious approach when deciding whether it is safe to treat the patient’s infection in the community. Using your clinical judgement in making a decision is paramount. In particular, carefully consider the need for hospital admission if:[50] [74] [140]
Initial

- The patient has one or more risk factors for sepsis (as listed above)
- The patient appears seriously unwell to you, based on experience and clinical judgement
- The patient lives alone with poor access to communication and/or transport
- A carer or parent expresses serious concern about the patient (e.g., “they’re just not right”).

» See our Diagnosis recommendations section for details of the NICE risk criteria.

» Treat the patient’s infection in line with local protocols and accepted practice. Antimicrobial prescribing guidelines from Public Health England and NICE are available for general practitioners in the UK.[203] [204]

Practical tip

If you decide that the patient is safe to treat in the community, written and verbal safety netting is vital.[50] Ensure the information is clear and specific rather than generalised advice; for example, do not say “come back if you get worse” — instead, specify key symptoms to watch out for (such as a non-blanching rash, change in behaviour or mental state, mottled skin, or ashen appearance) and explain where and how to access immediate medical care both in and out of hours.[50]

If you give the patient any safety netting advice, ensure you document this clearly in their medical notes, along with the patient’s observations and whether you have offered them any antibiotics. The 2015 national confidential enquiry into sepsis deaths found recorded evidence that safety netting advice had been provided in fewer than one quarter of cases.[60]

The UK Sepsis Trust advises the following acronym:[140]

- S lurred speech or confusion
- E xtreme shivering or muscle pain
- P assing no urine (in a day)
- S evere breathlessness
- ‘ I feel I might die’
- S kin mottled, ashen, blue, or very pale.

Advise the patient to call the emergency services if any of these symptoms develop. If the patient has a
change in condition or deterioration that is not covered by the acronym above, advise them to arrange another appointment to see their general practitioner or to call their out of hours service provider. It is also good practice to consider arranging a next-day review appointment or telephone call; if you will be unable to review the patient yourself, provide a written handover for your colleagues.[139]

consider oxygen

Treatment recommended for SOME patients in selected patient group

- If you have decided to refer the patient for emergency medical care and have called for an emergency ambulance, the UK Sepsis Trust/UK National Institute for Health and Care Excellence general practitioner toolkit recommends that, if indicated, you should start oxygen therapy while awaiting the ambulance if resources are available to do so.[139] [140]

- Give oxygen immediately to maintain target oxygen saturations >94%. [3] [43] [46] [47] Latest evidence suggests that liberal use of supplemental oxygen (target SpO₂ >96%) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy.[138] Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia.

- Target saturation of 88% to 92% in people at risk of hypercapnic respiratory failure (e.g., those with COPD. [3] [43] [46] [47]

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- Guidelines differ in their recommendations on target oxygen saturation in acutely unwell adults who are receiving supplemental oxygen. The 2017 British Thoracic Society guideline recommends a target SpO₂ range of 94% to 98% for patients not
at risk of hypercapnia,[47] whereas the 2015 Thoracic Society of Australia and New Zealand guideline recommends 92% to 96%.[167]

- A 2018 systematic review including a meta-analysis of data from 25 randomised controlled trials found that in adults with acute illness, liberal oxygen therapy (broadly equivalent to a target saturation >96%) is associated with higher mortality than conservative oxygen therapy (broadly equivalent to a target saturation ≤96%).[138] In-hospital mortality was 11 per 1000 higher for the liberal oxygen therapy group versus the conservative therapy group (95% CI 2-22 per 1000 more). Mortality at 30 days was also higher in the group who had received liberal oxygen (risk ratio 1.14, 95% CI 1.01 to 1.29). The trials included adults with sepsis, critical illness, stroke, trauma, myocardial infarction, and cardiac arrest, and patients who had emergency surgery. Studies that were limited to people with chronic respiratory illness or psychiatric illness, patients on extracorporeal life support, patients receiving hyperbaric oxygen therapy, or those having elective surgery were all excluded from the review.

- An upper $\text{SpO}_2$ limit of 96% is therefore reasonable when administering supplemental oxygen to medical patients with acute illness who are not at risk of hypercapnia. However, a higher target may be appropriate for some specific conditions (e.g., pneumothorax, carbon monoxide poisoning, cluster headache, and sickle cell crisis).[168]

consider broad-spectrum antibiotics

Treatment recommended for SOME patients in selected patient group

» Ensure you have a mechanism in place to administer antibiotics to any high-risk patient (either at your practice or via the ambulance service) if the transfer time to hospital is likely to be more than 1 hour.

» Give immediate, targeted antibiotics in people with sepsis thought to arise from a central nervous system source.[3]
<table>
<thead>
<tr>
<th>Initial</th>
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<tr>
<td>• Give benzylpenicillin before referring to hospital.[3]</td>
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</table>
**Acute**

<table>
<thead>
<tr>
<th>in hospital: sepsis highly suspected and clear source of bacterial infection identified</th>
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1st targeted antibiotics according to local protocols

» Once a definitive source has been identified, if appropriate to continue treating the patient with antibiotics, choose a treatment regimen in line with local or national policy (which will take into account specialist knowledge of resistance patterns). Also consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice.

» Assess the need to de-escalate antimicrobial therapy daily.

- Studies have shown that daily prompting about antimicrobial de-escalation is effective and may be associated with improved outcomes.

» Use the shortest effective course of antibiotics.

- Unnecessarily prolonged antibiotic treatment is associated with resistance.

**More info: Antimicrobial resistance**

* NHS England recommends following a ‘start smart then focus’ approach for antibiotic use in people with sepsis. This is derived from Public Health England guidance, which outlines an evidence-based approach to improving antimicrobial prescribing and stewardship in hospital settings. The prevalence of antimicrobial resistance (AMR) has risen alarmingly over the last 50 years and no new classes of antibiotics have been developed in decades. By 2050 it is estimated that AMR will kill 10 million people per year, more than cancer and diabetes combined. The relationship between antibiotic exposure and antibiotic resistance is unambiguous not only at the population level but also in individual patients.

Start smart – in the context of sepsis.
Sepsis in adults

Management

Acute

- Do not start antimicrobial therapy unless there is clear evidence of infection
- Take a thorough drug allergy history
- Initiate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients with sepsis or life-threatening infections. Avoid inappropriate use of broad-spectrum antibiotics
- Comply with local antimicrobial prescribing guidance
- Document clinical indication (and disease severity if appropriate), drug name, dose, and route on drug chart and in clinical notes
- Include review/stop date or duration
- Obtain cultures prior to starting therapy where possible (but do not delay therapy).

Then focus – in the context of sepsis:[136]

- Review the clinical diagnosis and the continuing need for antibiotics at 48 to 72 hours* and document in a clear plan of action – the ‘antimicrobial prescribing decision’
- The ‘antimicrobial prescribing decision’ options are:

  1. Stop antibiotics if there is no evidence of infection
  2. Switch antibiotics from intravenous to oral
  3. Change antibiotics – ideally to a narrower spectrum, or broader if required
  4. Continue and document next review date or stop date

- It is essential that the review and subsequent decision is clearly documented in the clinical notes and on the drug chart where possible (e.g., ‘stop antibiotic’).
Management

Acute

*In clinical practice, daily prompting about de-escalation is encouraged.

» Consult local microbiology guidance for other specific recommendations on de-escalation.

• Most protocols will recommend switching from intravenous to oral antibiotics as soon as possible.

» According to the Surviving Sepsis Campaign (SSC), most serious infections associated with sepsis and septic shock will need 7 to 10 days of antibiotic treatment. However, in practice, shorter courses of antibiotics are often appropriate. The optimal duration of antibiotic treatment in patients with sepsis remains contentious, with concerns regarding not only under-treatment but also the potential encouragement of antibiotic resistance. Consider seeking advice from microbiology/infectious disease colleagues.

• The SSC guideline suggests considering shorter courses in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis.

• Longer courses of treatment may be appropriate in patients who have:

  • A slow clinical response
  • Undrained foci of infection
  • Bacteraemia with *Staphylococcus aureus*
  • Some fungal and viral infections
  • Immunological deficiencies, including neutropenia.

» Baseline serum procalcitonin is increasingly being used in critical care settings to guide decisions on how long to continue antibiotic therapy.

• Procalcitonin is a peptide precursor of calcitonin, which is responsible for calcium homeostasis.
Sepsis in adults

Management

Acute

- It is currently excluded from key guidelines, but increasingly used in practice.

Respiratory

Ensure treatment regimens cover common respiratory pathogens and atypical organisms such as *Legionella pneumophila*.

- The respiratory tract is the most common site of infection in people with sepsis.[20] [60]
- See our topic Overview of pneumonia.

Abdominal

Ensure gram-positive and gram-negative organisms including anaerobes are covered.[172]

Arrange urgent surgical drainage or percutaneous drainage (where appropriate) for peritonitis or intra-peritoneal abscesses.[173]

Urinary tract

Ensure gram-negative coliforms and *Pseudomonas* are covered. Ensuring patency of the urinary tract is vital.

- In people older than 65 years of age, genitourinary tract infections are the most common cause of sepsis.[21] [22]

Soft tissue and joint

Includes septic arthritis, wound infections, cellulitis, and acute super-infections arising from chronic ulceration. Most infections are polymicrobial. Ensure gram-positive and gram-negative organisms including anaerobes are covered.

- Beware necrotising fasciitis, which requires immediate surgical intervention (as does septic arthritis).

Practical tip

Necrotising fasciitis is notoriously difficult to diagnose. The initial symptoms are non-specific and the clinical course is often slower than might be expected. Typically, the first sign is pain disproportionate to the clinical...
Sepsis in adults

Management

Acute findings, followed or accompanied by fever. See our topic Necrotising fasciitis.

Central nervous system

Relatively uncommon but potentially devastating source of sepsis. Beware meningococcal sepsis, which can be extremely rapidly fatal; if survived, can lead to greater morbidity than other forms of sepsis.

Give immediate, targeted antibiotics in people with sepsis thought to arise from a central nervous system source.

- Immediately give a third-generation cephalosporin, such as ceftriaxone or cefotaxime, for suspected meningitis or meningococcal sepsis.

plus reassess and monitor

Treatment recommended for ALL patients in selected patient group

» Ensure frequent and ongoing monitoring.

- Standard monitoring of vital signs, pulse oximetry, level of consciousness, and urinary output is important for any patient with suspected sepsis.
- The UK National Institute for Health and Care Excellence (NICE) recommends continuous or half-hourly monitoring (depending on setting) for any patient considered to be at high risk of deterioration (defined in the NICE guideline as meeting one or more of its high-risk criteria for severe illness or death from sepsis).
- See the Risk stratification subsection of Diagnosis recommendations for more information.

» Use a track-and-trigger scoring system such as National Early Warning Score 2 (NEWS2) to identify any signs of deterioration. Your monitoring should include:

- Vital signs: heart rate, blood pressure, oxygen saturations, respiratory rate, and temperature
Sepsis in adults
Management

Acute

• Measure blood pressure via an arterial line if the patient does not respond to initial treatment or needs vasoactive drugs. It provides precise, continuous monitoring, and access for arterial blood sampling

• Hourly urine output[3] [43] [46]

• Lactate

  • The lactate level should decrease if the patient is clinically improving
  • Frequency of repeat lactate measurement depends on the cause of sepsis and treatment given.

  » Measure serum lactate, on a blood gas, to monitor response to treatment. [3] [43] [46]

  • Lactate is a marker of stress and may be a marker of a worse prognosis (as a reflection of the degree of stress). Raised serum lactate highlights the possibility of tissue hypoperfusion and may be present in many conditions.[77] [78]
  • Lactate may normalise quickly after fluid resuscitation. Patients whose lactate levels fail to normalise after adequate fluids are the group that fare worst.
  • Lactate >4 mmol/L (>36 mg/dL) is associated with worse outcomes.

    • One study found in-hospital mortality rates as follows:[79]

      • Lactate <2 mmol/L (<18 mg/dL): 15%
      • Lactate 2.1 to 3.9 mmol/L (19 to 35mg/dL): 25%
      • Lactate >4 mmol/L (>36 mg/dL): 38%.

  » Sepsis guidelines from NICE and NHS England recommend escalating treatment depending on lactate level. [3] [41] #Alert critical care immediately if the patient is acutely unwell and has persistent lactate
Sepsis in adults

Management

Acute

>4 mmol/L (>36 mg/dL) [3] despite fluid resuscitation.

» Do not be falsely reassured by a normal lactate (<2 mmol/L [<18 mg/dL]).

• This does not rule out the patient being acutely unwell or at risk of deterioration or death due to organ dysfunction. You must take into account the full clinical picture of the individual patient in front of you including their NEWS2 score.

Practical tip

Lactate is typically measured using a blood gas analyser, although laboratory analysis can also be performed. Traditionally, arterial blood gas has been recommended as the ideal means of measuring lactate accurately. However, in the emergency department setting it is more practical and quicker to use venous blood gas, which is recommended by NICE.[3] Evidence suggests good agreement at lactate levels <2 mmol/L (<18 mg/dL) with small disparities at higher lactate levels.[80] [81] [82]

Evidence: Lactate clearance

The best available evidence supports lactate clearance (the rate at which lactate is cleared over a period of 6 hours) as being as useful as more invasive tests, such as central venous oxygen saturation (ScvO₂), in determining a patient’s response to treatment. [197] [198] [199] [200] [201] [202]

• In one study that looked at patients with septic shock who were treated to normalise central venous and mean arterial pressure, additional management to normalise lactate clearance compared with additional management to normalise ScvO₂ did not result in significantly different in-hospital mortality.[198]

• Of 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographics, comorbidities, and physiological features.
## Acute

<table>
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<th>Management</th>
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| There were no differences in treatments administered during the initial 72 hours of hospitalisation.  
- Thirty-four patients (23%) in the ScvO₂ group died while in the hospital (95% CI 17% to 30%) compared with 25 (17%, 95% CI 11% to 24%) in the lactate clearance group. This observed difference between mortality rates did not reach the predefined -10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, -3% to 15%). There were no differences in treatment-related adverse events between the groups.  
- Several trials have assessed the diagnostic accuracy of percentage lactate clearance over 0 to 6 hours. It is worth noting that these studies provide very low-quality evidence, owing mainly to a presumed lack of blinding of treating physicians to the patient’s lactate status.  
- The studies’ findings agree that lactate clearance early in the hospital course is associated with decreased mortality rate. Patients with higher lactate clearance after 6 hours of emergency department intervention had improved outcomes compared with those with lower lactate clearance.[197] [199] [200] [201] [202]  

» In the UK, use physiological track-and-trigger systems to monitor all adult patients in acute hospital settings.[3]  

» Consider using a validated scale such as the Glasgow Coma Scale or AVPU (‘Alert, responds to Voice, responds to Pain, Unresponsive’) scale to monitor the mental state of a patient with suspected sepsis. [3]  

### Practical tip

null
ACUTE

AVPU should raise concerns if the assessment shows the patient is anything other than ‘alert’.

» Any patient with sepsis may be at significant risk of severe illness or death so it is vital to consider escalation of care to senior colleagues and/or healthcare facilities where increased and more advanced monitoring can be given (e.g., high-dependency unit/intensive care unit). [7] [170] [171]

• Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

» Consult local protocols for specific escalation routes but in general:

• Ensure immediate review by a senior clinician (CT3/ST3 or higher in the UK) of any patient with a NEWS2 score of 5 or more, or who meets one or more of the NICE sepsis high-risk criteria. Also ensure the patient is discussed with a consultant [3] [41]

• Discuss with the admitting consultant [3] and consider alerting critical care immediately if the patient is acutely unwell and:

  • Has a NEWS2 score of 7 or more, persisting high lactate (more than 4 mmol/L [36 mg/dL]) despite fluid resuscitation, or a systolic blood pressure of less than 90 mmHg [3]

    • Discuss with the admitting consultant [3]

  • Has hypotension that doesn’t respond to initial fluid resuscitation

  • Is likely to require central venous access and the initiation of inotropes or vasopressors [3]

  • Has any feature of septic shock
Sepsis in adults

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- See our topic Shock
- Has neutropenia
  - See our topic Febrile neutropenia
  - Is immunodeficient
- Urgently discuss with a consultant or call them to attend if the patient:
  - Is treated with intravenous antibiotics and/or a fluid bolus for sepsis
  - Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour. [3] Failure to respond to treatment is defined as:
    - Systolic blood pressure remains less than 90 mmHg
    - Persistent reduced level of consciousness
    - Respiratory rate more than 25 breaths per minute or the new need for mechanical ventilation
    - Lactate has not reduced by more than 20%
- Refer to critical care any patient who is likely to require central venous access and initiation of inotropes or vasopressors
- This includes any patient with evidence of circulatory dysfunction or shock, or those who do not respond to initial therapy (as outlined above)
- ECG can be used to determine which vasoactive drug(s) to proceed with in critical care.

Practical tip

Ensure a clear escalation plan has been discussed and agreed with the clinical team; include specific points of contact for nursing staff if you are leaving a patient for later review.
MANAGEMENT

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**Involve a senior colleague and/or consider transferring to critical care sooner rather than later if the patient is not improving, or deemed high-risk.** Examples include if the patient:

- Is not responding to fluids
- Needs inotropic support
- Has a low Glasgow Coma Scale score
- Needs ventilatory support.

**plus urgent source control**

Treatment recommended for ALL patients in selected patient group

» **Once a site of infection has been identified, early and adequate source control is critical. Consider the need for urgent source control, as soon as the patient is stable, particularly for:** [43]

- Gastrointestinal sources (such as visceral abscesses, cholangitis, or peritonitis secondary to perforation)
- Severe skin infections (e.g., necrotising fasciitis)
- Infection involving an indwelling device, where a procedure or surgery is likely to be required.

» **Give immediate, targeted antibiotics in people with sepsis thought to arise from a central nervous system source** (e.g., suspected meningitis or meningococcal sepsis). [3]

- Immediately give a third-generation cephalosporin such as ceftriaxone or cefotaxime.
- In community settings, pre-hospital administration of benzylpenicillin is recommended.
- **Follow local policy and consider discussing with microbiology/infectious disease colleagues to determine the most appropriate choice; use a ‘start smart then focus’ approach.** [41] [136]

**Practical tip**

If intravenous access is not feasible or is likely to lead to a delay in starting
Sepsis in adults

Management

Acute

<table>
<thead>
<tr>
<th>Consider</th>
<th>Fluid resuscitation</th>
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<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
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<tr>
<td>» Give 500 mL of crystalloid fluid, with a sodium content between 130 mmol/L and 154 mmol/L (130 to 154 mEq/L) (e.g., 0.9% sodium chloride or Hartmann’s solution), over less than 15 minutes to patients who need fluid resuscitation (if there is any sign of circulatory insufficiency). [3] [41] [66]</td>
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<tr>
<td>• Reassess the patient’s haemodynamic status after the first bolus to consider whether a second is required. [3] If there is no response to either the first or second bolus, seek senior support. [3]</td>
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<tr>
<td>» Intravenous fluid resuscitation may be lifesaving in patients with hypotension. This is because in sepsis there is vasodilation and capillary leakage, which means that patients can rapidly become intravascularly deplete. [3]</td>
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<tr>
<td>• In patients with sepsis-induced hypoperfusion (as indicated by a systolic blood pressure &lt;90 mmHg, a raised lactate level, or signs of organ dysfunction), the Surviving Sepsis Campaign international guideline recommends a total of at least 30 mL/kg of intravenous crystalloid over the first 3 hours. [43]</td>
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<tr>
<td>• If the patient’s initial lactate level is raised, the guideline recommends serial lactate measurements to guide the need for further intravenous fluids (with the goal of normalising lactate levels). [43]</td>
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</table>

Practical tip

The delivery of appropriate rapid fluid challenges is intended to restore the imbalance between oxygen supply and demand to the tissues. Patients who do not respond to rapid delivery of adequate volumes of intravenous fluids are in septic shock and need immediate referral to critical care. The immediate priority in this group of patients is to
Acute

- Management

**Practical tip**

Monitor patients closely for **signs of fluid overload such as pulmonary or systemic oedema** before and after each additional fluid bolus, as they may require large volumes of fluid to support their circulating volume.\[43\] [152] [153]

**Evidence: Choice of fluid**

*Latest evidence suggests a balanced crystalloid may have marginal benefits over saline, but either option is a reasonable choice.* [3] [154]

- Although early fluid resuscitation is a cornerstone of sepsis treatment that is given high priority by both Sepsis Six and the UK National Institute for Health and Care Excellence, choice of fluid has been the source of much discussion. In particular, there has been extensive debate over the choice between a balanced crystalloid (such as Hartmann’s solution, Ringer’s lactate, or PlasmaLyte) and normal saline (an unbalanced crystalloid). There have been very few high-quality studies, but latest evidence from critically ill patients points to marginal benefits from using a balanced crystalloid in preference to saline.\[154\]

- A 2018 US multicentre cluster-randomised trial among 15,802 critically ill adults receiving care in the intensive care unit found small benefits from balanced crystalloid compared with saline. The 30-day outcomes showed 10.3% mortality in the balanced crystalloid group compared with 11.1% in the saline group (P = 0.06), and a major adverse kidney event rate of 14.3% compared with 15.4% in the two groups, respectively (marginal odds ratio 0.91, 95% CI 0.84 to 0.99).\[154\]

- Colloids (e.g., starches, dextrans, gelatins, albumin, or fresh frozen
Acute plasma) are no longer used in emergency medicine in the UK.

**Debate: Volume and rate of fluids**

*Studies have not shown benefits from early goal-directed therapy and your focus should instead be on adjusting treatment according to i) lactate level and ii) clinical assessment of the patient’s haemodynamic response to initial fluids.* [43] [155] [156] [157] [158] [159] [160]

- Previous versions of the Surviving Sepsis Campaign (SSC) guidelines recommended a protocolled approach to resuscitation, otherwise known as early goal-directed therapy (EGDT).[161] [162] [163] EGDT involves the use of a series of ‘goals’ including central venous pressure and central venous oxygen saturation (ScvO\(_2\)). This recommendation was largely based on data from one study that showed a significant survival benefit for patients receiving EGDT.[155]

- This approach has since been challenged following the failure to show a mortality reduction in three subsequent large multicentre randomised controlled trials: PROCESS, ARISE, and PROMISE.[156] [157] [158]

  - It is worth bearing in mind that these three trials included patients who were less severely ill (lower baseline lactate levels, ScvO\(_2\) at or above the target value on admission, and lower mortality in the control group) than the patients in the original study that outlined EDGT as a recommended approach.

  - Based on this latest evidence, the **SSC no longer specifically recommends EDGT**; it does, however, acknowledge the need for guidance on how to approach this group of patients who have significant mortality and morbidity.[43] The SSC therefore recommends that you:[43]
MANAGEMENT

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- View these patients as having a **medical emergency** that necessitates urgent assessment and treatment.
- Begin initial fluid resuscitation with 30 mL/kg of crystalloid within the first 3 hours.
  - This fixed volume of fluid enables initiation of resuscitation while giving an opportunity to ascertain more specific information about the patient and while awaiting more precise measurements of haemodynamic status.
  - Although scant data are available to support this volume of fluid, interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice.[159] [160]
  - The average volume of fluid pre-randomisation given was approximately 30 mL/kg in the PROCESS and ARISE trials, and approximately 2 L in the PROMISE trial.[156] [157] [158]
  - The SSC acknowledges that many patients will need more fluid than this, and it advocates giving further fluid to this group in line with functional haemodynamic measurements.[43]
  - The UK National Institute for Health and Care Excellence guideline on sepsis focuses on initial management and treatment, and therefore makes no recommendations regarding intensive...
Sepsis in adults

Management

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| Monitoring such as that used in EGDT.\[3\] |

**Practical tip**

To guide the need for further intravenous fluids, it can sometimes be helpful to use bedside ultrasound to monitor changes in inferior vena cava (IVC) diameter during respiration.\[164\]\[165\]

- In the spontaneously breathing patient: consider additional fluid resuscitation if there is a collapsed (or collapsing) IVC.
- In the mechanically ventilated patient: an increase in IVC size >18% (or visible to the naked eye) with positive pressure ventilation suggests fluid-responsiveness.

**Practical tip**

Use the passive leg-raising test to predict fluid-responsiveness if adequate monitoring is available.\[66\]\[166\]

- This is a useful indicator of fluid-responsiveness, which should be assessed using devices that can continuously monitor cardiac output in real time (e.g., Pulse index Continuous Cardiac Output (PiCCO) monitor or oesophageal Doppler), usually in an intensive care unit rather than general ward setting.
- Sit the patient upright at 45° and tilt the entire bed through 45°.
- Patients with a positive test have a >10% increase in cardiac output or stroke volume, indicating more fluids may be required.
- The passive leg-raise response may be misleading in conscious patients who are uncomfortable or in pain when lying flat.

**Consider oxygen**

Treatment recommended for SOME patients in selected patient group.
If indicated, give oxygen to maintain target oxygen saturations 94% to 96%. Latest evidence suggests that liberal use of supplemental oxygen (target \( \text{SpO}_2 > 96\% \)) in acutely ill adults is associated with higher mortality than more conservative oxygen therapy. Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia.

Target saturation of 88% to 92% if the patient is at risk of hypercapnic respiratory failure (e.g., those with COPD).

Evidence: Target oxygen saturation in acutely ill adults

Too much supplemental oxygen increases mortality.

Latest evidence supports a 96% upper limit for target oxygen saturation in non-hypercapnic acutely ill adults.

- Guidelines differ in their recommendations on target oxygen saturation in acutely unwell adults who are receiving supplemental oxygen. The 2017 British Thoracic Society guideline recommends a target \( \text{SpO}_2 \) range of 94% to 98% for patients not at risk of hypercapnia, whereas the 2015 Thoracic Society of Australia and New Zealand guideline recommends 92% to 96%.

- A 2018 systematic review including a meta-analysis of data from 25 randomised controlled trials found that in adults with acute illness, liberal oxygen therapy (broadly equivalent to a target saturation >96%) is associated with higher mortality than conservative oxygen therapy (broadly equivalent to a target saturation ≤96%). In-hospital mortality was 11 per 1000 higher for the liberal oxygen therapy group versus the conservative therapy group (95% CI 2.22 per 1000 more). Mortality at 30 days was also higher in the group who had received liberal oxygen (risk ratio 1.14, 95% CI 1.01 to 1.29). The trials included adults with sepsis, critical illness, stroke, trauma, myocardial infarction, and cardiac arrest, and patients who had emergency surgery. Studies that
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were limited to people with chronic respiratory illness or psychiatric illness, patients on extracorporeal life support, patients receiving hyperbaric oxygen therapy, or those having elective surgery were all excluded from the review.

- An upper SpO₂ limit of 96% is therefore reasonable when administering supplemental oxygen to medical patients with acute illness who are not at risk of hypercapnia. However, a higher target may be appropriate for some specific conditions (e.g., pneumothorax, carbon monoxide poisoning, cluster headache, and sickle cell crisis).[168]

> There is no specific evidence to show that giving oxygen improves clinical outcomes in sepsis. However, respiratory failure will lead to tissue hypoxia and anaerobic respiration. This is likely to lead to acidosis and consequently a poorer outcome.[169]

**Consider standard intensive care unit supportive care**

Treatment recommended for SOME patients in selected patient group

- Any patient with sepsis may be at significant risk of severe illness or death so it is vital to consider escalation of care to senior colleagues and/or healthcare facilities where increased and more advanced monitoring can be given (e.g., high-dependency unit/intensive care unit). [7] [170] [171]

  - Bear in mind that some patients (e.g., those who are frail) may not be suitable for management in intensive care settings. Consider the patient’s baseline health including their resuscitation status when determining the limits of treatment. Use this to feed into a personalised care plan appropriate to the individual patient.

> Consult local protocols for specific escalation routes but in general:

  - Ensure immediate review by a senior clinician (CT3/ST3 or higher in the UK) of any patient with a National Early Warning Score 2 (NEWS2) score of 5 or more, or who meets one or more of
### Acute

the UK National Institute for Health and Care Excellence (NICE) sepsis high-risk criteria. Also ensure the patient is discussed with a consultant[3] [41]

- **Discuss with the admitting consultant** [3] **and consider alerting critical care immediately** if the patient is acutely unwell and:
  - Has a **NEWS2 score of 7 or more**, persisting **high lactate** (more than 4 mmol/L [36 mg/dL]) despite fluid resuscitation, or a **systolic blood pressure of less than 90 mmHg** [3]
    - Discuss with the admitting consultant[3]
  - Has hypotension that doesn’t respond to initial fluid resuscitation
  - Is likely to require central venous access and the initiation of inotropes or vasopressors[3]
  - Has any feature of **septic shock**
    - See our topic Shock
  - Has **neutropenia**
    - See our topic Febrile neutropenia
    - Is immunodeficient
  - **Urgently discuss with a consultant or call them to attend** if the patient:[41]
    - Is treated with intravenous antibiotics and/or a fluid bolus for sepsis
    - **Does not respond to initial therapy (antibiotics/fluid resuscitation/oxygen) within the first hour.** [3] [41] Failure to respond to treatment is defined as:[3]
      - Systolic blood pressure remains less than 90 mmHg
      - Persistent reduced level of consciousness
      - Respiratory rate more than 25 breaths per minute or the new need for mechanical ventilation
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- Lactate has not reduced by more than 20%
- **Refer to critical care** any patient who is likely to require central venous access and initiation of inotropes or vasopressors.[3]
  - This includes any patient with evidence of circulatory dysfunction or shock, or those who do not respond to initial therapy (as outlined above)
  - ECG can be used to determine which vasoactive drug(s) to proceed with in critical care.[43]

**Practical tip**

Ensure a clear escalation plan has been discussed and agreed with the clinical team; include specific points of contact for nursing staff if you are leaving a patient for later review. **Involve a senior colleague and/or consider transferring to critical care sooner rather than later if the patient is not improving, or deemed high-risk.**

Examples include if the patient:
- Is not responding to fluids
- Needs inotropic support
- Has a low Glasgow Coma Scale score
- Needs ventilatory support.

» For any patient with suspected sepsis, consider the need for referral to a high-dependency unit for management by the critical care team. [155] [174]

» The following interventions should only be initiated by experienced members of the critical care team: [3] [43] [175]
  - Glycaemic control
  - Vasoactive drugs (vasopressors/inotropes)
  - Corticosteroids.

» Additional intensive care measures that will be considered include:[43] [176] [177]
  - **Stress ulcer prophylaxis** (in people at risk of gastrointestinal bleeding)
Management

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- With an H2 antagonist or proton-pump inhibitor

- **Deep venous thrombosis prophylaxis**
  - With heparin and compression stockings

- **Enteral or parenteral nutrition**
  - Administration of human albumin solution 4% to 5% in patients with sepsis and shock who have not responded to substantial volumes of crystalloids
  - **Transfusion of packed cells**
    - Consult local protocols for recommended threshold
    - The Surviving Sepsis Campaign recommends using a threshold of 70 g/L (7 g/dL).

**Evidence: Threshold for transfusion of packed cells**

*Studies in the general critical care population have shown no improvement with blood transfusions given at a higher haemoglobin threshold compared with a lower haemoglobin threshold* and have shown potential harm associated with liberal transfusion. [178]

- One multicentre parallel group randomised trial analysed data from 998 patients with septic shock, split into two intervention groups with similar baseline characteristics. In the intensive care unit, the group assigned to blood transfusion at a lower haemoglobin threshold received a median of 1 unit of blood (interquartile range, 0 to 3) and the group assigned to blood transfusion at a higher haemoglobin threshold received a median of 4 units (interquartile range, 2 to 7). [178]

- At 90 days after randomisation, 216 of 502 patients (43.0%) assigned to the lower-threshold group, compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died.
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Management

Acute

(relative risk 0.94, 95% CI 0.78 to 1.09; P = 0.44).
• The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations.
• The numbers of patients who had ischaemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.
• A second multicentre randomised controlled trial compared the rates of death from all causes at 30 days and the severity of organ dysfunction in 838 critically ill patients receiving a restrictive strategy of red-cell transfusion compared with those receiving a liberal strategy.[179]

• Overall, 30-day mortality was similar in the two groups (18.7% vs. 23.3%, P = 0.11).
• However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill and in patients younger than 55 years of age (5.7% and 13.0%, respectively; P = 0.02), but not in those with clinically significant cardiac disease (20.5% and 22.9%, respectively; P = 0.69).
• The mortality rate during hospitalisation was significantly lower in the restrictive-strategy group (22.3% vs. 28.1%, P = 0.05).

» There may be a case to consider giving transfusions at a higher haemoglobin level in people with myocardial ischaemia, severe hypoxaemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis.[43]
Acute

» In the initial resuscitative phase, transfusion to achieve a higher haematocrit of ≥30% may be appropriate.[155]

» In patients requiring prolonged ventilatory support, give lung-protective ventilation using minimal peak inspiratory pressures (<30 cm H₂O) and permissive hypercapnia to specifically limit pulmonary compromise.[180]

  • Titrate fraction of inspired oxygen (FiO₂) to lowest effective levels to prevent oxygen toxicity and maintain central venous oxygen tension.
  • Place patients in a semi-recumbent position with the head elevated to 30° to 45°.[43]

Glycaemic control

Although patients with sepsis are often hyperglycaemic, the optimal glucose target is unknown.

The Surviving Sepsis Campaign guideline recommends targeting a blood glucose level <10.0 mmol/L (<180 mg/dL).[43] The guideline also recommends a ‘sliding scale’ variable-rate intravenous insulin infusion.[43]

  • NICE makes no recommendations on glycaemic control in sepsis.[3]

Evidence: Glycaemic control

Recent years have seen a shift in opinion and practice regarding glycaemic control in critically ill people. Since 2001, the use of tight glycaemic control has been advocated in people with sepsis. More recent evidence, however, suggests an increase in adverse events (e.g., severe hypoglycaemia) in patients managed with very tight glycaemic control (targeting a blood glucose below 6.1 mmol/L [110 mg/dL]).[181][182] The conflicting evidence has led to variations in recommendations in different countries and settings. Follow your local protocol.

  • An international randomised controlled trial (RCT) of 6104 critically ill medical and surgical patients found increased 90-day mortality (odds ratio 1.14, 95% CI 1.02 to 1.28) with tighter glucose
control, possibly due to more frequent episodes of hypoglycaemia.[183]

- A 2010 systematic review of 6 RCTs and a meta-analysis investigating tight glucose control (4.4 to 6.1 mmol/L [80-110 mg/dL]) versus less strict glucose control in critically ill patients in the intensive care unit setting found no significant improvement in mortality with tight glucose control, but it was associated with significantly more hypoglycaemic episodes compared with less strict glucose control.[184]

- An RCT of critically ill patients in a primarily surgical intensive care setting found lower patient mortality with tight glucose control, 4.4 to 6.1 mmol/L (80-110 mg/dL), compared with ‘conventional’ more liberal glucose control.[185]

consider vasopressor (should only be initiated by experienced members of the critical care team)

Treatment recommended for SOME patients in selected patient group

Primary options

» noradrenaline (norepinephrine): 0.4 to 0.8 mg/hour intravenous infusion initially, adjust dose according to response
Dose refers to noradrenaline base.

Secondary options

» noradrenaline (norepinephrine): 0.4 to 0.8 mg/hour intravenous infusion initially, adjust dose according to response
Dose refers to noradrenaline base.

---AND---

» vasopressin: 0.01 units/minute intravenous infusion initially, adjust dose according to response, maximum 0.03 units/minute
-or-

» adrenaline (epinephrine): 2-10 micrograms/minute intravenous infusion initially, adjust dose according to response

OR

» dopamine: 2-5 micrograms/kg/minute intravenous infusion initially, adjust dose according to response
Acute

» Vasopressors are used in a critical care setting to maintain a mean arterial pressure (MAP) ≥65 mmHg if the patient is unresponsive to fluid resuscitation. [3] [43] [175]

- Failure to respond to initial fluid resuscitation is a sign of septic shock. [1]
- Noradrenaline (norepinephrine) is the vasopressor of choice, mainly because it increases MAP. [43]

- Noradrenaline is the vasopressor recommended by the Surviving Sepsis Campaign guideline. [43] The UK National Institute for Health and Care Excellence makes no recommendation on the choice of vasopressor. [3]
- If further vasopressor therapy is required to maintain adequate blood pressure or the noradrenaline dose needs to be reduced, add vasopressin or adrenaline (epinephrine) to noradrenaline.
- Dopamine is an option, but has been associated with higher mortality than noradrenaline. [186] [187] Therefore, it is only recommended in patients with a low risk of tachyarrhythmias and bradycardia. [43] It is rarely used in the UK. Do not use low-dose dopamine for renal protection. [43]

Practical tip

All infusions of vasoactive drugs to correct shock should be given via a secure catheter in a central vein with high flow, such as a central venous catheter. These patients should also have an arterial catheter inserted as soon as possible to ensure more accurate monitoring of arterial blood pressure. [43]

Evidence: Choice of vasopressor

Although a systematic review of 23 randomised trials of patients with shock found no convincing evidence for the superiority of one vasopressor over another [188] more...
Sepsis in adults

Management

Acute

Consider inotrope (should only be initiated by experienced members of the critical care team)

Treatment recommended for some patients in selected patient group

Primary options

» Dobutamine: 2.5 to 10 micrograms/kg/minute intravenous infusion initially, adjust dose according to response, maximum 40 micrograms/kg/minute

» Inotropes can be considered for patients with low cardiac output despite adequate fluid resuscitation and vasopressor therapy. [3] [43]

- Dobutamine is recommended first line by the Surviving Sepsis Campaign guideline for people with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure.[43]
- The UK National Institute for Health and Care Excellence makes no specific recommendations on inotrope selection in patients with sepsis.[3]

Practical tip

Suspect low cardiac output if the clinical examination reveals prolonged capillary refill times, low urine output, or poor peripheral perfusion. Confirm with cardiac output monitoring or by sampling central venous or pulmonary arterial blood to measure oxygen saturations. When using inotropes, keep the patient’s heart rate at less than 100 beats per minute to minimise myocardial ischaemia.[175]

Consider corticosteroid (should only be initiated by experienced members of the critical care team)

Treatment recommended for some patients in selected patient group

Primary options
Sepsis in adults

Management

**Acute**

- **hydrocortisone sodium succinate**: 200 mg/day intravenously

- The Surviving Sepsis Campaign guideline recommends *intravenous hydrocortisone* as an option to consider for patients who are unresponsive to both fluid resuscitation and vasopressor therapy. [43]

- The UK National Institute for Health and Care Excellence does not give any recommendations on the use of corticosteroids for managing sepsis in adults. [3]

**Evidence: Benefits and harms of corticosteroids**

Corticosteroids are a late critical-care intervention for patients in whom all other attempts to raise their blood pressure have failed. [3] In this critically ill group, corticosteroids may result in a small reduction in mortality. [189] [190] Possible harms include an increased risk of neuromuscular weakness, hyperglycaemia, and hypernatraemia with corticosteroids compared with no corticosteroids. [189]

- An international panel reviewing the inconsistent conclusions of large randomised controlled trials (RCTs) on the topic suggested in 2018 that the evidence for the use of corticosteroids was weak, but that “fully informed patients who value avoiding death over quality of life and function would likely choose corticosteroids”, although a no-corticosteroid approach remained reasonable. [189] This judgement was based on an assessment that corticosteroids may reduce mortality by around 2% (this effect was seen in sepsis with and without shock although the greatest benefit was among patients with septic shock), but can increase the risk of neuromuscular weakness and resulting functional deterioration. Most notably, the panel reviewed the following trials:

  - **ADRENAL**: 3658 patients who had septic shock [191]
Sepsis in adults

Management

Acute

- No statistically significant difference in 90-day mortality between the hydrocortisone and placebo groups
- APROCHSS: 1241 patients who had septic shock[192]
  - Hydrocortisone plus fludrocortisone reduced 90-day mortality.

BMJ Rapid Recommendations:
intravenous corticosteroids plus usual care versus usual care only
Lamontagne F, et al.
BMJ 2018;362:k3284

- A more recent systematic review and meta-analysis (comprising 37 RCTs, incorporating both ADRENAL and APROCHSS) included 9564 people with sepsis.[190] The review found corticosteroid use to be associated with significant improvement in healthcare outcomes as shown by:[190]
  - Reduced 28-day mortality (risk ratio [RR] 0.90, 95% CI 0.82 to 0.88) compared with placebo or standard supportive care
  - Reduced intensive care unit mortality (RR 0.85, 95% CI 0.77 to 0.94; I² = 0%) compared with placebo or standard supportive care
  - Reduced in-hospital mortality (RR 0.88, 95% CI 0.79 to 0.99; I² = 0%)
### Acute

2 = 38% compared with placebo or standard supportive care.

- However, corticosteroid use was also associated with increased risk of hyperglycaemia (RR 1.19, 95% CI 1.08 to 1.30) and hypernatraemia (RR 1.57, 95% CI 1.24 to 1.99) compared with placebo or standard supportive care.[190]
Monitoring

Ensure frequent and ongoing monitoring. [3]

- Standard monitoring of vital signs, pulse oximetry, level of consciousness, and urinary output is important for any patient with suspected sepsis.
- The National Institute for Health and Care Excellence (NICE) in the UK recommends continuous or half-hourly monitoring (depending on setting) for any patient considered to be at high risk of deterioration (defined in the NICE guideline as meeting one or more of its high-risk criteria for severe illness or death from sepsis).[3]

Use a track-and-trigger scoring system such as the National Early Warning Score 2 (NEWS2) to identify any signs of deterioration. [3] Your monitoring should include:

- Vital signs: heart rate, blood pressure, oxygen saturations, respiratory rate, and temperature
  - Measure blood pressure via an arterial line if the patient does not respond to initial treatment or needs vasoactive drugs. It provides precise, continuous monitoring, and access for arterial blood sampling
- Hourly urine output[3] [43] [46]
- Lactate
  - The lactate level should decrease if the patient is clinically improving
  - Frequency of repeat lactate measurement depends on the cause of sepsis and treatment given.

In the UK, use physiological track-and-trigger systems to monitor all adult patients in acute hospital settings.[3]

Consider using a validated scale such as the Glasgow Coma Scale or AVPU (‘Alert, responds to Voice, responds to Pain, Unresponsive’) scale to monitor the mental state of a patient with suspected sepsis. [3]

- AVPU should raise concerns if the assessment shows the patient is anything other than ‘alert’.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>renal dysfunction</td>
<td>short term</td>
<td>high</td>
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<tr>
<td>Transient oliguria is common and is related to hypotension. Rarely, anuria occurs. 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.</td>
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<tr>
<td>hypotension</td>
<td>short term</td>
<td>high</td>
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<tr>
<td>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 positive end-expiratory pressure, or acidosis. Fluid resuscitation is given with either colloids or crystalloids, and early central venous pressure 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.</td>
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<tr>
<td>acute respiratory distress syndrome (ARDS)</td>
<td>short term</td>
<td>medium</td>
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<tr>
<td>Respiratory failure often progresses quickly and is indicated by a respiratory rate &gt;30/minute, even though arterial oxygen levels may be normal. ARDS may resolve completely or can progress to fibrosing alveolitis with persistent hypoxaemia. Intubation and ventilation reduce respiratory muscle oxygen demand and the risk of aspiration and cerebral anoxia. Lung protective ventilation (low tidal volumes) should be used. 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 is recommended to prevent lung collapse at end expiration.</td>
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<tr>
<td>myocardial dysfunction and failure</td>
<td>short term</td>
<td>medium</td>
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<tr>
<td>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. 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, mixed venous oxygen saturation, and urine output. Clinicians should define specific goals and desired end points 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.</td>
<td></td>
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<tr>
<td>multiple organ system failure</td>
<td>short term</td>
<td>medium</td>
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| 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
Sepsis in adults

### Complications

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<td>phenotype, compounded by impaired organ perfusion due to hypotension, low cardiac output states, circulatory microthrombi, a disordered microcirculation, and tissue oedema.[262]</td>
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<tr>
<td>Failure of each additional organ increases the average risk of death by 15% to 20%. Lung dysfunction tends to occur early and persists. Serious central nervous system 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.[269]</td>
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<tr>
<td>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 intensive care setting care. This may include dialysis, ventilatory support, and sedation.</td>
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<tr>
<td>hepatic encephalopathy</td>
<td>short term</td>
<td>low</td>
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<td>Liver dysfunction may lead to hepatic encephalopathy, especially in those with established chronic liver disease.[265] Hepatic encephalopathy is thought to result primarily from ammonia entering the brain due to absorption from the gut bypassing effective hepatic clearance. This causes intracellular cerebral oedema and electrolyte abnormalities.[266]</td>
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<tr>
<td>The mainstay of therapy includes laxatives to empty the bowel, prevention of GI bleeding, and avoidance of sedative drugs, which further suppress consciousness. A low-protein diet is not recommended as these patients are often malnourished with muscle wasting, which is an important negative prognostic indicator for hepatic encephalopathy and cirrhosis. These patients’ protein requirements are also relatively higher than those of healthy patients. Protein intake should be 1.2-1.5g/kg/day.[267]</td>
<td></td>
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<tr>
<td>disseminated intravascular coagulation (DIC)</td>
<td>short term</td>
<td>low</td>
</tr>
<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.[270]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neurological sequelae</td>
<td>long term</td>
<td>medium</td>
</tr>
<tr>
<td>The incidence and severity of complications from sepsis depend on the pathogen, duration of disease, age, and presence of comorbidities. Focal neurological deficits and hearing loss occur in up to 30% of patients with bacterial meningitis. The mortality and morbidity is higher for pneumococcal meningitis than for meningococcal meningitis. Polyneuropathy occurs in 70% of patients with sepsis and multi-organ failure. The use of neuromuscular blocking agents may increase the severity of polyneuropathy.[271] [272][271]</td>
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Prognosis

Sepsis is present in many hospitalisations that culminate in death. In 2015, 23,135 people in the UK died from sepsis, where sepsis was an underlying or contributory cause of death. [NHS England: Sepsis] The true contribution of sepsis to these deaths is unknown. Most underlying causes of death in people with sepsis are thought to relate to severe chronic comorbidities and frailty.[5] [7] [8]

Multi-organ compromise is common in advanced sepsis with variable residual morbidity.[262] [263]

In a cohort study of 94,748 adult sepsis survivors, age, male sex, one or more severe comorbidities, pre-hospitalisation dependency, non-surgical status, acute severity of illness, site of infection, and organ dysfunction were independently associated with long-term mortality.[264]
# Diagnostic guidelines

## United Kingdom

**Sepsis: recognition, diagnosis and early management**  
*Published by: National Institute for Health and Care Excellence  Last published: 2017*

**Sepsis guidance implementation advice for adults**  
*Published by: NHS England  Last published: 2017*

## Asia

**The Japanese clinical practice guideline for management of sepsis and septic shock, 2016**  
*Published by: Japanese Society of Intensive Care Medicine; Japanese Association for Acute Medicine  Last published: 2018*

## Oceania

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

# Treatment guidelines

## United Kingdom

**Sepsis guidance implementation advice for adults**  
*Published by: NHS England  Last published: 2017*

**Sepsis: recognition, diagnosis and early management**  
*Published by: National Institute for Health and Care Excellence  Last published: 2017*

**Intravenous fluid therapy in adults in hospital**  
*Published by: National Institute for Health and Care Excellence  Last published: 2017*

## International

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

The Japanese clinical practice guideline for management of sepsis and septic shock, 2016

Published by: Japanese Society of Intensive Care Medicine; Japanese Association for Acute Medicine

Last published: 2018
Online resources

1. NHS England: Sepsis (external link)

2. Signs and symptoms of possible infection sources (external link)

3. Track and trigger map developed by the West of England Academic Health Science Network National Early Warning Score project team (external link)
Key articles

- Royal College of Physicians. National early warning score (NEWS) 2: standardising the assessment of acute-illness severity in the NHS. December 2017 [internet publication]. Full text Abstract

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233. Nova Scotia Health Authority. This is not my Mom. 2012 [internet publication] Full text


Figure 1: Capillary refill time. Top image: normal skin tone; middle image: pressure applied for 5 seconds; bottom image: time to hyperaemia measured

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission
Figure 2: Severe purpura fulminans; classically associated with meningococcal sepsis but can occur with pneumococcal sepsis

From the collection of Ron Daniels, MB, ChB, FRCA; used with permission
### Figure 3: National Early Warning Score 2 (NEWS2) is an early warning score produced by the Royal College of Physicians in the UK. It is based on the assessment of six individual parameters, which are assigned a score of between 0 and 3: respiratory rate, oxygen saturations, temperature, blood pressure, heart rate, and level of consciousness. There are different scales for oxygen saturation levels based on a patient’s physiological target (with scale 2 being used for patients at risk of hypercapnic respiratory failure). The score is then aggregated to give a final total score; the higher the score, the higher the risk of clinical deterioration.

Figure 4: The relative frequencies of sources of infection in sepsis

Created by the BMJ Knowledge Centre; based on NCEPOD. Just say sepsis! Nov 2015
**Figure 5: Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) criteria**

Figure 6: BMJ Rapid Recommendations: intravenous corticosteroids plus usual care versus usual care only

Contributors:

// Peer Reviewers:

Matt Inada-Kim, MBBS, FRCP
Consultant Acute Physician & Sepsis Lead
Department of Acute Medicine, Royal Hampshire County Hospital, Hampshire Hospitals NHS Foundation Trust, Winchester, UK
DISCLOSURES: MIK is a national clinical advisor on sepsis to NHS England and a national clinical advisor on deterioration to NHS Improvement. He was reimbursed for a slide set by Relias Learning.

// Expert Advisers:

Alexander Alexiou, MB, BS, BSc, DCH, FRCEM, Dip IMC RCSEd
Flight Doctor
Greater Sydney Area Helicopter Emergency Medical Service, Sydney, New South Wales, Australia
DISCLOSURES: AA declares that he has no competing interests.

Clovis Rau, MBBS, BSc, MRCEM
ST4 Emergency Medicine
Emergency Department, University College Hospital, University College London Hospitals NHS Foundation Trust, UK
DISCLOSURES: CR declares that he has no competing interests.

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Ron Daniels MBChB, FRCA, Chief Executive, United Kingdom Sepsis Trust, Chief Executive, Global Sepsis Alliance, Programme Director, Survive Sepsis, Consultant in Critical Care and Anaesthesia, Heart of England NHS Foundation Trust, Birmingham, UK, Matt Inada-Kim MBBS, FRCP, Consultant Acute Physician & Sepsis Lead, Department of Acute Medicine, Royal Hampshire County Hospital, Hampshire Hospitals NHS Foundation Trust, Winchester, UK, Aamir Saifuddin BMChB, BA, MRCP, AFFMLM, Specialty Registrar in Gastroenterology and General Medicine, Maidstone and Tunbridge Wells NHS Trust, UK, Tim Nutbeam MSc, Dip IMC FRCEM, Consultant in Emergency Medicine, Clinical Academic, University of Plymouth, Lead Doctor, Devon Air Ambulance Trust, Derriford Hospital, Plymouth, UK, Edward Berry MBChB, MCEM, Specialty Registrar in Emergency Medicine, Derriford Hospital, Plymouth, UK
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## Contributors:

**Editors:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Disclosures</th>
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</thead>
<tbody>
<tr>
<td>Tannaz Aliabadi-Oglesby</td>
<td>Lead Section Editor, BMJ Best Practice</td>
<td>TAO declares that she has no competing interests.</td>
</tr>
<tr>
<td>Jo Haynes</td>
<td>Head of Editorial, BMJ Knowledge Centre</td>
<td>JH declares that she has no competing interests.</td>
</tr>
<tr>
<td>Rachel Wheeler</td>
<td>Lead Section Editor, BMJ Best Practice</td>
<td>RW declares that she has no competing interests.</td>
</tr>
<tr>
<td>Julie Costello</td>
<td>Comorbidities Editor, BMJ Best Practice</td>
<td>JC declares that she has no competing interests.</td>
</tr>
<tr>
<td>Adam Mitchell</td>
<td>Drug Editor, BMJ Best Practice</td>
<td>AM declares that he has no competing interests.</td>
</tr>
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