Sepsis

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Abstract

Sepsis is a clinical syndrome that requires prompt recognition and control in order to optimize clinical outcomes in patients. It is very relevant to surgical practice, as it can affect perioperative patients and those recovering on surgical wards. A working knowledge of sepsis is essential to any medical or surgical practitioner, and here we cover the topic with relevance to surgery and the MRCS examination.

Keywords Antimicrobial stewardship; Definitions of sepsis; Pathophysiology of sepsis; Sepsis; Septic shock

Introduction

Sepsis is a clinical syndrome characterized by a dysregulated host response to infection, which can lead to life-threatening multiple organ dysfunction and death. It can be both an indication for surgery or a complication of it, and prompt identification and management of patients with sepsis is key to dramatically improving patient outcomes. As such, a practical knowledge of sepsis and septic shock is of critical importance in surgical practice and perioperative care of the surgical patient.

For the MRCS examination, sepsis and septic shock are found in two parts of the curriculum: Module 1 Basic Sciences and Module 5 Perioperative Management.

In this article we will outline advances in current understanding of sepsis with an up-to-date guide through its definitions, identification and management.

Epidemiology

The incidence of sepsis is increasing, with millions of new cases worldwide each year. Hospital episode statistics confirm rates are increasing in the UK (Figure 1). A recent study found that sepsis was the cause of 26% of cases of deterioration in hospital, carrying a 22% mortality rate.[1] A study of critical care outreach referrals found that 39% of ward referrals had sepsis, with a 25% mortality rate.[2]

Risk factors for sepsis are summarized in Table 1. Mortality estimates range from 10% to 52%, depending on disease severity. Factors associated with a poor prognosis in sepsis include immunosuppression, comorbidity, extremes of age, and inappropriate or late antibiotic treatment.

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Even following discharge from hospital, sepsis carries an increased risk of death as well as an increased risk of further episodes of sepsis and recurrent hospital admissions. There is also significant associated morbidity after sepsis, with many patients experiencing reduction in daily physical function, psychological disturbance, and on-going problems in a variety of systems (e.g. sensory, respiratory, digestive and musculoskeletal).[4]

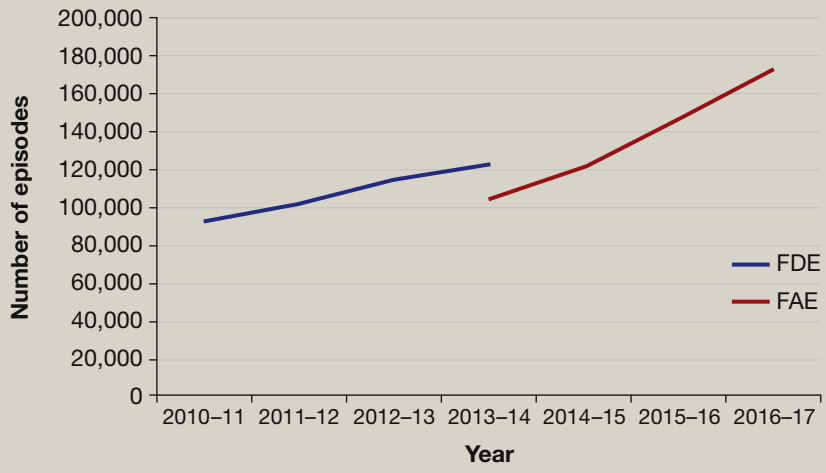
Pathophysiology

Sepsis can be thought of as a syndrome of physiological, pathological and biochemical abnormalities accompanied by organ dysfunction, that arise due to a dysregulated host response to infection. The pathophysiology is complex and as yet incompletely understood, but involves changes in cell biology, morphology, biochemistry and immunology, including activation of both pro- and anti-inflammatory pathways. Downstream effects on the cardiovascular, neuroendocrine, metabolic and coagulation systems lead to tissue hypoperfusion and impaired mitochondrial function causing organ dysfunction. Host genetic and environmental factors that induce variation in these pathways underlie some of the differences seen between individuals in the presentation of sepsis.

The normal response to infection involves the recognition and processing of microbial components by host innate immune cells (such as macrophages). Pattern recognition receptors are able to recognize and bind pathogen-associated molecular patterns (PAMPs) of microorganisms. Additionally, pattern recognition receptors can recognize danger-associated molecular patterns (DAMPs), which are cellular structures of the host in the extracellular environment – signaling host cell damage. The binding of these structures triggers the activation of genes involved in the host's inflammatory response, producing pro-inflammatory cytokines, chemokines, adhesion molecules and vasoactive substances including nitric oxide. Adhesion molecules are expressed on the vascular endothelium near the site of infection, and these attract leukocytes. Polymorphonuclear leukocytes (PMNs, such as neutrophils) activate and express their own adhesion molecules to aggregate on the endothelium in the site of infection. From here, they migrate to the site of infection, and release their own set of mediators that self-reinforce the response. These PMNs, along with other cell types (including macrophages) kill and ingest pathogens and debris in the infected tissue. The process is tightly regulated by the fine balance between pro-inflammatory and anti-inflammatory signals, which dictate the recruitment, activation and inhibition of immune cells. When the infectious insult is cleared, the inflammatory drive will reduce and anti-inflammatory mediators prevail, allowing the tissue to begin the process of repair. Sepsis develops when the pro-inflammatory response is signaled outside of the local tissue, resulting in systemic inflammation and organ dysfunction.

Previous understanding of sepsis has been as a disorder comprising a massive pro-inflammatory storm – i.e. a hyper-inflammatory disease. Later it became apparent that there was an anti-inflammatory period following an initial hyper-inflammatory phase, comprising a hypo-inflammatory phase. Current understanding is that these phases are seen in patients with sepsis, but the pro-inflammatory and anti-inflammatory mechanisms underlying them do not occur in such a temporal manner one after the other.

Number of sepsis episodes in the UK according to hospital episode statistics (2010-2017).[3]



FAE = finished admission episodes with a primary or secondary diagnosis of sepsis, and FDE = finished discharge episodes with a primary or secondary diagnosis of sepsis[3].

Figure 1

Rather, sepsis comprises simultaneous pro-inflammatory and anti-inflammatory mechanisms with the general phenotype of a hyper-inflammatory phase followed by a hypo-inflammatory phase. The precise phenotype depends on pathogenic load and virulence, host genetic characteristics (e.g. single nucleotide polymorphisms of genes encoding pro-inflammatory cytokines) and concomitant disease.

The hyper-inflammatory phase comprises a self-reinforcing pro-inflammatory response, mediated by sharp rises in inflammatory cytokines (such as tumour necrosis factor alpha (TNFa), interferon gamma, and interleukin-1), bacterial cell wall components and products (endotoxins), and activation of the complement cascade. Most patients who die in the first days of sepsis will likely die as a result of this profound hyper-inflammatory

Risk factors for developing sepsis

Increased risk of infection	• Environmental factors (hygiene, sanitation) • Susceptibility of individual organs to infection, e.g.: ○ Chronic obstructive pulmonary disease, bronchiectasis — respiratory infections ○ Lymphoedema, ulcers, psoriasis etc. — skin infections ○ Indwelling foreign bodies — urinary catheters and urinary infections, IV lines and skin infections ○ Recent trauma, surgery or invasive procedure
Impaired immune response	• Diabetes • Congenital immunodeficiency syndromes • HIV/AIDS • Neutropenia • Splenectomy/hyposplenism • Iatrogenic (corticosteroids, chemotherapy, biological agents) • Other chronic conditions (e.g. malnutrition, diabetes mellitus, malignancy)
Pre-existing organ dysfunction	• Increased risk of organ failure from reduced physiological reserve, e.g. heart failure, chronic respiratory disease, chronic kidney disease
Extremes of age	• Neonates and infants (immature immunity, limited physiological reserve) • Elderly patients (immune senescence, comorbidity)
Other genetic factors	• Ethnicity (incidence higher among some racial groups) • Sex (incidence higher among male patients) • Specific immune defects, e.g. defect in terminal complement pathway leading to increased risk of meningococcal sepsis
Infection management	• Delayed or inappropriate initial treatment of bacterial infections increases the risk of progression to sepsis

Table 1

Cellular injury in sepsis

Tissue ischaemia	• Metabolic autoregulation is the normal process that matches oxygen delivery to the temporally variable oxygen requirement of tissues. Significant disruption of this process is typical of sepsis, and may be as a result of lesions in the arterioles or capillaries (i.e. microcirculation), or injury of the endothelium itself • Microcirculatory lesions may result from imbalances in clot formation and breakdown due to faulty coagulation and fibrinolytic systems. In addition to this, erythrocytes lose their normal deformability during sepsis, and may occlude microvessels • There is increased adherence of activated neutrophils to the endothelium in sepsis. This stimulates the release of reactive oxygen species, lytic enzymes and vasoactive substances such as nitric oxide, which may injure endothelial cells. Lipopolysaccharide from the bacterial membrane can also cause disruption of endothelial cell cytoskeleton and barrier integrity
Apoptosis (programmed cell death)	• Apoptosis is the normal process by which inflammation ceases once an infection has subsided. As such this is normally a protective process, but it is altered via at least two mechanisms in sepsis • Delayed apoptosis in activated macrophages and neutrophils may be as a result of pro-inflammatory cytokines, and this prolongs the hyper-inflammatory phase of sepsis, contributing to organ failure • Increased apoptosis is induced in lymphocytes and dendritic cells, reducing the clearance of microorganisms and debris. This augments the immunosuppressive syndrome in sepsis and exposes patients to superimposed infection
Cytotoxic injury	• The mechanism of cytotoxicity in sepsis is thought to be via mitochondrial injury. Mitochondrial dysfunction is evident by reduced cellular adenosine triphosphate production in sepsis, and can be a result of direct inhibition of respiratory enzyme complexes, oxidative stress, or mitochondrial DNA damage • Important contributory factors to mitochondrial injury include nitric oxide, TNFa, endotoxin as well as an environment of depleted antioxidants and supranormal oxygen tension • Mitochondrial injury may be more important in organ dysfunction than cell death, as studies have suggested that the degree of organ dysfunction is not related to extent of cell death.[6] Indeed, as we have seen above, programmed cell death of damaged cells is prolonged in sepsis. Mitochondrial injury may be a further therapeutic target for prevention of organ failure

Table 2

phase and resulting organ failure. Patients unable to mount an acute pro-inflammatory response may be more difficult to diagnose with sepsis, as symptoms may be subtle with, for instance, alterations in mentation being the only clue to sepsis.

Resolving inflammation does not occur simply as a result of a relinquishing pro-inflammatory response. Rather, this is an active and coordinated process dependent on anti-inflammatory mediators. This anti-inflammatory response is mediated by anti-inflammatory cytokines (i.e. those that suppress the immune system by inhibiting cytokine production by mononuclear cells and monocyte-dependent T helper cells). Examples of anti-inflammatory cytokines include interleukin-1 receptor antagonist, and interleukins-4, -6, and -10. Note that some cytokines have both pro- and anti-inflammatory effects, depending on the receptor they activate and its downstream cellular effects.

After the initial hyper-inflammatory phase it has been observed that there is a hypo-inflammatory phase, in which the anti-inflammatory response to sepsis dominates, but immunocompromise becomes an issue. The majority of focus in sepsis management has been centred on the hyper-inflammatory phase, but patients who get through this stage of sepsis into a hypo-inflammatory phase may require an alternative therapeutic approach in immunostimulation.[5] The problems facing these patients surround further infection from latent bacterial foci or latent viral infection, as well as opportunistic or superimposed nosocomial infections. As such, patients dying further down the line with sepsis likely die as a result of superimposed infection in an immunosuppressed state.

During sepsis, organ dysfunction occurs as a result of cellular injury. At the cellular level there is incomplete understanding of the precise mechanism of injury; but tissue ischaemia, apoptosis, and cytotoxic injury are contributory to the disorder (Table 2).

At a systemic level, no organ system can avoid the effects of sepsis. Cellular injury results in organ dysfunction and failure in a variety of systems and contributes to swift clinical decline. The most common systems affected are included in Table 3, and the extent of dysfunction depends on the same factors contributing to the sepsis phenotype: pathogenic load and virulence, host genetic characteristics and concomitant disease.

Clinical definitions of sepsis

The third international consensus definitions of sepsis and septic shock[7] ('Sepsis-3', Box 1) have been endorsed by the UK Academy of Medical Royal Colleges and are incorporated into the new Surviving Sepsis Campaign international guidelines.[8] Once past the basic descriptive definitions, however, considerable difficulty arises in providing pragmatic definitions of sepsis for clinical, epidemiological and research purposes, and there is no consensus on the best clinical definition.

Various definitions have been proposed (Box 2). While these definitions differ in detail, the fundamentals are essentially the same: all seek to identify patients with severe infection, and thus

Systems in sepsis

Immune	The immune system is affected by sepsis on a cellular level and at the organ level, exemplified by the spleen and lungs. In particular at the level of the spleen, it has been shown that secretion of pro-inflammatory cytokines from splenocytes is markedly reduced when stimulated with pro-inflammatory mediators, and there is depletion of CD4+ and CD8+ T cells. In the lungs and spleen during sepsis there is increased expression of inhibitory receptor and ligands, as well as expansion of suppressor cell populations The immunosuppression found in sepsis may offer novel therapeutic approaches utilising immunostimulatory techniques
Neurological	The central nervous system is commonly affected in sepsis. Pathogenesis is not completely understood and is generally attributed to inflammatory mediators bringing about changes in cell signalling and metabolism, rather than direct infection of the brain and surrounding tissues (although this does occur). These cellular changes occur via several possible mechanisms and occur before any functional neurological deficit is observed Similarly to other tissues, impaired autoregulation of blood flow affects the cerebral microvasculature, with perivascular oedema, haemorrhage and ischaemia all possible Blood brain barrier dysfunction may result in infiltration of leukocytes, toxic mediators and cytokines, as well as neurotransmitter alterations Neuro-inflammatory reflex: • Carotid body chemoreceptors, vagal afferent nerves and brain areas respond to cytokines • These signal to brainstem nuclei that send signals via vagal efferent nerves • This results in acetylcholine release, and in turn this inhibits inflammatory cytokine production by immune cells in tissues including the spleen
Cardiovascular	Profound, resistant hypotension puts septic patients at risk of sudden decline. Globally within the cardiovascular system three mechanisms contribute to this 1. Vasoactive mediators including nitric oxide produce diffuse vasodilation 2. Intravascular fluid redistributes to the interstitium with increased endothelial permeability 3. Antidiuretic hormone secretion is reduced (as such, vasopressin is often found to be of use for patients requiring pharmacological blood pressure support) *Coagulation*: Sepsis is commonly associated with a pro-coagulant state and disseminated intravascular coagulation. Inflammation results in excessive fibrin deposition due to increased tissue factor, and reduced fibrin removal due to depression of fibrinolysis. Anticoagulant mechanisms (e.g. protein C and antithrombin systems) are also impaired in sepsis *Endothelium*: Direct and indirect interaction between bacterial components and the endothelium bring about an array of changes to its normal regulatory mechanisms. Tissue oedema results from increased permeability, adhesion of leukocytes, pro-coagulant properties and vasodilation *Capillaries*: Endothelial and coagulation changes result in luminal obstruction of microvessels. This may be via intraluminal microthrombi or non-deformable erythrocytes, or extraluminal pressure (e.g. from tissue oedema). Reduction in the number of functional capillaries also contributes to hypoxia and capillary pressures *Small vessels*: Normally in hypoxic states, blood flow is redirected from splanchnic organs to the heart and brain. In sepsis, this is disrupted via vascular hypo-responsiveness effects — i.e. reduced vasoconstrictive ability *Heart and large vessels*: Biventricular dysfunction occurs due to release of myocardial depressant substances, resulting in impaired systolic and diastolic performance. Despite this, there is commonly preservation and indeed increase in cardiac output. High lactate levels in these patients are related to increased mortality
Respiratory	Lung injury in sepsis is due to endothelial damage and altered microvascular flow. Enhanced permeability causes pulmonary and alveolar oedema, contributed to further by neutrophil entrapment Pulmonary oedema causes ventilation-perfusion mismatch and hypoxaemia. Along with arterial hypoxaemia and reduced lung compliance, this comprises the underlying pathology of Acute Respiratory Distress Syndrome seen in many septic patients
Renal	Acute kidney injury is common in sepsis, and substantially increases mortality. The notion that injury is as a result of hypoperfusion and associated hypoxaemia is not a full explanation, as sepsis has in fact been associated with normal or increased renal blood flow. There is alteration in the distribution of this blood flow, however, from the cortex to the medulla. Mechanisms may include direct renal vasoconstriction, release of pro-inflammatory cytokines, and activation of neutrophils in the renal vasculature
Hepatic	In the liver, sepsis impairs hepatic clearance. This results in cholestasis from impaired bilirubin clearance, and also disrupts the clearance of bacteria and their products entering the portal system from the gut. These may subsequently spillover into the systemic circulation
Gastrointestinal	Pro-inflammatory cytokines impair gastrointestinal barrier function in sepsis. This enables injury by luminal contents, such as pancreatic enzymes (i.e. autodigestion), and may allow translocation of bacteria and endotoxins into the systemic circulation

Table 3

Sepsis-3 definitions of sepsis and septic shock

Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection

Septic shock: a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone (hospital mortality rates >40%)

Box 1

require evidence of both infection (or suspected infection) and illness severity. The tools differ in how severity is defined - all are imperfect. They nevertheless provide both practical tools to aid rapid identification of sepsis in clinical practice, and case definitions for research.

Sepsis-3 guidelines

The Sepsis-3 guidelines published in 2016 (Box 1) defined sepsis as infection plus organ dysfunction measured by the Sequential Organ Failure Assessment (SOFA) score. Due to many of the parameters within the SOFA score requiring ICU-level monitoring, a quick SOFA (qSOFA) score was developed for ward-based assessment (Box 2). Septic shock is defined as the need for vasopressors to maintain a mean arterial pressure ≥65 mm Hg and a serum lactate >2 mmol/L in the absence of hypovolemia. These definitions replaced previous definitions based on SIRS criteria.

NICE sepsis guidelines

The UK National Institute for Health and Care Excellence (NICE) published the first national guidance for sepsis management in 2016. The NICE guidelines provide the basis for a consistent national approach to sepsis recognition and management based on a structured assessment and risk stratification. Like the Sepsis-3 guidelines they helpfully simplify the terminology, dropping the concept of 'uncomplicated sepsis', so that the term 'sepsis' now always — and appropriately — means a severe infection requiring prompt treatment.

The NICE guidelines do not use the international consensus definitions of sepsis, however. Instead patients with suspected sepsis are risk stratified according to defined 'high risk' ('red flag'), 'moderate to high risk ('amber flag') and 'low risk' criteria (Table 4). Management is then contingent on the presence or absence of these criteria, such that patients with 'high-risk' criteria require urgent clinical review and management for sepsis; those with 'moderate to high risk' criteria require clinical review within an hour and initiation of antibiotics within 3 hours if treatment appropriate; and those with 'low-risk' criteria only may be observed and treated according to clinical judgment.[9]

Although overall the NICE guidelines build on existing tools and progress in the management of sepsis, they have nevertheless attracted criticism for the complexity of some of the treatment algorithms, which makes them difficult to implement and for which there is a limited evidence base. Failure to include neutropaenia in the high-risk criteria is also inconsistent with established practice and other guidelines that appropriately prioritize this group for urgent treatment. As a result, many acute hospital Trusts have elected not to implement the NICE

Timeline of sepsis definitions

1. ***1991 — SIRS (Systemic Inflammatory Response Syndrome) based definitions***

Initial definitions focused on the then-prevailing view that sepsis resulted from a host's systemic inflammatory response to infection.

a. Sepsis with organ dysfunction was termed severe sepsis
b. Severe sepsis could progress to septic shock - I.e. 'sepsis-induced hypotension despite adequate fluid resuscitation'

2. ***2001 — SIRS continued***

An international task force recognized the limitations of these definitions, particularly the inadequate sensitivity and specificity of SIRS criteria, an excessive focus on inflammation, and a misleading model of progression through a continuum of sepsis stages. Due to lack of supporting evidence they could not offer alternative diagnostic criteria, but expanded upon previous diagnostic criteria.

3. ***2016 — Sepsis-3***

An international task force, equipped with a data from large cohorts thanks to more electronic record keeping, provided the latest revision of 'international consensus' definitions for sepsis. This included more focus on parameters signifying organ dysfunction, bundled into the Sequential Organ Failure Assessment (SOFA) score. A quick SOFA (qSOFA) score was developed for ward-based assessment. The presence of 2 or more of the following qSOFA criteria identified adult patients with suspected infection at highest risk of poor outcome:

- altered mentation
- systolic blood pressure ≤100 mm Hg
- respiratory rate ≥22/min

4. ***2016 — UK National Institute for Health and Care Excellence (NICE) Sepsis Guidelines***

These guidelines were developed to provide a nationally standardized approach to the early identification and management of sepsis. Sepsis risk/severity is stratified according to high, moderate to high, and low risk sepsis criteria (see Table 2 and main text for further information).

5. ***2017 — National Early Warning Score (NEWS) 2***

Alongside the evolution of sepsis definitions, the NEWS was developed as a tool for monitoring patients regularly and flagging patients who were acutely unwell in order to prompt clinical review. Large studies suggest that NEWS performs better than SIRS based criteria and qSOFA for identification of patients with sepsis at risk of death or ICU transfer.

NEWS 2 is the latest version of this clinical assessment tool and includes specific guidance about the recognition of sepsis (see Figure 1 for NEWS parameters, and the main text for further information).

Box 2

NICE criteria for sepsis risk stratification

High risk ('red flag')

- Behaviour:
  - Objective evidence of new altered mental state
- Heart rate:
  - >130 bpm
- Respiratory rate:
  - ≥25 rpm
    OR
  - New need for ≥40% O_2 to maintain saturation >92% (>88% in known COPD)
- Systolic blood pressure:
  - <90 mmHg or less OR
  - >40 mmHg below normal
- Urine output:
  - Anuric in previous 18 hours, or for catheterized patients passed <0.5 ml/kg of urine/h
- Mottled or ashen appearance
- Cyanosis of skin, lips or tongue
- Non-blanching rash of skin

Moderate to high risk ('amber flag')

- Behaviour:
  - (Collateral) history of altered behaviour or mental state
  - History of acute deterioration of functional ability
- Impaired immune system (illness or drugs, including oral steroids)
- Trauma, surgery or invasive procedures in the last 6 weeks
- Respiratory rate:
  - 21–24 rpm
- Heart rate:
  - 91–130 bpm
  - For pregnant women, 100–130 bpm
- New-onset arrhythmia
- Systolic BP 91–100 mmHg
- Urine output:
  - Anuric in the past 12–18 hours, or for catheterized patients passed 0.5–1 ml/kg of urine/h

Tympanic temperature less than 36°C

Signs of potential infection:

- Redness
- Swelling/discharge at surgical site
- Breakdown of wound

Low risk

- Normal behaviour
- No high risk or moderate to high risk criteria met
- No non-blanching rash

Table 4

sepsis algorithms in full, and a range of simplified algorithms are in use.

UK National Early Warning Score (NEWS)

The UK national approach to sepsis identification is also now moving in the direction of simplification. One of the limitations of all published clinical definitions of sepsis is the need for sepsis-specific screening tools. In clinical practice, however, sepsis is only one potential cause of severe illness that a clinician must consider. Early warning ('track and trigger') scores are widely used to identify patients at risk of clinical deterioration, so incorporation of sepsis screening into these tools is an attractive prospect.

Recent evidence demonstrating that the UK National Early Warning Score (NEWS) performs better than both SIRS-based and Sepsis-3 criteria for identification of sepsis suggests that such an approach should be both practical and effective.[10] In one large study of over 30,000 patients, Churpek and colleagues showed that of all the tools evaluated a NEWS score of ≥5 was the best predictor of death or ICU transfer due to sepsis.[11]

Recognizing this, the recently updated National Early Warning Score (NEWS2) from the Royal College of Physicians recommends that sepsis is considered in any patient with a known, suspected, or high risk of infection, and a NEWS2 score of 5 or more; and that these patients have an urgent clinical review with a high index of suspicion for sepsis. Published data on the performance of NEWS2, which incorporates additional parameters, are awaited. However the consistency of this approach with the Sepsis-3 and NICE guidelines is worth highlighting, since a NEWS2 score of ≥5 approximates very closely to a qSOFA score of ≥2, and would usually accompany NICE high risk criteria.[12]

NEWS2 has been endorsed by NHS England and NHS Improvement and its implementation has recently been mandated across the NHS in England, including to detect clinical deterioration in patients with suspected sepsis[13] in order to promote standardized care.

Initial management

The key priority in the management of sepsis is early recognition and treatment. With information from clinical assessment of a patient's history and examination, a diagnosis of sepsis can usually be made empirically, aided by rapidly available laboratory results. Physiological parameters and their need for support can be useful in making decisions regarding the optimal location of care: ward-based or on a high-dependency or intensive care unit. Radiological and microbiological data help in identifying the cause and tailoring antimicrobial therapy accordingly, but these investigations should not delay prompt treatment in the presence of sepsis.

Management includes antibiotics, organ support and source control. The Sepsis Six care bundle (Box 3) provides a

Sepsis Six Care Bundle

Sepsis Six Care Bundle (mnemonic: *"take 3 and give 3"*)

1. Take bloods
   - Venous blood gas (including lactate - consider serial lactate measurement)
   - Blood glucose
   - FBC, U&E, CRP, LFT, clotting
2. Take cultures
   - Blood cultures
   - Consider other cultures (e.g. urine, CSF, pus) as clinically indicated
3. Monitor urine output
   - Start accurate hourly urine output measurement
   - Consider urinary catheter (e.g. in septic shock)
4. Give Oxygen if hypoxic
   - Titrate to oxygen saturations (SaO_2)
   - Target SaO_2>94% (88–92% if at risk of hypercapnic respiratory failure)
5. Give Fluids guided by clinical assessment and lactate
   - E.g. stat bolus IV crystalloid 500mL
   - Repeat as necessary, monitoring clinical response
6. Prompt empirical intravenous antibiotics according to local protocols
   - Administer antibiotics as quickly as possible and within 1 hour

Box 3

simple way of delivering the basic elements of care in a timely fashion. In one study, delivery of the sepsis six care bundle within 1 hour was associated with a more than 50% reduction in mortality.[14] However a 2015 National Enquiry into Patient Outcome and Death (NCEPOD) report found that management of patients with sepsis was good in only a third of cases.[15]

Obtaining specimens for microbiology

An attempt should always be made to make a microbiological diagnosis to guide further antimicrobial treatment and investigations. As antibiotics reduce the sensitivity of culture, specimens should ideally be obtained before starting antimicrobial therapy. It should almost always be possible to obtain blood cultures prior to administering antibiotics. If possible without incurring a long delay, other relevant specimens should be obtained for culture prior to antibiotics, guided by the clinical presentation. Examples of specimens that might be obtained relatively quickly include urine (suspected urinary tract infection); joint aspirates (suspected septic arthritis); and pus (incision and drainage of abscess). The timing of specimen collection should be balanced against the need to initiate antibiotic therapy promptly, and is therefore a clinical decision informed by the patient's clinical condition, available resources, and the role of source control (see below).

Further management and escalation

Further management is guided by the individual presentation, and includes:

- frequent observations (e.g. every 30 minutes initially)
- investigations to identify the infection focus or alternative diagnoses
- source control if appropriate (see below)
- serial blood tests (e.g. lactate) guided by clinical response.

Patients with septic shock or a persistently elevated lactate (e.g. >4 mmol/L), or who remain critically ill despite aggressive medical management, should be referred to the critical care team for review. Early referral is associated with improved outcomes.

Source identification and control

Once treatment is initiated in a patient with recognized sepsis, the next step is to attempt source identification, tailored to findings on clinical examination. For example, urinalysis, imaging or cerebrospinal fluid sampling may be appropriate to identify the source of sepsis and target therapy towards this. Discussion with senior members of the team will help guide the best methods for source identification. Any indwelling foreign bodies that may be contributory to infection should be considered for removal if necessary and feasible, and cultured where appropriate. If source control requires input from particular teams (e.g. general surgery, orthopaedics), discussions should be initiated early to gain source control as quickly as possible in the course of disease.

Antimicrobial stewardship

Antimicrobials should be reviewed daily in the light of clinical response and investigations including culture results. Antibiotics should then be narrowed or stopped as soon as possible, guided by clinical progress and the available evidence for treatment of a particular clinical syndrome. This is important to limit selection of antimicrobial-resistant organisms in the patient's own microbiome, which not only increases the general pool of antimicrobial resistance at a population level, but importantly also serves as the reservoir for their own future infections. ◆

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