8.1.2 Clinical features and general management of

8.1.2 Clinical features and general management of patients with severe infections 656

656 SECTION 8 Infectious diseases Neumann G, Kawaoka Y (2006). Host range restriction and patho- genicity in the context of influenza pandemic. Emerg Infect Dis, 12, 881–6. Roumagnac P, et al. (2006). Evolutionary history of Salmonella typhi. Science, 314, 1301–4. van Riel D, et al. (2007). Human and avian influenza viruses target different cells in the lower respiratory tract of humans and other mammals. Am J Pathol, 171, 1215–23. 8.1.2 Clinical features and general management of patients with severe infections Peter Watkinson and Duncan Young ESSENTIALS Pathophysiological mechanisms The host response to an infection involves an intricate link between the inflammatory and coagulation systems, and mechanisms de- signed to limit damage to normal tissues. Key elements are: (1) the inflammatory cascade—antigens from infecting organisms stimulate macrophages and monocytes (and other cells) via Toll-like recep- tors to release tumour necrosis factor α. This results in a cascade of proinflammatory cytokine release which is a vital component of the host's attempt to control and eradicate infection, but unfortunately can also result in damage to both infected and uninfected host tis- sues; (2) the anti-inflammatory cascade—a compensatory response involving anti-inflammatory cytokines, soluble receptors, and re- ceptor antagonists directed against proinflammatory cytokines that is intended to localize and control the systemic proinflammatory response to the infection; (3) the coagulation cascade—activated in an attempt to contain infection locally and prevent spread to other parts of the body; platelets are activated, procoagulant pathways are initiated, and anticoagulant mediators are downregulated; (4) the anticoagulation cascade—the coagulation response to sepsis is regu- lated via antithrombin, tissue factor pathway inhibitor, activated pro- tein C, and fibrinolysis. Clinical features Definitions—(1) Systemic inflammatory response syndrome—which

can occur as a result of an infectious or noninfectious insult— requires the presence of at least two of the following: (a) hyper- or hypothermia, (b) tachycardia, (c) tachypnoea or hyperventilation, (d) leucocytosis, leucopaenia, or left shift. (2) Sepsis—a suspected or confirmed infection plus criteria for systemic inflammatory response. (3) Severe sepsis—sepsis resulting in the acute dysfunction of at least one organ system. (4) Septic shock—infection resulting in hypoten- sion despite adequate fluid resuscitation. Management—key elements are (1) antibiotics—often initiated empirically before culture results are available; (2) control of the source of infection—searching for the site of infection so that it can be eradicated should begin as soon as haemodynamic and respira- tory status are stabilized, antibiotics without source control often fail; (3) early resuscitation—requiring (a) crystalloid infusions to maintain circulating volume, (b) vasopressors if arterial pressure remains low, and (4) other treatments—organ support if needed, refining antibiotic treatment based on culture results, and measures to minimize further nosocomial infections. Introduction Although originally describing both localized and disseminated in- fections, the term sepsis is now more commonly used to describe the systemic response to a severe infection. The symptoms and signs of sepsis include fever and rigors, flushing and vasodilation, an ele- vated heart and respiratory rate, confusion, hypotension, and oli- guria. Occasionally a reduced core temperature and pallor occur with late presentations, especially in children. To these are added symptoms and signs relating to the specific infection site and patho- genic organism, such as a cough with russet sputum, pleuritic chest pain, cyanosis, and signs of pulmonary consolidation in a patient with pneumococcal pneumonia. The need for a reasonably precise definition of sepsis arose when drugs designed to modify the host response to severe infections (e.g. antibodies against endotoxin or tumour necrosis factor-α, TNFα) were tested in clinical trials. These drugs were given as soon after presentation as possible, so a simple, clear definition of sepsis that did not require positive culture results was required to determine which patients entered the studies. Three concepts were developed; the systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis. SIRS, which can occur as a result of an infectious or noninfectious illness, is an indication of an activated inflammatory response. It requires any two or more of: (1) hyperthermia or hypo- thermia (core temperature ≥38°C or ≤36°C), (2) tachycardia (heart rate >90 beats/min), (3) tachypnoea or hyperventilation (>30 respir- ations/min or $PaCO_2$ <4.2 kPa (32 mm Hg)), and (4) leucocytosis, leucopaenia, or left shift (≥12 or ≤4 × 109 white blood cells/litre or

> 10% immature neutrophils). Sepsis is defined as a suspected or confirmed infection causing at least two of the SIRS criteria. Severe sepsis is used to describe sepsis resulting in the acute dysfunction of at least one organ system. When the infection results in hypotension despite adequate fluid resuscitation, the patient has septic shock. Patients with septic shock are a subset of those with severe sepsis. Terms such as septicaemia, ‘catheter shock’, blood poisoning, and toxaemia are less well defined. Although this set of definitions is still in use in clinical research, it has very limited applicability in clinical medicine. The SIRS component is very sensitive, but is not specific. Most acutely hospitalized patients demonstrate two or more SIRS criteria at some point, as do nearly all patients in critical care units. In addition, these clinically based diagnostic rules are of very limited value in patients who do not mount the

> conventional inflammatory response to sepsis, including immunocompromised patients and those at the extremes of age. As a result, recognition of sepsis still relies on a physician suspecting or confirming infection based on history, clinical signs, laboratory findings, and imaging. Variants of these definitions have been created for clinical trial entry criteria, management guidelines, and retrospective analyses of

8.1.2 Clinical features and general management of patients with severe infections 657 clinical and administrative databases. The difference in definitions in part explains the wide range of estimates of the incidence of sepsis and severe sepsis in developed healthcare systems. The incidence in the United States might lie between 300 and 1000 cases per 100 000 population per year. This incidence might be increasing over time as the population ages and more aggressive treatments are offered to older people. In part because of the limitations of this set of definitions, a model for risk stratification of patients with sepsis, based conceptually on the tumour, node, and metastasis (TMN) system used in oncology, has been proposed. The PIRO model (Predisposition, Infection, Response, and Organ dysfunction) can be used to generate a nu- meric score indicating the risk of mortality from sepsis at the point of presentation. It can also be used in clinical practice as a framework for assessing and describing patients with sepsis. Predisposing risk factors for infection include extremes of age, immunocompromising conditions or drugs, and anything that alters the risk of sepsis. Infection describes the likely source or pathogen and the site of in- fection; Response describes the physiological effects of the infection; and Organ dysfunction (renal, respiratory, and so on) describes organ system damage or failure caused by the infection. As yet, this classification/descriptive system is not widely used. Very recently a revised set of diagnostic criteria for sepsis (‘Sepsis- 3’) was published. The new definition hinges on the SOFA score (Sequential Organ Failure Assessment), a severity scoring system used in critical care practice. A serum lactate above 2 mmol/litre (18 mg/dl) despite adequate fluid resuscitation is used as part of the definition of septic shock. The Sepsis-3 definitions are still based on laboratory and physiological variables. They are as yet unproven for either clinical or research practice. Pathophysiology of infection Inflammatory cytokines mediate the physiological changes seen in patients with sepsis. A consumptive coagulopathy, with microthrombi in the small vessels of various organs, is a common feature of severe sepsis. In infected patients, changes in the inflam- matory and coagulation systems are linked. Early on in an infection, cell wall antigens from infectious agents stimulate macrophages and monocytes to release TNFα. The cell wall components initially bind to transmembrane Toll-like recep- tors (TLR2 and TLR4) found on the surface of macrophages, neu- trophils, fibroblasts, and some epithelial and endothelial cells. The cells then release TNFα into the circulation stimulating the release of other proinflammatory cytokines from macrophages and neutro- phils, especially interleukins 1 and 6 (IL-1, IL-6). This is frequently referred to as an inflammatory cascade. Clinical trials with anti-Toll-like receptor drugs showed no benefit, presumably because the cascade had already been activated at the time of administration. The infection-triggered increase in circulating TNFα is so short-lived that most patients with sepsis have undetectable levels at the time of presentation. As a result, clin- ical trials using antibodies to TNFα also showed no benefit. High levels of circulating proinflammatory cytokines cause the fever, tachycardia, and tachypnoea seen with severe infections. This inflammatory response is a component of the immediate host de- fence to severe infection, but directly and indirectly it can

result in damage to both infected and uninfected host tissues. By about three days after presentation, the levels of IL-6 and other proinflammatory cytokines are decreasing. However, the inflammatory state is main- tained by other mediators such as high-mobility group box protein 1 (HMGB1), which further stimulates the release of proinflammatory cytokines but, in addition, regulates coagulation by inducing the se- cretion of plasminogen activator inhibitor type 1 (PAI-1, procoagu- lant) and tissue plasminogen activator (fibrinolytic). There are checks on the inflammatory cascade. A compensatory anti-inflammatory response exists to maintain homeostasis. TNFα and IL-1 also stimulate leucocytes to release anti-inflammatory mediators such as IL-10, IL-13, and transforming growth factor β (TGFβ) which exert a direct anti-inflammatory effect on macro- phages and endothelial cells. They also inhibit monocyte presenta- tion of antigens to other immune cells. The inflammatory response is further controlled by the release of soluble receptors and receptor antagonists directed against proinflammatory cytokines. This com- pensatory anti-inflammatory response, in the later stages of sepsis, can lead to a degree of immune paresis. The activation of the coagulation response is intricately linked to the inflammatory response. TNFα and IL-1 both stimulate the release of tissue factor (also called factor III, thromboplastin) and activate endothelial tissue factor. Tissue factor (TF) combines with circulating factor VII to form a TF:VIIa complex. This in turn ac- tivates factor X, stimulating the formation of fibrin clots in the microcirculation via thrombin. Thrombin, TF:VIIa complex, and activated factor X also function as potent inflammatory mediators. Anticoagulant mechanisms such as protein C, antithrombin, and tissue factor pathway inhibitor are impaired. Both antithrombin and activated protein C have been tried as treatments for severe sepsis, but neither showed any efficacy.
Diagnosis The key element of a diagnosis of sepsis remains a clinical suspi- cion of an infective process raised by findings in history and exam- ination. Laboratory studies can assist with the diagnosis. Most patients with sepsis have an increased white cell count, predomin- antly neutrophils. More rarely, in severe cases, a neutropaenia is seen. Immature neutrophils (band forms or a left shift) might be present as a result of increased white cell production.
A modest thrombo- cytopaenia, associated with clotting abnormalities such as an in- creased activated partial thromboplastin time or increased ‘R’ time on a thromboelastograph are found in patients with an associated consumptive coagulopathy. Other nonspecific abnormalities are often found. Hypotension, and dehydration, especially in late-presenting patients, can cause a prerenal acute kidney injury so both plasma creatinine and urea might be elevated. In common with all critically ill patients, blood glucose is often elevated by increased circulating catechol- amines. An elevated arterial plasma lactate concentration is com- monly found, as the infection causes actual and functional tissue hypoperfusion. The increased capillary permeability that occurs in the lungs causes noncardiogenic pulmonary oedema, a condition usually termed acute respiratory distress syndrome (ARDS). Body fluids sampled from sites of infection might show markers of infection that can be measured long before the results of cultures

 of body fluids are available. For example, pleural fluid in patients with a bacterial empyema will have a reduced pH and contain in- flammatory cells. Cerebrospinal fluid from patients with bacterial or fungal meningitis might have raised protein and reduced glu- cose concentrations, often with increased white cells. Infected urine may show blood, nitrites, and leucocytes. Microscopy of body fluid samples treated with Gram’s stain might reveal Gram-positive or Gram-negative organisms. Patients with Legionella pneumophilia or Streptococcus pneumoniae pneumonia can have a specific bacterial antigen present in their urine. A major clinical challenge is distinguishing patients with infec- tions from patients with another reason for systemic

inflammation caused by a noninfectious process, such as pancreatitis. The com- bination of the time taken to culture pathogenic organisms and the high false-negative rate for culture-based tests has led to a search for markers that identify patients with an infection quickly. Ideally the marker could be determined at the point of care or rapidly in a laboratory, and would give information about the pathogen species and antibiotic resistance. C-reactive protein (so-called because it reacts with the C- polysaccharide of pneumococci) plasma concentration increases within hours in response to acute infections. It has a short half-life (19 hours) so concentrations largely reflect production rates, and so can be used to track the effects of treatment. However, C-reactive protein is produced by hepatocytes in response to increases in plasma IL-6 concentrations, and these also occur with tissue damage, inflamma- tion, and malignancy. Plasma IL-6 levels themselves have been used as an entry criterion for clinical trials of antisepsis agents, but are not in clinical use. Procalcitonin, a polypeptide prohormone rises to very high values in response to bacteraemia or fungaemia. While procalcitonin ex- hibits a degree of specificity for bacterial infection, it can be raised as a result of other proinflammatory stimuli such as tissue damage or severe viral infections. Presepsin (a soluble C14 receptor subtype) is released into the circulation when monocytes are activated by lipopolysaccharide from Gram-negative organisms, limiting its use as a rule-in test to this class of pathogens. The soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) can also increase early in sepsis. Presepsin and sTREM-1 might, in future, be useful as markers of bacterial infection but remain research tools at present. The hallmark of sepsis is a positive culture from a normally sterile body fluid or site, such as blood, urine, or cerebrospinal fluid. However, culture-based diagnosis is of little value in an acute setting. Blood cultures require careful techniques to ensure an ad- equate inoculum of blood and to avoid contamination. Culturing of micro-organisms to the point where infection can be confirmed can then take 12–72 hours, often with more time to confirm spe- cies and antibiotic sensitivity. Gram’s stain and other techniques to identify micro-organisms in body fluids immediately after sampling are generally ‘rule-in’ tests. If positive they make the diagnosis, but false negatives are common, especially in patients who have received antibiotics prior to collection of blood or body fluids for culturing. Culture results are rarely available to make early treatment deci- sions, and are more commonly used to fine tune the initial empiric antibiotic treatment. Molecular tests for pathogens, particularly bacteria, show par- ticular promise. These techniques allow the rapid detection of bacteria in blood and other clinical specimens, overcoming the de- lays and lack of sensitivity of conventional culture techniques. There are several techniques that are available commercially. Some decrease the time to identify pathogens but still requires the automated blood culture system to identify cultures with multiplying pathogens. For example, fluorescent in situ hybridization is a staining method for the detection of pathogens in positive blood cultures. Slides of posi- tive blood cultures are prepared, hybridized with fluorochrome- labelled oligonucleotide probes targeted at ribosomal RNA (rRNA), and visualized under a microscope. Broad-range DNA amplification (PCR), detecting conserved sequences of bacterial/fungal chromo- somal genes encoding ribosomal DNA, can detect bacteria in a few hours in blood cultures but secondary steps are needed to determine the species. Panels of primers can be used, with or without con- served sequences, to look for specific species or resistance patterns to make this process more efficient (multiplex techniques). Molecular techniques applied directly on whole blood samples for rapid identification of a circulating microorganism would be ideal for acute care. They are quicker and more sensitive than culture-based techniques. Available amplification techniques include both broad-range and multiplex PCR. These approaches will give a re- sult in 3–8 hours and have been shown to be sensitive and specific, though their impact on care pathways and outcomes is still under in- vestigation. The cost

per test is high, and sample handling and DNA extraction remain a problem. The ideal solution, a simple point-of- care or rapid-turnaround laboratory device, with a wide range of detectable pathogens and antibiotic resistance markers, has yet to reach routine clinical medicine. Treatment of sepsis The mainstays of treatment for severe sepsis are resuscitation, early treatment with antibiotics, and source control. Resuscitation At first presentation a rapid ‘Airway, Breathing, Circulation’ assess- ment is needed. Not all patients with sepsis will require immediate resuscitation but a significant proportion will have an increased alveolar to arterial oxygen gradient. This might result from pul- monary infection, ARDS, or ventilation/perfusion mismatching due to poor cardiac output. Supplemental oxygen may be required. Severe cases might require endotracheal intubation and artificial ventilation. The inflammatory cytokines released in sepsis cause vaso- and venodilatation. Increased insensible fluid losses from fever, sweating, vomiting and diarrhoea, and worsening microvascular permeability all contribute to decreased intravascular volume, manifesting as hypotension. Intravenous fluid remains the mainstay of cardiovas- cular resuscitation, and initial treatment of sepsis-induced hypo- tension in an adult usually requires at least a litre of intravenous crystalloid solution given rapidly over half an hour. An average of about 4 litres is required in the first 6 hours after presentation. If hypotension does not resolve after 2 litres of fluid it might be ne- cessary to administer a pressor agent as a continuous infusion, usu- ally via a central venous catheter. The most commonly used pressor agent is noradrenaline (norepineprine) though some centres will augment this with vasopressin. Treatment with potent vasopressors

8.1.2 Clinical features and general management of patients with severe infections 659 needs suitably trained staff and physiological monitoring and so is usually confined to critical care or equivalent high-care areas. The endpoint for discontinuing ‘aggressive’ fluid resuscitation re- mains ill-defined. The increased capillary permeability associated with sepsis causes fluid to accumulate as peripheral oedema very quickly, and noncardiogenic pulmonary oedema (ARDS) will be worsened by excess fluid. A bedside test of adequate fluid resusci- tation is to simply raise both legs to 45 degrees when the patient is supine. If the patient has received inadequate fluid resuscitation raising both legs will cause an immediate increase in blood pressure as venous blood returns to the thorax. An alternative is to assess the response to a rapid 250 ml fluid bolus. Patients who are adequately resuscitated will often begin to need less vasopressors and have an improving arterial lactate concentration, increasing urine output and resolving confusion. There have been attempts to codify the fluid and vasopressor treatment of patients with septic shock. Probably the best-known regimen is early goal-directed resuscitation, which was shown to considerably decrease mortality in one single-centre study of pa- tients with severe sepsis and lactic acidosis or septic shock. The ‘goals’ were target values for central venous pressure, central venous oxygen saturation, and blood pressure. Three large, multicentre studies subsequently failed to show any benefit of early goal-directed resuscitation over usual care. In the 1980s a reversible reduction in cardiac performance in some patients with severe sepsis was first recognized. Aided by the rise in echocardiography use on critical care units, this condition has been studied in more detail. It is a global, short-lived (a few days) signifi- cant reduction in left ventricular inotropy, probably with modestly increased lusitropy (ventricular relaxation). Right ventricular dila- tation is often a feature. This condition is not caused by a cardiac oxygen supply/demand mismatch or coronary artery disease, but is likely caused by high levels of circulating cytokines such as TNFα or IL-1β. After diagnosis using transthoracic echocardiography, some centres will use β-agonists (usually dobutamine infusions) to increase inotropy in these cases. Antibiotics Early administration

of appropriate intravenous antibiotics reduces morbidity and mortality in patients with sepsis. In clinical trials, an appropriate antibiotic regimen is begun in a timely fashion in 85–95% of occasions, but failure to do so is associated with a 25% higher mortality. Almost invariably the choice of initial antibiotics cannot be based on culture results. Most hospitals will have local prescribing advice based on the suspected site/type of infection, local resistance patterns, where the patient developed the infection (community or nosocomial), whether the patient has any antibiotic allergies, the patient's immune status, and the cost and local avail- ability of the drugs. Sometimes this advice needs modifying because of recent antibiotic use, laboratory findings, and previous micro- biology results. In general, initial antibiotic therapy should cover a broader spectrum of pathogens when the patient is critically ill or the certainty about the likely causative organism is low; for example, in neutropaenic sepsis the recommended initial empirical treatment is intravenous piperacillin with tazobactam. Once microbiological data are available, therapy should be changed promptly to the narrowest spectrum, least toxic, and least costly agent. When the risk of developing complications of sepsis is low patients should be switched early from intravenous to oral antibiotics. Selective oral decontamination and selective digestive decon- tamination are techniques that use antibiotics to reduce the burden of nosocomial infections in patients treated in critical care units. The benefits of this approach seem to depend on the healthcare settings in which it is used, and concerns remain about the risk of generating resistant strains of bacteria. As a result, this technique is not widely used. Source control Source control is a term used to describe removal of infected ma- terial. Antibiotics have little penetration into areas of devitalized tissue, or avascular collections of infected fluid. Common examples of infected fluid collections include infected urine retained behind a renal calculus, a gall bladder empyema, a thoracic empyema, or a leak of enteric content into the abdominal cavity. As soon as a patient's haemodynamic and respiratory function are sufficiently stable any required imaging should be undertaken. Usually this in- volves ultrasound investigation or a computed tomography (CT) scan. In some patients, for example patients who have had prior sur- gery, it is sometimes difficult to distinguish between collections of sterile and infected fluid. Enhancement of the rim of the fluid collec- tion, gas formation, tissue oedema around the fluid collection, and large-sized collections all suggest infected rather than sterile collec- tions on CT images. Significant collections of infected fluid require either surgical or radiological drainage. Patients who develop nosocomial sepsis, especially those who are immunocompromised, might have bacteraemia caused by infected indwelling devices such as intravascular catheters (catheter related bloodstream infections). If no other cause for the nosocomial infec- tion is found, these devices should be removed and replaced with new devices if they are still required. Many centres take blood cul- tures from central venous catheters before removing them, though a positive result could indicate colonization of the catheter rather than showing the catheter as the source of the bloodstream infec- tion, or could simply reveal a bacteraemia unrelated to the device. Culture of the distal portion of the catheter (tip culture) suffers from the same limitations. Simultaneous sampling of blood for cul- ture from the device and using venepuncture might show the same pathogen in both samples, and if the sample from the device flags positive earlier than the venepuncture sample the device is likely the source of infection. However, in practice if there is a suspicion of catheter-related bloodstream infection, the device is usually just removed. Corticosteroid treatment The use of corticosteroids in patients with septic shock dates back to the 1970s, when high doses (30 mg/kg methylprednisolone or equivalent) were used to reduce the inflammatory response to sepsis. The use of high-dose corticosteroids declined as clinical trials failed to show a survival benefit. However, in the 1990s the use of lower doses to counter relative adrenal insufficiency (identified using a short

adrenocorticotropic hormone (ACTH) stimulation test) gained popularity, though again trials failed to show benefit. The use of steroids is now mostly confined to patients who have se- vere septic shock which is not responding to fluid resuscitation or pressors. Moderate doses of steroids (200 mg hydrocortisone/day or

 equivalent) might allow less pressor use, but meta–analysis of the 35 trials of steroids in sepsis to date suggests there is no survival benefit. Care bundles Activated protein C (drotecogin alfa) is a recombinant form of human activated protein C that has antithrombotic, anti-inflammatory, and profibrinolytic properties. It was marketed for 10 years until it was withdrawn in 2011 after trials failed to confirm earlier studies that had suggested it improved survival in patients with severe sepsis. Part of the marketing strategy used by the manufacturers included funding the Surviving Sepsis campaign, designed to promote bun- dles of basic care for patients with sepsis. This campaign has now been taken on by the critical care community who update the core 'bundle' of interventions regularly. The core recommendations are listed in Boxes 8.1.2.1 and 8.1.2.2. Mortality from sepsis has reduced during the time in which sepsis bundles have been popularized. Sepsis bundles are complex pack- ages of treatments only appropriate for critical care or high-care areas. Some centres have implemented a simpler set of six steps spe- cifically designed to facilitate early intervention in busy hospital and prehospital settings. This 'Sepsis Six' bundle has three diagnostic and monitoring steps and three therapeutic interventions: • Deliver high-flow oxygen • Take blood cultures prior to antibiotics but do not delay treatment • Administer empirical intravenous antibiotics • Measure serum lactate • Start intravenous fluid resuscitation with crystalloid solutions • Commence urine output monitoring via either a catheter or chart Box 8.1.2.1 Initial resuscitation and treatment of patients with severe sepsis Initial resuscitation 1 Resuscitate patients with sepsis-induced tissue hypoperfusion (hypo- tension persisting after initial intravenous fluid challenge or blood lac- tate concentration ≥4 mmol/litre). Goals during the first 6 hours of resuscitation can include: a) Mean arterial blood pressure (MAP) ≥65 mm Hg b) Urine output ≥0.5 ml/kg/h c) Central venous pressure 8–12 mm Hg. 2 In patients with elevated blood lactate levels use lactate levels to assess the effects of resuscitation. Diagnosis 1 Obtain cultures as clinically appropriate before antimicrobial therapy (if this will not delay starting antimicrobials by more than 45 minutes). 2 Obtain at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy with at least one sample drawn percutaneously and one sample drawn through each vascular access device, unless the device was recently (<48 hours) inserted. 3 Use rapid pathogen antigen tests (e.g. 1,3 β-D-glucan assay or mannan for invasive candidiasis, legionella or clostridium difficile antigens) where available. 4 Obtain prompt imaging to confirm a potential source of infection. Antimicrobial therapy 1 Administer empiric intravenous antimicrobials within the first hour after recognition of severe sepsis using one or more drugs that have activity against all likely pathogens. Use antimicrobials that pene- trate into tissues presumed to be the source of sepsis in adequate concentrations. 2 Reassess the antimicrobial regimen daily. Empiric combination therapy should not be administered for more than 3–5 days. De-escalate to the most appropriate single therapy as soon as the antimicrobial sus- ceptibility profile is known. 3 Duration of therapy is typically 7–10 days; longer courses may be ap- propriate in patients who have a slow clinical response, undrainable foci of infection, bacteraemia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropaenia. 4 Inflammatory markers may assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection. Source control 1 Seek a specific anatomical site of infection. Achieve source control

within 12 hours if possible. 2 When source control is required, use the intervention associated with the least physiologic insult (e.g. percutaneous rather than surgical drainage of an abscess). 3 Remove vascular access devices if they are a possible source of sepsis. Nosocomial infection prevention 1 Use routine screening and monitoring of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy. 3 Instigate hospital–based performance improvement efforts in severe sepsis. After Dellinger R et al. (2013) Crit Care Med 41(2): 580–637. Box 8.1.2.2 Fluid, vasopressor, inotropes, and steroids in the treatment of patients with severe sepsis Fluid therapy of severe sepsis 1 Crystalloids are the initial fluid of choice in the resuscitation of severe sepsis. Do not use hydroxyethyl starch solutions. 2 Use an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion of 30 ml/kg of crystalloids. Vasopressors 1 Use norepinephrine (noradrenaline) as the first-choice vasopressor to maintain a mean arterial pressure of 65 mm Hg. 2 Consider using vasopressin 0.03 units/minute as an intravenous infu- sion added to norepinephrine to either raise mean arterial pressure, or decrease norepinephrine infusion rates. 3 Phenylephrine is not recommended in the treatment of septic shock except in circumstances where norepinephrine is associated with ser- ious arrhythmias. 4 All patients requiring vasopressors should have an arterial catheter placed as soon as practical. Inotropic therapy 1 A trial of dobutamine infusion up to 20 micrograms/kg/min can be administered or added to vasopressor (if in use) in the presence myo- cardial dysfunction. Corticosteroids 1 Do not use intravenous hydrocortisone to treat adult septic shock pa- tients if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability. 2 In cases where this is not achievable, use intravenous hydrocortisone in divided doses. 3 Do not use the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone. 4 Taper off hydrocortisone treatment when vasopressors are no longer required. After Dellinger R et al. (2013) Crit Care Med 41(2): 580–637.

8.1.2 Clinical features and general management of patients with severe infections 661 There is a clear emphasis on early treatment in both the campaign and the Sepsis Six bundle. Conclusion Although there have been many studies of therapeutic agents acting on the inflammatory cascade triggered by infection, to date none are in routine use. The mainstay of care still remains fluid resuscitation, timely and well-chosen empiric antibiotics, and control of the source of infection. It is likely that PCR-based rapid diagnostic tests will continue to advance so the time to identifica- tion of the pathogen species and its resistance pattern will continue to shorten. This will allow a reduction in the total use of broad- spectrum antibiotics. FURTHER READING Dellinger RP, et al. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med, 41, 580–637. Maurin M (2012). Real-time PCR as a diagnostic tool for bacterial dis- eases. Expert Rev Mol Diagn, 12, 731–54. Singer M, et al. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA, 315, 801–10.

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