Sepsis is an overwhelming, uncontrolled, systemic inflammatory response that is mediated by the immune system and inflammatory pathways in response to an infection. In 2010, an international lay definition was agreed—the Merinoff definition of the Global Sepsis Alliance, which succinctly describes what sepsis is (The Global Sepsis Alliance, 2010). It is also a very helpful summary definition for health professionals.

The Merinoff definition (lay definition) is as follows: ‘Sepsis is a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs. Sepsis can lead to shock, multiple organ failure and death especially if not recognised early and treated promptly. Sepsis remains the primary cause of death from infection despite advances in modern medicine, including vaccines, antibiotics and acute care. Millions of people die of sepsis every year worldwide.’ It is estimated that there are up to 37 000 deaths per year in the UK (National Intensive Care Audit data; Harrison et al, 2006).

Sepsis is a medical emergency like stroke, heart attack, or major trauma, and, in common with these conditions, there is a small window of opportunity in which timely treatment can dramatically improve survival. There are few other disease processes with such a high risk of mortality. An admission with severe sepsis places the patient at a level of risk many times greater than if he/she were admitted with an acute myocardial infarction or acute stroke.

Unfortunately, sepsis is not recognised as a medical emergency, and patients do not experience rapid transfer to specialist centres, such as hyper-acute stroke units or major trauma centres. There is also no national target for sepsis care, unlike for the major cancers or for heart attack or stroke.

The incidence of sepsis has been dramatically increasing by an annual rate of 8–13 % over the last decade, and it now claims more lives than bowel cancer and breast cancer combined (Vincent et al, 2006). Reasons are diverse, but include an ageing population, increasing use of high-risk interventions in all age groups, and development of drug-resistant and more virulent varieties of microbes.

It has been estimated in European studies that a typical episode of severe sepsis costs a healthcare organisation approximately €25 000 (Vincent et al, 2006). Assuming that we see 100 000 cases of severe sepsis per annum, this equates to a direct current cost to the NHS of over £2.5 billion. Nurse prescribing has proven to be safe for patients and has provided improved access to medications for many patients in an environment in which there are less junior doctors available as a result of the European Working Time Directive and New Deal (Jones et al, 2011).

A recent report by the Royal College of Physicians (2012) predicts that, in the future, there will be even fewer doctors available, particularly in the specialties of emergency medicine and general medicine, in which the majority of patients with sepsis are seen. Nurse prescribers will be vital to ensure the delivery of safe, timely, and evidenced-based sepsis care.

Presentation of sepsis
Sepsis is increasingly common and can present from a variety of infective sources, the most common being the urinary tract and pneumonia. Causative organisms in sepsis vary between countries, age groups, and sources of infection, and relative frequencies change with time.
Are any two of the following SIRS criteria present and new to your patient?

Observations:
- Temperature >38.3 or <36°C
- Respiratory rate >20 breaths/minute
- Heart rate >90 bpm
- Acutely altered mental state

Blood tests:
- White cell concentration <4 x 10⁹/litre / >12 x 10⁹/litre
- Glucose level >7.7 mmol/litre (if patient is not diabetic)

If yes, patient has SIRS

Is this likely to be due to an infection?

- Cough, sputum, chest pain
- Abdominal pain, diarrhoea, distension
- Line infection
- Cellulitis, wound infection, septic arthritis

If yes, patient has SIRS

Senior staff: Check for severe sepsis

Severe sepsis = sepsis + evidence of organ dysfunction
((one or more of the following)

BP Systolic <90 mmHg / Mean <65 mmHg (after initial fluid challenge
Lactate >4 mmol/litre
Urine output <0.5 ml/kg/hour for 2 hours
INR >1.5
aPTT >60s
Bilirubin >34 µmol/litre
Oxygen Needed to keep SpO₂ >90%
Platelets <100 x 10⁹/litre
Creatinine > 177 µmol/litre or UO < 0.5 ml/kg/hour

Severe sepsis: Ensure outreach and senior doctor attend immediately, take blood cultures, give antibiotics immediately, measure lactate level, fluid resuscitate

Clinical Focus

Most cases are bacterial, although, in the European SOAP study by Vincent et al (2006), a surprisingly large number of cases (17%) were identified as fungal in origin, although this study included only intensive care patients. Until the late 1980s, Gram-negative organisms predominated, but now a small majority of cases are caused by Gram-positive organisms, particularly staphylococci including methicillin-resistant *Staphylococcus aureus* (MRSA), streptococci including *Streptococcus pneumoniae* and *Streptococcus pyogenes*, *Enterococcus* species, and *Bacillus* species. In older patients, in part owing to the increasing frequency of urosepsis, Gram-negative species account for a slight majority of cases and include, in decreasing order of frequency, *Pseudomonas* species, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Acinetobacter* species, *Proteus* species, and *Haemophilus* species (Vincent et al, 2006). Broad-spectrum empirical antibiotics, targeted to the presumed source of infection, when this is known, should therefore target some or all of these organisms, although the specific choice of agent should be determined locally. *Candida albicans* comprises the majority of fungal causes, but it must be remembered that many non-*C albicans* species are resistant to azole agents (e.g. fluconazole) and must be treated with an echinocandin, such as micafungin.

The majority of patients presenting with sepsis will, therefore, be medical patients; however, sepsis is also common in surgical patients pre- and postoperatively and is the most common direct cause of maternal death (Centre for Maternal and Child Enquiries, 2011).

**Diagnosing sepsis**

International consensus definitions exist for sepsis, and these should be used by all healthcare professionals.

The internationally accepted definition of severe sepsis is drawn from a consensus definitions conference in 2001 (Figure 1) (Levy et al, 2001). This requires a battery of physiological and laboratory indices together with a clinical suspicion of a new infection as the source of the abnormalities, in addition to maintaining an awareness of sepsis while completing other, co-existing care pathways such as for pneumonia.

Sepsis is a continuum ranging from uncomplicated sepsis (such as might be experienced with a throat infection or dental abscess) to severe sepsis and septic shock, where a patient will commonly have multi-organ failure:

- Sepsis is a systemic inflammatory response (defined by the presence of two or more systemic inflammatory response syndrome criteria) to an infection
- Severe sepsis is present when one or more organs begin to fail as a result of sepsis
- Septic shock is present when there is evidence that the tissues and organs are receiving insufficient oxygen and nutrients, and is characterised by low blood pressure or other evidence of impaired perfusion such as a high serum lactate, a rapid heart rate and rapid breathing. Septic shock can be considered the most severe end of the spectrum of disease.

In hospitals, early warning scoring systems (EWS) are routinely used in order to identify patients with physiological deterioration . Any patient with an infection and any patient who has a raised EWS should be screened for the suspicion of sepsis. Some EWS charts also contain a sepsis screening tool.

Neutropenic sepsis and meningococcal sepsis benefit from the red flag signs, symptoms and history of recent chemotherapy (in neutropenic sepsis), or photophobia and neck stiffness for meningitis associated with meningococcal disease, but unfortunately this isn’t...
the case for general sepsis. The characteristic purpuric rash seen in meningococcal sepsis is also seen in pneumococcal disease, which can be equally rapidly fatal.

**Management of sepsis**

International guidelines exist for the management of severe sepsis and are due to be updated by early 2013 (Dellinger et al, 2008). There are also nursing considerations to complement the guidelines (Aitken et al, 2011).

The Surviving Sepsis Campaign guidelines recommended a resuscitation bundle for severe sepsis and septic shock. This care bundle should be delivered in the first six hours after recognition. The bundle contains simple tasks such as antibiotics and fluids along with more complex tasks such as insertion of a central venous catheter and treating hypotension resistant to fluids with vasopressors.

As an operational solution to this complex bundle, the UK Sepsis Group developed the concept of the ‘sepsis six’—a set of six tasks, including oxygen, cultures, antibiotics, fluids, lactate measurement and urine output monitoring, to be instituted within 1 hour by non-specialist practitioners at the front line (Box 1) (Daniels et al, 2011). These basic care tasks are likely to realise the greatest benefit for patients, yet are unreliably performed in hospital (Levy et al, 2010).

Compliance with the sepsis six has been shown to reduce the relative risk of death by 46.6% (Daniels et al, 2011), meaning that one additional life might be saved for every four care episodes. In this same study, compliance with the sepsis six meant a reduction in length of critical care stay of 2 days and a reduction of 3.4 days in hospital stay.

Evidence supporting the sepsis six has led to it becoming a standard of care within the first hour adopted by the Royal College of Nursing, Intensive Care Society, National Outreach Forum, and College of Emergency Medicine and Society for Acute Medicine, and it is promoted by the NHS Institute, Welsh Saving 1000 Lives Campaign, and by NHS Scotland.

**Prescribing for sepsis**

Two key interventions require prescribing: antibiotics and intravenous fluids. The current Surviving Sepsis Campaign Guidelines recommend that initial antibiotic therapy is empirical and ‘includes one or more drugs that have activity against all the likely pathogens (bacterial and or fungal) and that penetrate in adequate concentrations into the presumed source of sepsis’ (Dellinger et al, 2008). Choosing which antibiotic is complex and the decision will be influenced by a number of factors:

- Patients history and underlying diseases
- Drug allergies or intolerances
- Pathogens that have previously infected or colonised the patient

**Box 1. The ‘sepsis six’**

1. Give high-flow oxygen via non-rebreath bag
2. Take blood cultures
3. Give intravenous antibiotics
4. Start intravenous fluid resuscitation—Hartmanns or equivalent
5. Check haemoglobin and lactate levels
6. Monitor accurate hourly urine output—consider urinary catheter

As patients with severe sepsis or septic shock are critically ill, there is little margin for error in the choice of antibiotic, and the agent(s) chosen must be broad enough to cover all likely pathogens. Please make sure you are familiar with your institution’s antibiotic guidelines for empirical treatment of sepsis. This will list which antibiotics to give for each likely source such as abdominal/biliary, urosepsis, bone and joint, line infection, and sepsis of unknown cause. You should also ensure you are familiar with your NHS trust or institution guidelines for neutropenic sepsis and the National Institute for Health and Clinical Excellence (2012) guidelines.

Concerns about use of antibiotics, together with the risks of creating resistant organisms and increasing the number of *Clostridium difficile* infections in the presence of strict reduction targets must be balanced with the need to give urgent antibiotics within 1 hour for patients who meet the criteria for severe sepsis. Some antibiotics have been identified as high risk with regard to the spread of *C difficile*: these include second- and third-generation cephalosporins, fluoroquinolones, and clindamycin (Aldeyab et al, 2012).

Antimicrobial stewardship is not only about reducing antimicrobial prescriptions, it is also about ensuring that appropriate antibiotics are given in the right dose, by the right route, and for the right duration to patients who need them. Antibiotic prescription and administration when severe sepsis is identified is urgent, but almost as important is consideration to de-escalation of the antimicrobial spectrum when the organism responsible for sepsis becomes known.

The guidelines caution against restricting antibiotics for patients with severe sepsis: ‘Restriction of antibiotics as a strategy to reduce development of antimicrobial resistance or to reduce costs is not an appropriate initial strategy in this patient population’ (Dellinger et al, 2008).

If unsure about the diagnosis of severe sepsis and whether to give antibiotics, refer for senior medical review and speak to the microbiologist on call to prevent development of resistant organisms, optimise...
activity, and reduce toxicity. The guidelines recommend that antibiotic regimens are reassessed daily (Dellinger et al, 2008). The sensitivity of blood cultures to identify causative organisms is low, with a large longitudinal observational study over some 20 years identifying pathogens in only 50% of cases (Martin et al, 2006). This means that decisions to stop or narrow antibiotics will be made using clinical judgement.

Antibiotics: Start smart then focus
The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (2010) recommend a 'Start smart then focus' approach for all antibiotic prescriptions.

Start smart is:

- Not starting antibiotics in the absence of clinical evidence of bacterial infection
- If there is evidence or suspicion of bacterial infection using local antibiotic guidelines to initiate prompt effective antibiotic treatment (within 1 hour for severe sepsis)
- Obtain cultures first
- Document indication, duration, route, dose, review date on drug card and in medical notes.

Then focus is:

- Review the clinical diagnosis and continued need for antibiotics at 48 hours and make a clear plan—the antimicrobial prescribing decision. This would include the options to stop, switch intravenous to oral, change, or continue antibiotics

Antibiotic resistance is a big problem and many patients still receive antibiotics for presumed infections when they are not indicated. For patients in primary care presenting with severe sepsis, the authors suggest that nurse prescribers could consider giving antibiotics in situations when transfer times to hospital mean a significant delay in the patient receiving antibiotics. Each hour's delay in giving antibiotics to a patient with severe sepsis increases risk of mortality by 7.6% (Kumar et al, 2006).

Antibiotics are rarely given within the 1 hour target (Simmonds et al, 2008). One reason may be poor communication. Antibiotics are frequently prescribed with little attention being paid to the lag time between prescription and administration. In severe sepsis, the prescriber must either administer the antibiotic directly or delegate the task to ensure that they are given as a matter of urgency.

A report from the National Patient Safety Agency (2010) report showed how doses of antibiotics are sometimes missed or delayed resulting in severe harm or death to patients.

On the subject of 'stat' dose drugs (like first-dose antibiotics for sepsis) the report says: 'Unless nursing staff are told verbally that a stat dose has been prescribed these new prescriptions may go unnoticed for several hours before they are identified during the next regular medicines administration round. It is the responsibility of the prescriber to verbally inform nursing staff that they have prescribed a stat medicine'.

The report also recommended that NHS trusts produce a local list of critical drugs where timeliness of administration is crucial. These are drugs like antibiotics that are to be given within a set time frame. Nurse prescribers should make themselves familiar with the critical drugs list in their hospital.

As mentioned above, in 2006, a landmark paper demonstrated that each hour's delay of administration of antibiotics to patients with septic shock was associated with a 7.6% greater risk of death (Kumar et al, 2006). Two recent prospective studies support this, and the Surviving Sepsis Campaign improvement programme showed an odds ratio for death of 0.86 in patients receiving antibiotics within the first 3 hours following presentation (Gaieski et al, 2010; Levy et al, 2010; Daniels et al, 2011).

Intravenous fluid challenges
In sepsis, organs fail due to a lack of perfusion with oxygen-rich blood. The reasons behind this are many, but include a loss of blood volume. This is both absolute—capillaries 'leak', and water, proteins, and salts leave the circulation into the spaces between cells—and relative—blood vessels dilate, so that the volume of the circulation is larger. Restoration of blood volume, using intravenous fluid challenges, is thus a central tenet of sepsis management.

There is significant evidence available governing the type of intravenous fluid that should be used; thus, clinicians and nurse prescribers are able to make an informed choice. What is less clear is how quickly intravenous fluids should be commenced, by whom, and what volume should be administered. The Surviving Sepsis Campaign revised guidance for 2012 is likely to recommend that fluid resuscitation should consist of a target total volume of 30 ml per kg body weight during the first 3 hours, and it is generally accepted that this should be achieved through repeated divided boluses of 250–500 ml with re-assessment of response between boluses.

The selection of intravenous fluid is a source of controversy. There is little evidence to support the use of crystalloid solutions over colloid solutions. A recent Cochrane systematic review of the use of colloids versus crystalloids in critically ill patients including those with trauma or burns concluded that 'there is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids' (Perel et al, 2012). Furthermore, increasing evidence appears to point toward colloid solutions containing hydroxyethyl...
starch as being responsible for increased risk of renal failure in patients with severe sepsis, with the most recent randomised multi-centre trial showing a 35% increased risk of renal failure in patients treated with starch solutions and 17% higher mortality at 90 days (Brunkhorst et al, 2008; Perner et al, 2012).

In recent years, there has been renewed interest in the use of human albumin in patients with severe sepsis as a resuscitation fluid. A meta-analysis has shown albumin to be associated with reduced mortality compared with other fluids, although further research is needed in this regard (Delaney et al, 2011). At present prescribers will need to adhere to local guidelines on the use of albumin solutions.

This evidence, coupled with the widely publicised association with hyperchloaraemic metabolic acidosis when high volumes of 0.9% normal saline are administered and acknowledging that glucose-containing solutions are suboptimal as resuscitation fluids, has led many to conclude that at present Hartmann’s solution is the most appropriate resuscitation fluid in severe sepsis (Daniels, 2011).

The delivery of adequate volumes of intravenous fluid remains more important than the type of fluid, and prescribers in this time-critical condition should avoid situations where therapy is delayed seeking an elusive bag of fluid.

When patients do not respond immediately to fluid challenges, or if severe hypotension, profound oliguria or a reduced level of consciousness exists, the attending team should consider the urgent involvement of the critical care team. If the circulatory parameters are not corrected by an infused total volume of 30 ml per kg body weight, the critical care team should be summoned as a matter of urgency.

Conclusions

Nurse prescribers will play an increasingly vital role in the management of time-critical conditions as the immediate availability of adequately skilled doctors becomes more and more diluted. Sepsis is a prime example of such a condition, with evidence suggesting that the rapid, reliable delivery of basic interventions such as appropriate antibiotics and intravenous fluids is more effective at reducing mortality than early intervention in acute coronary syndrome.

As part of the multidisciplinary team, nurse prescribers will be able to not only prescribe and administer therapies, but also assist in recognition of the patient with sepsis and co-ordination of care with appropriate escalation and safety netting. The non-medical prescriber is responsible for ensuring, whenever possible, that blood cultures are taken prior to giving antibiotics—unless this will delay administration. They are not responsible for sensitivity testing—this is the job of microbiology laboratory staff—but they are responsible to review any sensitivities after 48 hours as part of good antibiotic stewardship.

Antibiotics should be administered, ideally within the first hour following the onset of severe sepsis, according to local protocol. Hospitals should consider not only who is available to prescribe these life-saving therapies, but also whether stocks are available and accessible. The system should be designed so as to minimise delays both from recognition of sepsis to prescription, and from prescription to administration.

Intravenous fluids should be administered in divided boluses with, where necessary (threatened or confirmed shock suggested by low blood pressure or urine output or high serum lactate), a target total volume of 30 ml per kg body weight being administered. Consideration should be given to urgent referral to critical care when patients fail to respond rapidly and in a sustained manner to intravenous fluids. At present, crystalloid solutions such as Hartmann’s appear to be the most appropriate solutions, although albumin may become increasingly important. Evidence suggests that glucose-containing solutions are poorly effective in this context and that starch-containing colloids may be associated with harm.

Prescribers should evaluate the need for adding a selection of intravenous fluids and antibiotics for patients with sepsis to their armamentarium, and work within their organisation to identify how best they can contribute to improving the delivery of care to this critically ill group of patients.


Gaieski DF, Mikkelsen ME, Band RA et al (2010) Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 38(4): 1045–53

Further Reading
■ For guidance on the management of sepsis in paediatric patients, please see the Surviving Sepsis Campaign guidelines (Dellinger et al, 2008)
■ The Surviving Sepsis Campaign guidelines have been updated in 2012 and will be formally published in February 2013 in a special issue of Critical Care Medicine; please see Surviving Sepsis Campaign website: www.survivingsepsis.org/Guidelines/Pages/default.aspx

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