CHAPTER 6 Sepsis

By the end of this chapter you will be able to:

- Know the definition of sepsis
- Understand the basic pathophysiology of sepsis
- Understand the difference between sepsis and infection causing an inflammatory response

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- Know how to use NEWS2 and qSOFA scores
- Be aware of the Surviving Sepsis Campaign guidelines and the 'sepsis six'
- Know how vasopressors and inotropes work
- Appreciate the effects of sepsis on the lungs and kidneys
- Apply this to your clinical practice

Sepsis is a life-threatening medical emergency with a high mortality. It has been recognised by the World Health Organization as a global health priority¹ and several international initiatives in recent years have led to improvements in the management and outcomes of patients with sepsis. Sepsis is a clinical syndrome which can originate from virtually any infection, resulting in a wide variety of presentations which can sometimes make it difficult to recognise. In the UK, it is estimated that there are at least 250,000 cases of sepsis each year with at least 44,000 deaths. Over half of survivors report long-term reductions in their quality of life with both physical and cognitive impairments.^{2,3}

Definition of Sepsis

The definition of sepsis has evolved over the last 30 years with the latest definition aiming to facilitate earlier recognition and timely management of patients. The new definition also provides greater consistency for epidemiological studies and clinical trials which may help to define the true incidence of sepsis and further our understanding of this complex clinical syndrome.

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Sepsis-1 was developed in 1991 at the first international consensus conference⁴ and used four criteria for the 'systemic inflammatory response syndrome'. Sepsis was defined as an infection leading to two or more of: a high or low temperature, tachycardia, high respiratory rate, and high or low white cell count. Severe sepsis was defined as sepsis plus organ dysfunction. This definition was further developed in 2001^5 (sepsis-2), but in 2016, the third international consensus conference redefined sepsis in recognition of the fact that a systemic inflammatory response is unhelpful in identifying sepsis.⁶ A systemic inflammatory response can be normal in infection and not life threatening and can be present in people without infection. *Sepsis, on the other hand, is life-threatening organ dysfunction caused by a dysregulated host response to infection.* In clinical practice, this can be represented by an increase in the SOFA (sepsis-related organ failure assessment) score of 2 points or more, which is associated with an in-hospital mortality of greater than 10%. Septic shock is defined as persisting hypotension requiring vasopressors and a serum lactate of >2 mmol/L in the absence of hypovolaemia. This has a hospital mortality in excess of 40%. The new definitions are outlined in Table 6.1 and the SOFA score in Table 6.2.

A normal host response to infection (e.g. tachycardia, fever, and high respiratory rate in pneumonia) is not sepsis. Local organ dysfunction caused by specific infections (e.g. abnormal liver tests in cholecystitis, reduced oxygen saturations in basal pneumonia) is not sepsis. The normal physiological decompensation seen in frail elderly patients with a serious infection (e.g. acute kidney injury and hypotension that rapidly resolves with intravenous fluid) is not sepsis either. As we will see later in this chapter, what is happening in sepsis is a multifaceted *dysregulated host response* leading to life-threatening organ dysfunction, the presentation of which can be modified by pre-existing illness, longstanding comorbidities, and medication (e.g. immunosuppressants). Patients with a normal response to infection can still be sick and require urgent treatment. On the other hand, patients with sepsis can sometimes look deceptively well, especially to inexperienced clinicians.

	Definition
Sepsis	 Life-threatening organ dysfunction caused by a dysregulated host response to infection For clinical operationalisation, this can be represented by an increase in the SOFA score of 2 or more In-hospital mortality >10%
Septic shock	 A subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities occur Clinically identified by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of >65 mmHg and a serum lactate of >2 mmol/L in the absence of hypovolaemia In-hospital mortality >40%

Table 6.1 Sepsis-3 definitions.

SOFA = sepsis-related organ failure assessment.

The terms 'systemic inflammatory response syndrome' (SIRS) and 'severe sepsis' are no longer used.

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Table 6.2 SOFA score.

			Score		
System	0	1	2	×	4
Respiration PaO ₂ /FiO ₂ mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver Bilirubin µmol/L	<20	20-32	33-101	102-204	>204
Cardiovascular MAP mmHg (doses in µg/kg/min for at	≥70	<70	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or noreninenhrine <0.1	Dopamine >15 or epinephrine >0.1 or noreninenhrine >0.1
CNS CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6 6
Renal Creatinine µmol/L	<110	110-170	171–299	300-440	>440
Urine output mL/24 h				<500	<200
Source: Modified from Vincent JL	, Moreno R, Tak	ala J et al. Working gro	oup on sepsis-related problems	of the European Society of Intensive	Care Medicine. The

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SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22(7): 707–710, Springer Nature.

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No. failing organs	% ICU patients	% Mortality
0	35.1	3.2
1	24.9	10.6
2	16.8	25.5
3	12.1	51.4
4	6.5	61.3
5	3.0	67.4
6	1.6	91.3

 Table 6.3
 Mortality of sepsis on ICU according to number of failing organs.

Without a doubt it is important to 'think sepsis' because it can have a very high mortality (see Table 6.3) – but that is not the same as diagnosing and treating *every* patient with abnormal vital signs plus an infection as sepsis. So, what exactly is sepsis and how can we screen for and diagnose it?

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Basic Pathophysiology of Sepsis

Sepsis can be thought of as the body's over-response to an infection. Why some people develop sepsis and others do not is unclear. The pathophysiology of sepsis is complex, incompletely understood, and the focus of ongoing research. However, it is now recognised that sepsis involves early activation of both pro- and anti-inflammatory cytokines, along with major changes in non-immunologic pathways involving the cardiovascular, endocrine, metabolic, and coagulation systems. While bacterial infections remain the primary cause of sepsis, viral and fungal infections also occur, especially among immunocompromised patients and those with other comorbidities. The most common sites of infection leading to sepsis in the UK are the lungs, urinary tract, abdominal organs, and pelvis, followed by skin/soft tissue, bone, and joint infections.

Immune Response in Sepsis

Bacterial surface toxins, such as lipopolysaccharide and other secreted bacterial pathogenassociated molecular patterns (PAMPs), stimulate toll-like receptors (TLRs), and other cell surface receptors on host cells.⁷ TLRs are also stimulated by damaged cell contents (e.g. mitochondria). Intracellular signalling then initiates a pro-inflammatory cascade and more inflammatory cell recruitment releasing both pro-inflammatory and anti-inflammatory mediators. Cytokines (e.g. tumour necrosis factor and interleukins) cause neutrophil– endothelial cell adhesion, increased endothelial permeability, and activate the complement and clotting cascades leading to various immunothrombotic complications ranging from microvascular thrombosis to disseminated intravascular coagulation and a generally disrupted microcirculation (see Figure 6.1). It is this abnormal host response, not the infection itself, that causes the organ dysfunction characteristic of sepsis.⁸

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Figure 6.1 Immune response and the disrupted microcirculation in sepsis. Bacterial surface toxins stimulate cell surface receptors on host white cells. A disproportionate inflammatory cascade results involving mitochondrial dysfunction, endothelial damage, microvascular thrombosis, tissue hypoxia, cardiac and other organ dysfunction. For a really good visual representation of the changes in the microcirculation caused by sepsis, go to https://youtu.be/xAo1GsYUr7Q.

The sepsis process creates a biphasic reaction whereby immune hyper-responsiveness is followed by a hypo-responsive state due to immune exhaustion. Excessive strain on the heart from activation of the autonomic nervous system creates a state of global cardiac hypokinesis, hypotension, and hypoperfusion. This further exacerbates ischaemia from excessive coagulation within the organs and creates further tissue abnormalities.⁹ Ultimately, these converging mechanisms lead to a hypotensive patient with organs failing at various rates due to ischaemic injury and pro-inflammatory tissue damage. This inflammatory stage of sepsis can last from hours to days and early sepsis mortality peaks at approximately 3–5 days. If the patient survives the inflammatory stage, immunosuppression sets in over the next several days after the exhaustion of pro-inflammatory resources. At this point, an anti-inflammatory situation results and at 20–30 days following the onset of sepsis, deaths from secondary infections peak due to commensal flora and opportunistic bacteria.^{10,11}

Metabolic Changes in Sepsis

The metabolic dysfunction in sepsis is caused not only by tissue hypoxia as a result of impaired oxygen delivery to the tissues, but also by mitochondrial dysfunction together with a complex set of interactions between multiple non-immunologic pathways. Damage

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to mitochondria from high levels of reactive oxygen species leads to a fall in adenosine triphosphate (ATP) levels. In order to prevent a lethal drop in ATP, cells enter a state similar to hibernation. This generalised reduction in ATP and energy expenditure leads to, or exacerbates, acute kidney injury, myocardial depression, hepatic dysfunction, encephalopathy and acute lung injury, with increased lung permeability and decreased gastrointestinal barrier and transport function.

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Tissue Hypoperfusion

Historically, septic shock was understood in simple terms to be tissue hypoperfusion causing tissue hypoxia. However, we now know it is far more complex than that. For example:

- · Cardiac output may be preserved, increased, or depressed in patients with sepsis
- Intravenous fluid loading has sometimes little, if any, effect on cardiac output in critical illness and any increase in blood pressure is not sustained
- Cellular hypoxia is not observed in experimental models of sepsis or in clinical studies
- The elevated serum lactate in sepsis is produced aerobically, probably in response to adrenergic stimulation as an adaptive response to increase bioenergetic efficiency, rather than because of tissue hypoxia
- Organ failure in sepsis involves cellular dysfunction unrelated to hypoxia/hypoperfusion, including structural mitochondrial changes and reduced oxygen consumption

Tissue ischaemia occurs because of either a systemic or local mismatch between oxygen delivery and tissue demand. Although the vascular endothelium and microcirculation play a key role in sepsis, these microcirculatory alterations are not always related to macrocirculatory indices such as blood pressure and cardiac output. In fact, it has been suggested that sepsis with hypotension and/or an elevated serum lactate is not strictly a 'shock' state, but an adaptive (i.e. a beneficial) alteration in haemodynamics and metabolism as a result of sepsis. Some patients with sepsis have a normal blood pressure (see self-assessment case 2). The discrepancy between micro- and macrocirculations makes standard treatments difficult to define and helps explain the failure of previous treatments in sepsis where 'supramaximal' oxygen delivery targets caused harm. It also begins to question the aggressive use of intravenous fluids in resuscitating the hypotensive patient with sepsis (see mini-tutorial on fluid resuscitation in sepsis).

Screening Tools for Sepsis

The 2016 Surviving Sepsis Campaign guidelines¹² recommend that all hospitals screen acutely ill patients for sepsis. The UK Sepsis Trust¹³ and the National Institute for Health and Care Excellence (NICE)¹⁴ have published screening tools designed to help healthcare professionals 'think sepsis'. Both state that if one or more of the following criteria are present, the patient is at high risk and treatment for sepsis should be started immediately:

- New altered mental state
- Blood pressure ≤90 mmHg systolic

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- Heart rate >130/min
- Respiratory rate $\geq 25/\min$
- Needs oxygen to maintain SpO₂ ≥92% (or ≥88% in known chronic obstructive pulmonary disease)

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- Poor urine output
- Lactate $\geq 2 \, \text{mmol/L}$
- Recent chemotherapy
- Mottled or ashen appearance

Using the above criteria, a frail elderly person admitted with pneumonia, delirium, and fast atrial fibrillation (arguably a normal physiological response) should be treated for sepsis – and this is the problem: 'think sepsis' does not mean the patient *has* sepsis. In a letter published in the *Lancet* in 2019,¹⁵ two of the authors of the third international consensus statement definitions for sepsis and septic shock (sepsis-3) wrote:

Sepsis – 'life-threatening organ dysfunction caused by a dysregulated host response to infection' – only develops in a tiny minority of patients ... A small proportion of patients with infection are admitted to intensive care units, of whom approximately 70% survive their hospital stay. Although hard data are unavailable, most patients with substantial organ dysfunction who receive full, active management are likely to be admitted to intensive care. Patients with infection who die outside of intensive care (and many who die inside it) are predominantly older, frail, and at the end of life. Indeed, 77.5% of sepsis-related deaths in England are in patients aged 75 years or older. By comparison, approximately 150 sepsis-related deaths occur annually in children aged 0–18 years: a hospital mortality of 0.075%. The high incidence of frailty and severe comorbidities makes most sepsis-related deaths neither attributable to sepsis, nor preventable through timely and effective healthcare.¹⁶

In response to concerns about overdiagnosis of sepsis and antibiotic stewardship, the updated 2019 UK Sepsis Trust care bundle and the NICE guideline have 'immediate review by a senior clinical decision maker to assess the person and think about alternative diagnoses to sepsis' as the first step.

The most common screening tool used in UK hospitals is the NEWS2 score, described in Chapter 1, which has been found to be a good predictor of mortality. A score of 5 or more, or a score of 3 in any single parameter, triggers an assessment by a qualified clinician which includes asking the question: 'Is this patient unwell because of an infection?' If the answer is yes and any high-risk features of sepsis are present (see list above), then the 'sepsis six' care bundle should be completed within 1 hour. The UK Sepsis Trust has also produced screening tools for telephone triage, primary care, and ambulance services.

In addition to regularly used screening tools, the third international consensus definitions for sepsis and septic shock (sepsis-3) introduced a 'quick SOFA' or qSOFA score as a

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bedside tool designed to rapidly identify patients who are likely to have poor outcomes. The qSOFA score is positive if the patient has two or more of the following:

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- Respiratory rate of $\geq 22/\min$
- Altered mentation (Glasgow Coma Score of less than 15)
- Systolic blood pressure of ≤100 mmHg

A positive qSOFA score should prompt clinicians to look for organ dysfunction, initiate or escalate therapy if appropriate, and consider referral to the intensive care unit. It is important to note that qSOFA is not a screening tool for sepsis. A metanalysis by the American Academy of Emergency Medicine found that it consistently performed poorly as a screening tool for identifying sepsis in the emergency department but was good in predicting organ dysfunction, the need for ICU admission and in-hospital mortality compared with other clinical tools in patients already diagnosed with sepsis.¹⁷

There is currently no diagnostic test for sepsis. However, efforts have targeted identifying biomarkers of sepsis which could be used both in the hospital and community setting. In the meantime, *think about* sepsis if:

- The patient looks ill
- Or is triggering on an early warning score
- And has symptoms or signs of an infection

Sepsis Six

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The 'sepsis six' refers to six steps in the initial management of patients with suspected sepsis. But where did it come from?

The international Surviving Sepsis Campaign (SSC) was formed in 2002 as a collaboration of the European Society of Intensive Care Medicine, International Sepsis Forum and the Society of Critical Care Medicine. It was established to improve the diagnosis and management of sepsis through education and the implementation of evidence-based guidelines. Deaths from myocardial infarction have been reduced from 30 to 8% over several decades as a result of education, care bundles, re-organisation of services and new treatments. The idea behind the SSC was to give sepsis the same level of intense clinical commitment. In 2018, it combined its previous initial resuscitation and ongoing management care bundles in to a single 1 hour sepsis bundle.¹⁸ A care bundle is a group of evidencebased interventions that, when executed together, result in better outcomes than when implemented individually. The 1 hour sepsis bundle is based on the fact that outcomes from sepsis can be improved by simple, timely interventions outside the intensive care unit.

The UK Sepsis Trust has taken the SSC guidelines and created a memorable care bundle known as the 'sepsis six'. It is now used in over 30 countries across the world and has been updated as new evidence has emerged. The SSC 1 hour bundle and the sepsis six are shown in Tables 6.4 and 6.5.

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Table 6.4 SSC 1 hour sepsis bundle.

Bundle element	Grade of recommendation and level of evidence
Measure lactate [*]	Weak recommendation. Low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad spectrum antibiotics	Strong recommendation. Moderate quality of evidence
Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L	Strong recommendation. Low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP >65 mmHg	Strong recommendation. Moderate quality of evidence
MAP = mean arterial pressure.	

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* Re-measure if initial lactate >2 mmol/L.

Table 6.5 Sepsis six.

If the patient looks unwell or NEWS2 is five or above, ask 'could this be due to an infection?' Any high-risk features present ('red flags'), start sepsis six:

1 Ensure senior clinician attends

Not all patients with red flags will need the sepsis six urgently. A senior decision maker may seek alternative diagnoses/de-escalate care

2 Oxygen if required

Start if oxygen saturations <92% – aim for saturations of 94–98%. If at risk of hypercapnic respiratory failure, aim for saturations of 88–92%

3 Obtain intravenous access, take bloods

Blood cultures, glucose, lactate, FBC, U&E, CRP, and clotting

4 Give intravenous antibiotics

Maximum-dose broad spectrum therapy. Consider: local policy/allergy status/antivirals

5 Give intravenous fluids

Give fluid bolus of 500 mL (adults). NICE recommends using lactate to guide further fluid therapy

6 Monitor

Use NEWS2, measure urine output, this may require a urinary catheter. Repeat lactate at least once per hour if initial lactate elevated or if clinical condition changes

Management of Sepsis and Septic Shock

This section will look at the management of sepsis and septic shock in more detail and some of the evidence supporting the different interventions. Most cases of sepsis require admission to the intensive care unit (if appropriate), as even with optimal initial management, support for failing organ systems is usually required.

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Oxygen Therapy

The airway should be managed in any patient with a reduced conscious level. As outlined in Chapter 2, oxygen should be given for hypoxaemia, not sepsis *per se. Hyper*oxaemia can lead to mitochondrial damage and depletion of ATP and result in peripheral vasoconstriction, coronary vasoconstriction and a decrease in cardiac output. Thus both the molecular and physiological effects of high levels of oxygen may counteract the positive effects of oxygen supplementation. Several studies have described a clear association between hyper-oxaemia and increased mortality after cardiac arrest, stroke, and traumatic brain injury.¹⁹ The association between hyperoxaemia in sepsis outcomes remains to be studied.

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Serum Lactate Measurements

A persistently raised serum lactate is a poor prognostic indicator with a linear relationship between lactate and mortality, and reductions in lactate levels are associated with improved outcomes.^{20,21} Serial measurements of lactate are recommended to guide resuscitation in sepsis in the SSC and NICE guidelines. A high lactate can occur due to sepsis in the absence of hypotension (so called 'cryptogenic shock'). Popular understanding of sepsis-associated hyperlactateaemia (SAHL) is that it is a marker of hypoperfusion and tissue hypoxia due to anaerobic glycolysis. However, a large body of evidence challenges this idea. Experimental and human studies consistently support the view that SAHL is better explained by increased aerobic glycolysis due to activation of the stress (adrenergic) response. It may actually serve to facilitate bioenergetic efficiency through an increase in lactate oxidation.²² So lactate production increases as the severity of disease increases.

Blood Cultures

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Blood cultures should be taken in suspected sepsis *even if the patient has no fever*. Fever is only one sign of sepsis and may be absent. A second set of blood cultures increases the sensitivity for the detection of bacteraemia from approximately 70 to 90%²³ and the more blood, the greater the yield, so aim for around 10 mL of blood in each bottle. Only half of patients with sepsis have positive blood cultures, falling to one-third of patients with septic shock. In the UK, two thirds of positive blood cultures grow gram negative and a third grow gram positive bacteria.²⁴ Ideally, blood cultures should be taken before antibiotic administration, but if there is any difficulty in obtaining blood cultures, do not delay the administration of antibiotics in a sick patient. Other potentially infected fluid or tissue should be sampled as soon as possible e.g. urine, pleural fluid, wounds/collections, diarrhoea, cerebrospinal fluid, etc.

Broad Spectrum Intravenous Antibiotics

Broad spectrum intravenous antibiotics are recommended in sepsis. However, the timing of antibiotics (recommended to be administered within 1 hour of recognition of suspected sepsis) is controversial. A popularly quoted retrospective study found an average increase in mortality of 7.6% for every 1 hour delay in the administration of antibiotics for patients presenting with *septic shock*.²⁵ For patients with suspected sepsis, there is no evidence that

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antibiotics should be administered within this timeframe and a 2015 systematic review and metanalysis of 11 studies showed no survival benefit from administering antibiotics within 3 hours for sepsis and 1 hour for septic shock.²⁶ There is also no difference in mortality when patients with sepsis or septic shock receive antibiotics en route to hospital versus those who receive antibiotics after arrival.²⁷

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The recommendation for antibiotics to be administered within 1 hour in suspected sepsis led to the Infectious Diseases Society of America to publish a statement²⁸ explaining why they did not endorse it: 'If there is a possibility that a patient with shock might have an infection, it is understandable and appropriate to administer broad spectrum antibiotics and fluids immediately ... for patients with less severe disease and in whom the presence of infection is uncertain [or who may have a viral infection] there is often more time to gather diagnostic data to generate a more informed and precise therapeutic plan ... Overuse of antibiotics has negative consequences for hospital populations in general in addition to the specific patient receiving treatment.'

The choice of antibiotic is normally determined by local hospital guidelines and if in doubt, advice should be sought from microbiology or infectious disease specialists, especially if the patient is a returning traveller. Antibiotic therapy should be tailored at 48–72 hours depending on results of cultures. The de-escalation of antibiotics should be considered daily as the clinical situation permits. Serum procalcitonin levels have shown to be of value in stopping antibiotics in a timely fashion but may not be available.

Source Control

Controlling the source of infection is vital and observational data have shown that inadequate early source control was associated with an increase in 28-day mortality from 26.7 to 42.9%.¹³ Investigations such as ultrasound or computed tomography may be required to identify and drain or aid surgical removal of infected tissue. The principles of source control can be described by the four D's:

- Drainage of pus or liquid e.g. liver abscess, empyema
- Debridement of necrotic or infected solid tissue which is often a surgical emergency e.g. necrotising fasciitis, bowel perforation
- Device removal e.g. indwelling catheter, central line, etc.
- Definitive repair of anatomical abnormality e.g. perforated viscus

It is important to re-evaluate the adequacy of source control if the patient fails to improve on treatment.

Intravenous Fluid Administration

There is continuing debate about the role of intravenous fluids in the resuscitation of patients with sepsis. Intravenous fluids should be administered to patients with evidence of haemodynamic instability, defined by either hypotension (systolic blood pressure \leq 90 mmHg or a decrease in systolic blood pressure of >40 mmHg from baseline) or an

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elevated lactate (\geq 4 mmol/L). However, sepsis-induced hypotension results from different pathological processes that require different treatments. For example, hypovolaemia from intravascular volume loss due to increased vascular permeability requires fluid resuscitation, but vasodilatation affecting both venous capacitance and arterial resistance is better treated with vasopressors, and sepsis-related myocardial dysfunction may require inotropes.

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Despite these different processes, the goals of resuscitation are to restore intravascular volume, improve organ perfusion, and optimise oxygen delivery. The principle of oxygen delivery was described in Chapter 2 in simple terms, but will be expanded on here. In most tissues, oxygen consumption (VO_2) is determined by metabolic demand and does not rely on oxygen delivery (DO_2) . But if oxygen delivery is reduced to a critical level, oxygen consumption becomes 'supply dependent'. In sepsis, the tissues become supply dependent at higher levels of oxygen delivery. This is shown diagrammatically in Figure 6.2. Oxygen demand increases in sepsis but oxygen delivery is impaired by the pathophysiological changes taking place in both the micro and the macrocirculation. The abnormalities in the microcirculation have already been described. In the macrocirculation, these are hypovolaemia, vasoregulatory dysfunction, and myocardial depression. Using the oxygen delivery equation, we can see how the macrocirculation can be manipulated in various ways to optimise global oxygen delivery (see Figure 6.3) but the macro-scopic goals of blood pressure and cardiac output do not always reflect what is happening at the cellular level.

There is accumulating observational evidence that the injudicious use of intravenous fluid is associated with adverse outcomes in sepsis, including increased requirement for organ support and mortality.²⁹ More information about fluid administration in sepsis is given in the mini-tutorial.



O₂ delivery (DO₂)



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Figure 6.3 Manipulating the macrocirculation in sepsis to optimise global oxygen delivery. $DO_2 = oxygen$ delivery, Hb = haemoglobin, $SaO_2 = oxygen$ saturation, CO = cardiac output, BP = blood pressure, SVR = systemic vascular resistance, SV = stroke volume.

Mini-Tutorial: Fluid Resuscitation in Sepsis

What Fluid?

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The 2016 SSC guidelines recommend crystalloids as the fluid of choice in patients with sepsis and septic shock. Among crystalloids, studies comparing the use of balanced crystalloid solutions (e.g. Hartmann's or Ringer's lactate) with sodium chloride 0.9% ('normal saline') in critical illness suggest that a chloride-restrictive resuscitation strategy is associated with a reduced incidence of death, acute kidney injury, and the need for renal replacement therapy.^{30,31} Albumin is recommended 'when patients require substantial amounts of crystalloids' although the evidence for its benefit remains equivocal. Gelatins are associated with increased risks of anaphylaxis, bleeding, renal failure, and mortality when compared with crystalloids or albumin for the treatment of hypovolemia. Several guidelines recommend against hydroxyethyl starch (HES) due to well-documented safety concerns of nephrotoxicity and a significantly increased risk of death. A restrictive approach to blood transfusion is safe. Transfusing when haemo-globin levels fall below either 7 or 9 g/dL results in equivalent mortality and morbidity.

How Much Fluid?

The SSC guideline recommends rapid administration of 30 mL/kg of crystalloid for hypotension or a lactate $\geq 4 \text{ mmol/L}$ in sepsis. NICE recommends 500 mL of crystalloid over 15 minutes and a total of 30 mL/kg in the first hour. For a 70 kg patient, this is roughly 2 L in the first hour. However, the goal of therapy is not to administer a specific volume of fluid but to optimise tissue perfusion. Crystalloids leave the intravascular

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space after 20–40 minutes. Therefore, it is easy to administer several fluid challenges over a short space of time in an effort to correct hypotension and create a potentially damaging large positive fluid balance. Once hypovolaemia has been corrected, the patient needs vasopressors and/or inotropes to treat persisting hypotension. There is some evidence that a sustained positive fluid balance in sepsis is harmful and exacerbates sepsis-induced lung injury and increases the risk of death.³²

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Suggested mechanisms by which the excess administration of intravenous fluids may cause harm include:

- Tissue oedema leading to increased requirements for ventilatory support, increased translocation of gut organisms, and increased renal venous pressure compromising perfusion
- Opening of shut-down capillary beds (the so-called 'hibernating circulation') leading to flooding of the systemic circulation with cytokine-rich blood, exacerbating systemic inflammation
- Degradation of the glycocalyx layer lining the luminal wall of the vascular endothelium. The glycocalyx plays a critical role in vascular homeostasis by maintaining endothelial cells in a quiescent state. Loss of integrity of the glycocalyx is a critical step in endothelial cell activation and propagation of the systemic inflammatory state.

At the time of writing, two multicentre randomised controlled trials are underway to compare a conventional resuscitation strategy with a fluid-restrictive approach for patients with septic shock.

Monitoring, Including Urine Output

Monitoring is extremely important in patients with sepsis. Regular measurement of vital signs and repeat lactate measurements are recommended. Patients who do not respond to initial treatment within the first hour should be escalated to the intensive care unit if appropriate. Urine output is a good measure of renal perfusion and should be monitored closely, usually with a urinary catheter.

Vasopressors and Inotropes

Although the definition of septic shock is 'persisting hypotension requiring vasopressors to maintain a mean arterial pressure of >65 mmHg and a serum lactate of >2 mmol/L in the absence of hypovolaemia', this definition does not define adequate volume resuscitation. Therefore, knowing when to start vasopressors can be difficult and relies on the clinician using their best efforts to determine whether the patient is intravascularly replete, using the techniques outlined in Chapter 5.

Unlike other causes of shock, the cardiac output is often maintained or even increased in sepsis. Hypotension results from a low systemic vascular resistance (SVR) or a reduced

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cardiac output (CO). SVR may be thought of as the resistance against which the heart pumps and is mainly determined by the diameter of arterioles. It is calculated as follows:

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SVR = MAP - CVP in mmHg × 80 (correction factor) / CO in L / min (The normal range is 1000 - 1500 dyne s / cm⁵)

A vasopressor is an agent that vasoconstricts and increases systemic vascular resistance. An inotrope is an agent that increases myocardial contractility. A vasoactive drug is a generic term for either. In order to understand how vasopressors and inotropes work, it is important to know about the main types of receptor in the circulation. These receptors act via G proteins and cyclic adenosine monophosphate (AMP) at the cellular level. Table 6.6 shows the action of various receptors in the circulation and the action of commonly used vasoactive drugs.

The selection of the ideal vasopressor in the setting of septic shock has been the source of several large-scale multicentre trials. All the drugs described below are short acting and

Receptor	Where					
α receptors	Vasoconstrictio	on		Peripheral, renal, coronary		
β1 receptors	 ↑ Contractility ↑ Heart rate ↑ Cardiac outp 	out		Heart		
β2 receptors	Vasodilatation			Peripł	neral, ren	al
DA (dopamine) receptors	ns (see below)		Renal, gut, coronary			
V1a (vasopressin) receptors	Vasoconstriction, myocardial hypertrophy, platelet aggregation, glycogenolysis, uterine contraction			Vascular smooth muscle, platelets, hepatocytes, myometrium		
Vasoactive drug		α 1	β 1	β 2	DA	V1a
Norepinephrine (noradrenal	++++	+				
Arginine-vasopressin						++++
Dopamine						
• Low dose		++	++	+	+++	
Medium dose			++	+	++	
• High dose					+	
Dobutamine			+++	++		
Epinephrine (adrenaline)	+ to +++	+++	++			
Phenylephrine	++++					
Dopexamine			+	+++	++	

 Table 6.6
 Receptors in the circulation and the action of common vasoactive drugs.

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their effects on the circulation are seen immediately. It is generally recommended that all agents (except phenylephrine and metaraminol) should be given through a central line to avoid tissue necrosis. However, short-term infusions via large peripheral veins have been shown to be a safe alternative for norepinephrine if managed appropriately. Delays or difficulties in obtaining central venous access should not necessarily delay the administration of norepinephrine. A retrospective analysis of patients with septic shock enrolled in a large, international database found that every hour delay in vasopressor initiation was associated with a 7% increase in mortality.³³

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The 2016 SSC guidelines recommend:

- Norepinephrine as the first-choice vasopressor
- Adding vasopressin or epinephrine to norepinephrine if needed
- High-dose dopamine as an alternative to norepinephrine only in selected patients (those with a low risk of tachyarrhythmias and bradycardia). Low-dose dopamine for 'renal protection' is not recommended
- Dobutamine for patients who show evidence of persistent hypoperfusion despite adequate fluid loading and vasopressor treatment

Phenylephrine is an α 1 receptor agonist which principally affects large arterioles with little effect on terminal arterioles. With few cardiac effects, it does not cause tachycardia. It is sometimes used in the emergency department as a temporary measure as it can be infused through peripheral veins before central access is obtained. However, due to its potential for decreasing stroke volume, the SSC guidelines do not recommend it for the treatment of septic shock unless patients experience serious arrhythmias with norepinephrine, have a high cardiac output, or require salvage therapy. Metaraminol (an α 1 receptor agonist with some β effects) is also used in emergency departments as a temporary measure using peripheral veins.

Norepinephrine (noradrenaline)

Norepinephrine is the first-line vasopressor in septic shock on the basis of many clinical trials that showed either better outcomes or fewer adverse events compared with dopamine and other vasoactive drugs. It is a potent α agonist (vasoconstrictor), raising blood pressure by increasing systemic vascular resistance. It has some β 1 receptor activity causing increased myocardial contractility, heart rate, and cardiac output, but it has no effect on β 2 receptors. Therefore, it acts mainly as a vasopressor with little inotropic effect. Through vasoconstriction, norepinephrine reduces renal, gut, and muscle perfusion, but in patients with sepsis, it can increase renal and gut perfusion by increasing perfusion pressure.

Vasopressin

Vasopressin (antidiuretic hormone) is a V1 receptor agonist and is a potent alternative to norepinephrine in the treatment of fluid and catecholamine-refractory septic shock. In vasodilatory shock, vasopressin levels are inappropriately low due to reduced production

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Table 6.7 Location and functions of vasopressin receptors.

There are three subtypes of vasopressin receptor: V1a, V1b, and V2. All are G protein coupled receptors.

Receptor	Location	Functions
V1a (previously V1) V1b (previously V3)	Mainly in vascular smooth muscle Anterior pituitary gland	Vasoconstriction, uterine contraction Releases ACTH, prolactin, endorphins
V2	Mainly in distal convoluted tubule and collecting ducts of kidney	Antidiuretic effect, vasodilatation

ACTH = adrenocorticotropic hormone; AQP = aquaporin receptor.

by the pituitary gland. Corticosteroids also inhibit vasopressin secretion. At low levels, the antidiuretic actions of vasopressin predominate, but increasing levels leading to progressively greater vasoconstrictor effects.

The Vasopressin and Septic Shock Trial (VASST) compared norepinephrine with vasopressin and showed similar outcomes and no increased adverse events across all study patients and a survival benefit in subgroup analysis of patients with less severe shock.³⁴ The Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock Trial (VANISH) found no difference in kidney failure-free days or mortality with early initiation of vasopressin therapy compared with norepinephrine alone in septic shock patients.³⁵ These data may suggest that vasopressin is a viable first-line alternative to norepinephrine. However, the SSC guidelines do not recommend vasopressin as a single agent in the management of septic shock and instead suggest that it can be added to norepinephrine monotherapy with the intent of either increasing MAP or decreasing norepinephrine dose.

Terlipressin and selepressin are more selective V1a receptor agonists and may be more potent than vasopressin in improving catecholamine-refractory septic shock. The location and functions of the different vasopressin receptors are summarised in Table 6.7.

Dopamine

Dopamine stimulates adrenoreceptors and dopaminergic receptors. The effects of dopamine change with increasing dose:

- At low doses, the predominant effects are those of dopaminergic stimulation causing an increase in renal and gut blood flow
- At medium doses, β1 receptor effects predominate causing increased myocardial contractility, heart rate, and cardiac output
- At high doses, α stimulation predominates causing an increase in systemic vascular resistance and reduction in renal blood flow. High doses of dopamine are associated with arrhythmias and increased myocardial oxygen demand

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There is marked individual variation in plasma levels of dopamine in critically ill patients, making it difficult to know which effects are predominating. Dopamine used to be administered in low doses for 'renal protection' in sepsis, but this is no longer recommended as studies have shown it has no benefit and may cause harm.³⁶

Dobutamine

Cardiac depression with impaired left ventricular function is a well-recognised manifestation of septic shock in up to 60% of patients and is associated with increased mortality compared to patients without cardiac impairment. Its presentation can manifest as decreased contractility, elevated troponin levels, an impaired ventricular response to fluid, or ventricular dilatation. The SSC guidelines recommend that dobutamine be administered or added to pre-existing vasopressor therapy in the presence of myocardial dysfunction, defined as elevated cardiac filling pressures and low cardiac output.³⁷

Dobutamine has predominant $\beta 1$ effects which increase heart rate and contractility and hence cardiac output. It also has $\beta 2$ effects which reduce systemic and pulmonary vascular resistance. Mild α effects may be unmasked in a patient on beta-blockers (because of down regulation). The increase in myocardial oxygen consumption from dobutamine administration is offset by the reduction in afterload that also occurs. Dobutamine has no effect on visceral vascular beds but increased renal and splanchnic blood flow occurs as a result of increased cardiac output. The increase in cardiac output may increase blood pressure but since systemic vascular resistance is reduced or unchanged, the effect of dobutamine on blood pressure is variable.

Epinephrine (Adrenaline)

Epinephrine is a potent $\beta 1$, $\beta 2$, and α agonist. The cardiovascular effects of epinephrine depend on its dose. At lower doses, $\beta 1$ stimulation predominates (i.e. increased contractility, heart rate, and cardiac output). There is some stimulation of $\beta 2$ receptors (which causes vaso- and bronchodilation) but this does not predominate and therefore blood pressure increases. α stimulation becomes more predominant with increasing doses leading to vasoconstriction which further increases systolic blood pressure. Renal and gut vasoconstriction also occurs. There is a greater increase in myocardial oxygen consumption than seen with dobutamine. Metabolic effects include a fall in plasma potassium, a rise in serum glucose, and stimulation of metabolism which can lead to a rise in serum lactate.

Corticosteroids

The role of corticosteroids in patients with sepsis remains controversial. Recent meta-analyses have concluded that low-dose corticosteroids produce either no or a very small reduction in short-term mortality, but their use is associated with more rapid resolution of shock and shorter ICU stays.³⁸ Currently, the SSC guidelines recommend against using low-dose

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corticosteroids if fluid resuscitation and vasopressor therapy are effective. If hemodynamic instability persists despite adequate fluid resuscitation and vasopressor therapy, intravenous hydrocortisone can be added at a dose of 200 mg/day.

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The Effects of Sepsis on the Lungs and Kidneys

The inflammation and microcirculatory changes that take place in sepsis also affect the lung. Respiratory dysfunction ranges from subclinical disease to acute lung injury (ALI) to acute respiratory distress syndrome (ARDS). ARDS can be caused by a variety of insults, but is common in sepsis – 50% of patients with sepsis develop acute lung injury or ARDS. Patients with ALI/ARDS have bilateral patchy infiltrates on the chest X-ray and a low PaO_2 to FiO₂ ratio which is not due to fluid overload or heart failure.

The pathological changes in ARDS are divided into three phases:

- The early exudative phase (days 1-5) characterised by oedema and haemorrhage
- The fibro-proliferative phase (days 6–10) characterised by organisation and repair
- The fibrotic phase (after 10 days) characterised by fibrosis

The hallmark of ARDS is alveolar epithelial inflammation, air space flooding with plasma proteins, surfactant depletion, and loss of normal endothelial reactivity. In ALI/ARDS, compensatory hypoxic vasoconstriction is impaired, leading to shunting of blood through non-ventilated areas of lung; refractory hypoxaemia therefore occurs. There is also increased airway resistance and reduced thoracic compliance. The development of ARDS complicates the management of sepsis. Oxygenation is important, but high ventilation pressures can cause more lung damage and also have detrimental effects on the systemic circulation.

Research in to ARDS has led to several different lung protection strategies, including better fluid management, different ways of ventilating patients, and the use of steroids in non-resolving ARDS. Ventilating patients with ALI/ARDS using smaller tidal volumes and lower peak inspiratory pressures in sepsis improves outcome. The modest hypercapnia which results is thought to be safe. Therefore, the SSC guidelines recommend ventilating patients with sepsis using lower tidal volumes (6 mL/kg ideal body weight) with inspiratory plateau pressures of $30 \text{ cmH}_2\text{O}$. The rationale for this is that mechanical ventilation, through shear forces and barotrauma, can perpetuate the inflammation and lung damage which is part of the process in ARDS. In intensive care units with the capability to ventilate patients in the prone position, it is recommended to ventilate patients with severe ARDS in the prone position for 16 hours each day. Extracorporeal membrane oxygenation (ECMO) may reduce mortality in very severe ARDS and should be considered in these patients if an ECMO service is available.

Although in health, blood flow through the kidneys remains fairly constant over a range of blood pressures due to autoregulation, in critical illness, this is disrupted and as cardiac output falls, the urine output falls too. However, sepsis associated acute kidney injury

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(SA-AKI) is not solely due to hypoperfusion and there is mounting evidence to suggest it is multifactorial. SA-AKI can also result from direct inflammatory injury, endothelial cell and microcirculatory dysfunction, microvascular thrombosis, and ischaemia-reperfusion damage. Up to 60% of patients with sepsis have AKI and sepsis is associated with up to 50% of all AKI. Patients with sepsis complicated by AKI have a significantly increased mortality compared with patients without AKI, and AKI associated with sepsis has a significantly increased mortality compared with those who have AKI from another cause.³⁹ Strategies to prevent SA-AKI include careful fluid balance and the avoidance of further kidney injury from nephrotoxic drugs.

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Other Supportive Care on the Intensive Care Unit

As well as the different treatments described above, the SSC guidelines also recommend careful glucose monitoring and starting intravenous insulin in patients with a glucose greater than 10 mmol/L, aiming to avoid hypoglycaemia. Other supportive care includes thromboprophylaxis, stress ulcer prophylaxis for patients with risk factors for gastrointestinal bleeding, and early initiation of enteral feeding. Compromised gut perfusion leads to breakdown of the mucosal barrier and allows bacteria to translocate in to the circulation where they stimulate cytokine production, inflammation, and organ dysfunction. This theory has been demonstrated in animal studies, but the role of 'bacterial gut translocation' in the development of multiple organ failure in humans is still an area of research. Nutritional support via nasogastric tube is considered important in sepsis to help maintain gut mucosal integrity, as well as prevent stress ulcers and provide nutrition in this hyper-catabolic state.

Key Points: Sepsis

- Sepsis is defined as life-threatening organ dysfunction caused by a *dysregulated host response* to infection
- A normal response to infection (e.g. tachycardia, fever, and high respiratory rate in pneumonia) is not sepsis
- In sepsis, there are profound immune, cardiovascular, metabolic, and coagulation abnormalities that lead to microcirculatory dysfunction and tissue hypoxia, as well as changes in blood pressure and cardiac output
- Early warning scores such as NEWS2 can be used to alert clinicians to patients with abnormal vital signs who may have sepsis
- The qSOFA score can be used to predict organ dysfunction and the need for ICU admission in patients with sepsis
- Early recognition and timely interventions, including the Surviving Sepsis Campaign's 1 hour sepsis bundle and the 'sepsis six', can improve outcomes for patients with sepsis
- Patients with septic shock (clinically identified by persisting hypotension and a serum lactate of >2 mmol/L in the absence of hypovolaemia) should be referred *early* to the intensive care unit, if appropriate

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Self-Assessment: Case Histories

- 1 A 29-year-old woman is brought to the emergency department drowsy with the following vital signs: blood pressure 80/50 mmHg, pulse 130/min, respiratory rate 28/min, SpO₂ 95% on 10 L/min via reservoir bag mask, and temperature 38.5°C. Her arterial blood gases show: pH 7.3, PaO₂ 35.5 kPa (273 mmHg), PaCO₂ 3.5 kPa (26.9 mmHg), st bicarbonate 12.7 mmol/L, BE –10, and lactate 6 mmol/L. She has a purpuric rash on her trunk. She responds to voice, her bedside glucose measurement is 6.2 mmol/L (103 mg/dL), and there is no neck stiffness. Her NEWS2 score is 14. What is your management?
- 2 A 40-year-old man is admitted with community-acquired pneumonia and is started on appropriate intravenous antibiotics. Twenty-four hours later you are asked to review him because he appears unwell. On examination, he is alert, respiratory rate 36/min, SpO₂ 94% on 15 L/min via reservoir bag mask, pulse 105/min, and blood pressure 130/70 mmHg. He has a temperature of 38°C and his NEWS2 score is 7. He has not passed urine all day and a bladder scan done by the nursing staff shows only 60 mL of urine. His arterial blood gases show pH 7.3, PaO₂ 21 kPa (161 mmHg), PaCO₂ 3.5 kPa (26.9 mmHg), st bicarbonate 12.7 mmol/L, BE –10, and lactate 4.5 mmol/L. His blood glucose is normal. What is your management?
- 3 A 60-year-old man is admitted from the heart failure clinic with increased breathlessness and a productive cough. His most recent echocardiogram shows a left ventricular ejection fraction of 35%. His vital signs on admission are: alert, blood pressure 88/60 mmHg, temperature 38.1°C, respiratory rate 24/min, SpO₂ 93% on air, and pulse 90/min. His NEWS2 score is 8. A venous blood gas shows a lactate of 1.2 mmol/L. A chest X-ray shows left basal consolidation and his CURB-65 score is 1. What is your management?
- 4 A 52-year-old woman with no past medical history attends the emergency department feeling unwell. Her daughter describes her as having a fever, being confused at times, feeling nauseated, and 'feeling really ill'. On arrival, her vital signs are: alert, pulse 90/ min, temperature 38°C, blood pressure 120/70 mmHg, respiratory rate 18/min, SpO₂ 96% on air, and urine output normal. While she is being examined, the doctor notices rapidly appearing purpuric spots on her abdomen and limbs which neither the daughter nor the patient had noticed before. Her NEWS2 score is 0. What is your management?
- 5 A 60-year-old woman was seen in the emergency department and treated for a urinary tract infection on the basis of symptoms and a positive urine dipstick. The next day she returns having collapsed. On arrival, her vital signs are: alert, pulse 120/min, temperature 39°C, blood pressure 80/50 mmHg, respiratory rate 20/min, SpO₂ 95% on air, and urine output normal. Hew NEWS2 score is 7. What is your management?

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- 6 A 19-year-old intravenous drug user is admitted at 3 am with a severe hand infection due to injecting with dirty needles. His hand and arm are becoming increasingly swollen. He is alert but his other vital signs are: blood pressure 70/40 mmHg, temperature 39°C, respiratory rate 24/min, SpO₂ 95% on air, and pulse 130/min. He has no peripheral venous access so the admitting junior doctor has prescribed high-dose oral antibiotics and decided to 'review him in the morning'. His NEWS2 score is 9. Describe your management.
- 7 A 45-year-old woman with severe rheumatoid arthritis is admitted with a painful right hip. She is on monthly infusions of Infliximab (an immunosuppressant drug) as well as daily steroids. Her admission blood tests show a high C-reactive protein and neutrophil count. Her vital signs on admission are: blood pressure 130/60 mmHg, temperature 36.7°C, respiratory rate 16/min, SpO₂ 98% on air, and pulse 80/min. She is alert. Twenty-four hours later she develops hypotension (75/40 mmHg) and a tachy-cardia (110/min). A blood culture result is phoned through showing Staphylococcus aureus in both blood culture bottles. When you go to see her, her other vital signs are: alert, apyrexial, respiratory rate 24/min, and SpO₂ of 87% on air. She has new bilateral basal crackles on auscultation of the chest. Her NEWS2 score is 9. What is your management?
- 8 A 95-year-old woman is admitted from her nursing home with drowsiness and not eating and drinking. She had been started on antibiotics by her general practitioner 2 days before for a chest infection. Her past medical history includes dementia, heart failure, chronic kidney disease, and atrial fibrillation for which she is taking a diuretic, ACE inhibitor, and an anticoagulant. Her vital signs on admission are: blood pressure 90/60 mmHg, temperature 36.7°C, respiratory rate 22/min, SpO₂ 93% on air, and pulse 135/min. She is drowsy but responds to voice and is more confused than usual. Her NEWS2 score is 13. Her chest X-ray shows right lower zone consolidation. What is your management?
- **9** A 30-year-old woman is sent to hospital by her general practitioner (GP) because she triggered on the community sepsis screening tool. She went to the GP that morning because of a fever, sore throat, and feeling awful. She has no past medical history. On examination, she has enlarged tonsils covered in white exudate. Her vital signs on arrival are: blood pressure 130/70 mmHg, temperature 38.9° C, respiratory rate 20/min, SpO₂ 98% on air, and pulse 115/min. Her NEWS2 score is 3. She is alert and walked in to the department. She is able to swallow. What is your management?
- 10 A 50-year-old woman attends the emergency department complaining of backache for the last 4 days. She was seen 2 days previously with the same symptoms and had X-rays of her lumbar spine which were normal. Her blood pressure was measured once during this visit and was recorded as 85/45 mmHg. She was given painkillers and sent home. The back pain is now worse and she has vomited twice. Her husband states that she appears to be confused and he is very concerned because she is 'not

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herself at all' and looks unwell. Her vital signs are: blood pressure 90/60 mmHg, temperature 36.7° C, respiratory rate 20/min, SpO₂ 96% on air, and pulse 110/min. She is alert and her NEWS2 score is 4. What is your management?

Self-Assessment: Discussion

- 1 This patient has sepsis. The purpuric rash is a pointer to meningococcal sepsis (although other infections can cause this rash). Her qSOFA score is 3 - call for senior help now. Start the sepsis six, starting with A (airway and oxygen therapy if required), B (breathing), and C (circulation). Establish intravenous access and take blood for cultures, full blood count, urea and electrolytes, liver tests, clotting, and lactate. Lactate can be measured either by the lab urgently or by most arterial blood gas machines. Broad spectrum antibiotics should be administered as per local guidelines. Ensure the patient is closely monitored and refer her immediately to the intensive care unit. In this case, the patient is hypotensive. Fluid challenges should be given to correct hypotension and hypoperfusion. Physiologically, 'fluid responsiveness' means that cardiac output depends on cardiac preload, i.e. the slope of the Frank-Starling curve is steep, as described in Chapter 5. Unfortunately, many studies have shown that fluid responsiveness, which is a normal physiological condition, exists in only half of patients receiving a fluid challenge in intensive care units.⁴⁰ Take care not to administer too much intravenous fluid in this case - early vasopressors are likely to be required.
- 2 This patient also has sepsis even though his blood pressure is normal. He has evidence of respiratory failure, acute kidney injury, and signs of infection causing a severe metabolic acidosis just at the bedside. Start the sepsis six, starting with A (airway and oxygen therapy if required), B (breathing e.g. treat any wheeze), and C (circulation). Blood should be sent as in case 1 and fluid boluses given to correct the metabolic acidosis. This patient may rapidly respond to fluid resuscitation and may simply require close ongoing monitoring of vital signs, respiratory function, and lactate levels. However, if there is a persisting metabolic acidosis and evidence of organ failure, he should be referred to the intensive care unit. Be aware he would be at risk of developing ALI/ARDS with over-aggressive fluid administration.
- This patient probably does *not* have sepsis. Many people with severe heart failure have a low blood pressure, so an important question to ask is what is normal for him. He *does* have pneumonia. Basal consolidation often causes hypoxaemia as described in Chapter 2. His lactate is normal. So far, there is no evidence of 'life-threatening organ dysfunction caused by a dysregulated host response to infection' – which is the definition of sepsis. He should be started on treatment for pneumonia as per local guidelines pending further assessment.
- 4 This patient probably has sepsis most likely meningococcal sepsis even though her NEWS2 score is 0. The rapidly appearing purpuric spots on her abdomen suggest a

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rapidly progressing disease. Start the sepsis six. Blood cultures should be sent and intravenous antibiotics administered without delay. She should be referred to the intensive care unit immediately. This is an example of when the NEWS2 score can be normal in a critically ill patient. (This patient went to intensive care and was ventilated and in multi-organ failure by the next morning.)

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- 5 This patient has sepsis. Start the sepsis six. Blood should be sent as in case 1, a urine sample should be obtained for culture, and broad spectrum intravenous antibiotics given. Fluid boluses should be given to treat hypotension and hypoperfusion. A venous blood gas should be obtained so lactate levels can be measured. She should be monitored closely. If hypotension and/or metabolic acidosis persist despite initial fluid therapy, she should be referred to the intensive care unit.
- 6 This patient also has sepsis, but young patients who are alert can look 'well' from the end of the bed and inexperienced clinicians may miss the fact that they are critically ill. This patient has a qSOFA score of 2 which predicts organ dysfunction, the need for ICU admission, and in-hospital mortality. Start the sepsis six. Intravenous access, blood tests and cultures, and broad spectrum intravenous antibiotics are a priority. In this case, you should also consider necrotising fasciitis and developing compartment syndrome which can cause rhabdomyolysis. The probability of necrotising fasciitis can be assessed using the LRINEC (Lab Risk Indicator for Necrotising Fasciitis) score.⁴¹ A score of ≥6 makes necrotising fasciitis likely, although a score less than this does not rule it out. If necrotising fasciitis is a possibility in any patient (suggested by a 'toxic' looking patient, rapid progression, severe pain, and sometimes crepitus at the site of the infection, which often looks like cellulitis), an emergency surgical consultation should be requested.
- 7 This patient is immunosuppressed. She has probably has sepsis caused by septic arthritis and may be developing acute lung injury (non-cardiogenic pulmonary oedema). Her qSOFA score is 2. This case also illustrates how immunosuppressed patients do not necessarily get a fever. Start the sepsis six: oxygen, intravenous access and send blood samples (including further cultures), and administer fluid challenges. Appropriate broad spectrum intravenous antibiotics should be given and she should be monitored closely. She should be referred to the intensive care unit. Arterial blood gas analysis and a repeat chest X-ray is also recommended to assess oxygenation, ventilation, and perfusion (ABC).
- 8 This patient probably does *not* have sepsis. This case illustrates the normal physiological decompensation that occurs in frail elderly patients who present with an acute illness, as described in Chapter 1. She does have a community-acquired pneumonia. She appears to have a hypoactive delirium. She probably has an acute kidney injury because of dehydration, infection, and pre-existing kidney disease and nephrotoxic medications. She is sick because of an infection. But that is not the same as sepsis which is a *dysregulated host response* to infection.

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- 9 This patient probably does *not* have sepsis. This case illustrates the problem of sepsis screening tools that ask clinicians to 'think sepsis' which are then used to diagnose sepsis. A clinical assessment by an experienced clinician is likely to reveal a patient with a normal response to infection tonsillitis in this case. A very high temperature causes tachycardia and increases the respiratory rate. Patients with tonsillitis feel unwell. If there are no signs of quinsy, the patient can swallow and there are no other concerns; the usual treatment for this condition is oral antibiotics and anti-pyretics with advice to seek medical attention if symptoms are not improving.
- 10 This patient might have sepsis. There are high-risk features present that should make you concerned: a systolic blood pressure ≤90 mmHg and new onset of confusion. Her husband is telling you he is concerned. This is an example of when a patient is clearly sick, but the cause is not immediately obvious. She has no fever. Hypotension and tachycardia could be due to bleeding or anaemia as well as sepsis. If you are in doubt and the patient is sick, start the sepsis six, call for senior help, and gather more information. This patient had pneumonia and died on intensive care of multi-organ failure.

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