Sepsis and the systemic inflammatory response

Definitions

Sepsis

Patients with suspected infection who have 2 or more of:

1. Hypotension – systolic blood pressure <100 mmHg
2. Altered mental status – Glasgow Coma Scale score ≤14
3. Tachypnoea – respiratory rate ≥22 breaths/min

Sepsis can also be diagnosed by suspected infection and an increase of ≥2 points on the Sequential Organ Failure Assessment (SOFA) score (p. 214)

Septic shock

Septic shock is the clinical manifestation of overwhelming inflammation . It is characterised by excessive production of pro-inflammatory cytokines by macrophages, causing hypotension, hypovolemia and tissue edema

A subset of sepsis with underlying circulatory or cellular/metabolic abnormalities associated with a substantially increased mortality:

- **Sepsis and both of (after fluid resuscitation):**
    1. Persistent hypotension requiring vasopressors to maintain a MAP >65 mmHg
    2. Serum lactate >2 mmol/L (18 mg/dL

Sepsis is one of the most common causes of multi-organ failure.
Sepsis requires the presence of infection with a resultant systemic inflammatory state; organ dysfunction occurs from a combination of the two processes.

etiology and pathogenesis

To understand how an infection can lead to progressive multi- organ failure, it is essential to have a grasp of the pathophysiology.

Initiation of the inflammatory response

The process begins with infection in one part of the body that triggers a localized inflammatory response. Appropriate source control and a competent immune system will, in most cases, contain the infection at this stage. However, if certain factors are present, the infection may become systemic. The causative factors are not fully elucidated but probably include:

- a genetic predisposition to sepsis
- a large microbiological load
- high virulence of the organism
- delay in source control (either surgical or antimicrobial)
- resistance of the organism to treatment
- patient factors (immune status, nutrition, frailty).

Mediators are released from damaged cells coupled with direct stimulation of immune cells by the molecular patterns of the microorganism, trigger the inflammatory response. An example of such direct stimulation is that of lipopolysaccharide, which is found on the surface of Gram-negative bacteria.

Viral and fungal infections can cause a syndrome that is clinically indistinguishable from bacterial sepsis.

Propagation of the inflammatory response

Once activated, immune cells such as macrophages release the inflammatory cytokines , which, in turn, activate neutrophils. Activated neutrophils express adhesion factors and release various other inflammatory and toxic substances; the net effects are vasodilatation and damage to the endothelium.

Activation of the coagulation system

Damaged endothelium triggers the coagulation cascade and thrombus forms within the microvasculature. A vicious circle of endothelial injury, intravascular coagulation and microvascular occlusion develops, causing more tissue damage and further release of inflammatory mediators.
In severe sepsis, intravascular coagulation can become widespread. This is referred to as disseminated intravascular coagulation (DIC) and usually heralds the onset of multi-organ failure.

Lactate physiology

Lactate is an excellent biomarker for the severity of sepsis.
Hyperlactataemia (serum lactate > 2.4 mmol/L or 22 mg/dL) is used as a marker of severity. it is caused by all types of shock and therefore is not specific to sepsis. A lactate level of > 8 mmol/L (>73 mg/dL) is associated with an extremely high mortality and should trigger immediate escalation.

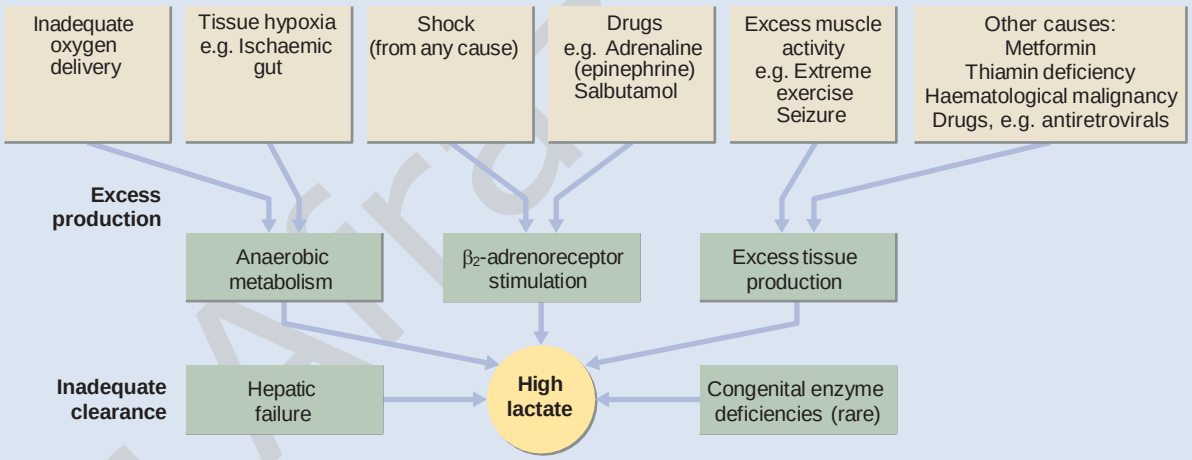

Fig. 10.13 Physiology of hyperlactataemia.

The anti-inflammatory cascade

As the inflammatory state develops, a compensatory antiinflammatory system is activated . While such mechanisms are necessary to keep the inflammatory response in check, they may lead to a period of immunosuppression after the initial septic episode.

Organ damage from sepsis

Any and all organs may be injured by severe sepsis. The pathological mechanisms are shown in Figure 9.13

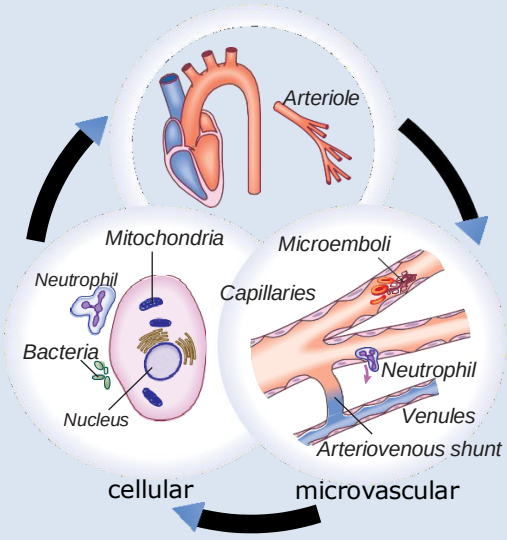

Fig. 10.12 Pathophysiology of organ damage in sepsis.

Macrovascular. Severe hypovolaemia, vasodilatation or septic cardiomyopathy can reduce oxygen delivery, causing tissue hypoxia. Paradoxically, most patients with sepsis have an increased cardiac output and oxygen delivery. *Microvascular*. Tissue injury can occur from hypoxia secondary to microvascular injury and thrombosis. Damaged epithelium permits neutrophils, proteins and fluid to leak out.

Shunting. Organs fail in sepsis despite supranormal blood flow. It is likely that arteriovenous shunt pathways exist within vascular beds; these shunts open up in septic shock.

Cellular. Cells are damaged by a number of mechanisms in sepsis: (1) direct injury by microorganisms; (2) injury from toxins produced by immune cells, e.g. oxygen free radicals; (3) mitochondrial injury causing cytopathic hypoxia – cells are unable to metabolise oxygen; (4) apoptosis – if the cell injury is sufficient, capsase enzymes are activated within the nucleus and programmed cell death occurs; (5) hypoxia from micro- and macrovascular pathology.

Management

The most important action is to consider sepsis as the cause of a patient's deterioration. Aligned to this is the requirement to consider other diagnoses that could be causing the presentation, such as haemorrhage, PE, anaphylaxis or a low cardiac output state.

Resuscitation in sepsis

Early resuscitation can be aided by following the requirements of the 'Sepsis Six'

1. Deliver high-flow oxygen
2. Take blood cultures
3. Administer intravenous antibiotics
4. Measure serum lactate and send full blood count
5. Start intravenous fluid replacement
6. Commence accurate measurement of urine output

Red cell transfusion should be used to target a haemoglobin concentration of 70–90 g/L (7–9 g/dL).
Albumin 4% can be used as colloid solution and has the theoretical benefit of remaining in the intravascular space for longer than crystalloid.
Early intubation is recommended in severe cases to facilitate further management and reduce oxygen demand.
Appropriate **antibiotics** should be administered as early as possible .

10.29 Early administration of antibiotics in suspected sepsis

- Broad-spectrum antibiotics should be administered as soon as possible after sepsis is suspected
- Every hour of delayed treatment is associated with a 5–10% increase in mortality

The antibiotic choice will depend on local patterns of resistance, patient risk factors and the likely source of infection.
samples (such as blood cultures, urine or CSF) should be taken, but this should not delay antibiotic administration, if obtaining samples is difficult.

Early source control

Source control requires an accurate diagnosis; urgent investigations should be performed as soon as possible. A CT scan of the chest and abdomen with contrast is a high-yield test in this context. Specific points in the history should be reviewed, such as risk factors for human immunodeficiency virus (HIV), contacts with tuberculosis and underlying immune status.

Noradrenaline (norepinephrine) for refractory hypotension

Central venous access should be established early in the resuscitation process and a noradrenaline infusion commenced.
Early vasopressor use may improve the outcome from acute kidney injury

Other therapies for refractory hypotension

Refractory hypotension is due to either inadequate cardiac output or inadequate systemic vascular resistance . It may be necessary to add vasopressin (antidiuretic hormone, ADH). This is a potent vasoconstrictor that may be used to augment noradrenaline (norepinephrine) in achieving an acceptable MAP. Intravenous glucocorticoids are also commonly used in refractory hypotension. There is little evidence that they improve the overall outcome, but they do lead to a more rapid reversal of the shocked state. There is a small increased risk of secondary infection following glucocorticoid use.

Septic cardiomyopathy

The myocardium can be affected by the septic process, presenting as either acute left or right ventricular dysfunction.
A bedside echocardiogram is particularly useful to confirm the diagnosis, as ECG changes are usually non-specific.
Dobutamine or adrenaline (epinephrine) can be used to augment cardiac output, and intravenous calcium should be replaced if ionized calcium is low.
Other interventions such as intravenous bicarbonate in profound metabolic acidosis, high-volume haemofiltration/haemodialysis and extracorporeal support are sometimes used, but currently lack evidence of benefit.

Review of the underlying pathology

While sepsis is the most common cause of acute systemic inflammation, up to 20% of patients initially treated for sepsis will have a non- infectious cause, that is, a sepsis mimic

Sepsis mimics

- Pancreatitis
- Drug reactions
- Widespread vasculitis – catastrophic antiphospholipid syndrome, Goodpasture's syndrome
- Autoimmune diseases – inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus
- Malignancy – carcinoid syndrome
- Haematological conditions – haemophagocytic syndrome, diffuse lymphoma, thrombotic thrombocytopenic purpura

These conditions should be considered where
o the clinical picture is not typical,
❷ no source of sepsis can be found, or
❸ the inflammatory response seems excessive in the context of local infection