The Intensive Connection

Sepsis and Septic Shock

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Sepsis and Septic Shock

Current Status 2017

Completed

This module is updated and maintained by the Systemic Inflammation and Sepsis section

Latest Update

Second Edition

Systemic Inflammation and Sepsis

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Update Info

Learning Objectives

After studying this module on Sepsis and Septic Shock, you should be able to:

- Describe the clinical features of sepsis in the critically ill patient
- Identify the core principles of resuscitation and haemodynamic support of the septic patient
- Explain the importance of identification and control of the source of infection
- Outline the role of adjunctive therapies for sepsis

eModule Information

COBATrICe competencies covered in this module:

Competencies

- Adopts a structured and timely approach to the recognition, assessment and stabilisation of the acutely ill patient with disordered physiology
- Obtains appropriate microbiological samples and interprets results
- Recognises and manages the septic patient
- Manages antimicrobial drug therapy
- Uses fluids and vasoactive / inotropic drugs to support the circulation

Faculty Disclosures:

Duration: hours

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Both sepsis and septic shock are major world-wide healthcare problems. Conservative estimates suggest that it can affect over 30 million people each year, accounting for billions in health care costs annually. Sepsis is a lethal process with mortality rates ranging from 10-50% and those who survive often suffer long-term physical, psychological and cognitive disability. Despite this, it is largely unknown to the lay public and until recent years, not recognised for the worldwide threat that it is.

Sepsis is responsible for about a quarter of all ICU admissions in Europe (Singer et al. 2016). It is not a specific illness, but rather a syndrome which is defined by consensus rather than diagnosed by “gold standard” clinical or laboratory tests. The pathobiology is still unclear. The multifaceted host response to an infecting pathogen can be significantly amplified by endogeneous factors and lead to secondary organ system failure. This multiple organ dysfunction syndrome (MODS) is the main cause of death in septic patients. For example, for a patient admitted with pneumonia, the infection may be appropriately treated. After an ICU course characterised by renal failure, persistent hypotension, failure to wean from the ventilator and recurrent bouts of nosocomial infection, often with relatively low virulence organisms, this patient may still succumb weeks later.

The concept of sepsis has been a part of medicine since the time of Hippocrates, but it remains an entity that continues to challenge our collective understanding – often protean in its presentation, variable in its response to treatment, and unpredictable in its outcome. With the creation of The Surviving Sepsis Campaign (SSC), the past three decades have seen great changes in the approach to the septic patient – the very definition of sepsis has undergone three major revisions since 1991 and the newest sepsis definition was published in 2016 in the Sepsis-3 paper by Singer, et al. Where intravenous fluid was once thought an anathema, it is now a cornerstone of resuscitation practice; where tight, aggressive glycaemic control was hailed as a life-saving intervention, it has now largely been replaced by a more judicious, moderate approach. The contemporary history of sepsis management is defined by a series of such “course corrections”, where every element has come under question and where widely espoused dogma is often discarded within a matter of a few years.

Most importantly, the dynamics of the SSC strongly influenced our clinical practice, making it clear that to save septic patients’ lives, there needs to be a strong investment in professional and institutional development to ensure early recognition of sepsis and prompt initiation of treatment.

There are three priorities in the approach to the septic patient that have shown to reduce mortality:

1. Early recognition with prompt disease stratification and rapid treatment initiation
2. Prevention and support of organ dysfunction, based on oxygen delivery (DO_2) optimisation, conditio sine qua non for the maintenance of optimal oxygen consumption (VO_2) in tissues during sepsis
3. Rapid infection source control based on the immediate administration of adequate antimicrobial therapy and surgical/instrumental intervention when indicated.

The following module is an introduction to the identification and treatment of sepsis and septic shock. It is not designed to address the many nuances and controversies that still surround our understanding of sepsis. It has four core sections:

1. Recognising Sepsis in the Critically Ill Patient
2. Resuscitation and Hemodynamic Support of the Septic Patient
3. Identification and Control of Infection in Patients with Sepsis
4. Adjunctive Therapies for Sepsis.

The information in each section is based upon, encompasses the most robust clinical and experimental evidence presently available and reflects much of the work of the Surviving Sepsis Campaign, supported by the Society for Critical Care Medicine and the European Society of Intensive Care Medicine. None of the recommendations provided by this module are meant to replace the skilled clinician's decision-making at the bedside, but rather intended to provide guidance and define a unified approach to this common, yet incompletely understood pathophysiological process.

In text References

(Angus and van der Poll. 2013; Rhodes et al. 2017)

References

- Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Ber-nard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishim, Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016., 2017, PMID:28101605
- Angus DC, van der Poll T., Severe sepsis and septic shock., 2013, PMID:23984731

- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC., The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)., 2016, PMID:26903338

1. 1. Micro-organisms, Colonisation and Infection

In health, humans live in a state of symbiosis with microbes. Micro-organisms are consumed during eating, they colonise mucosal surfaces and promote the fundamental processes of cellular metabolism. Bacteria in the gut facilitate food digestion, stimulate intestinal epithelial development, and inhibit the growth of exogenous and potentially more virulent organisms. In turn, the human body provides them with nutrients and a favourable environment for growth.

In sepsis, however, this state is disrupted: micro-organisms invade normally sterile host tissues and become a threat to the host. The host activates a series of processes to kill the micro-organism. Normal patterns of microbial colonisation are altered, as are normal patterns of the host antimicrobial response. Infection becomes both the cause of sepsis and a clinical manifestation of the disorder. The host response, heralded by pro- and anti-inflammatory responses, becomes both evidence of the disorder and a cause of the tissue destruction that results.

1. 2. Definition of Sepsis

Sepsis describes a variable, non-specific acute syndrome that suggests the presence of uncontrolled infection and the threat of imminent clinical deterioration. Sepsis was first formally defined at the 1991 ACCP/SCCM consensus conference (Figure 1) (Bone et al. 1992) as: the presence of infection in conjunction with the systemic inflammatory response syndrome (SIRS). SIRS was defined by the presence of 2 or more of the following criteria: heart rate >90 beats per minute, respiratory rate >20 per minute or the need for mechanical ventilation, temperature <36.0 °C or >38.0 °C, and leukopenia or leukocytosis (a white blood cell count <4000/mm^3 or >11 000/mm^3). These **SIRS Criteria** could be used to quickly recognise and classifiy the severity of sepsis. Other definitions were introduced: **severe sepsis** was defined as sepsis in association with hypoperfusion and mediator-induced organ dysfunction, while **septic shock** was described as sepsis of such severity that perfusion was profoundly jeopardised, vasoregulatory mechanisms

were lost and ischemia ensued. Because of its simplicity, SIRS criteria became very popular and were even expanded in 2001 by a task force of the SCCM/ESICM/ACCP/ATS/SIS (Levy et al. 2001).

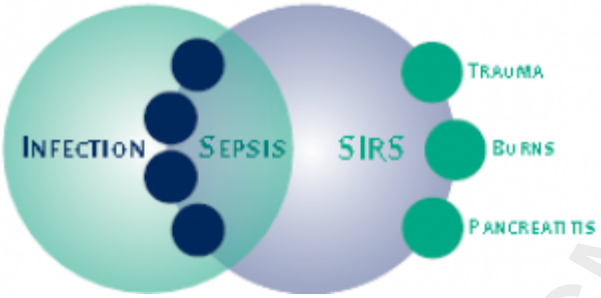

Figure 1: The presence of infection in conjunction with the systemic inflammatory response syndrome (SIRS). Bone et al, 1992

However, the use of SIRS for the definition of sepsis has been challenged, because it focused solely on inflammatory excess. It was argued that SIRS could simply be an adaptive response that is beneficial to the host in the presence of infection. Furthermore, both sensitivity and specificity of the SIRS criteria to identify sepsis were found to be limited (Kaukonen et al. 2015). Approximately 10-12% of patients with sepsis in ICU do not have ≥2 SIRS criteria (Vincent et al. 1998). On the other hand, the majority of infected patients will meet SIRS criteria without having sepsis and systemic inflammation may result from a sterile insult such as multiple trauma, burns, blood transfusion, a drug reaction, pancreatitis, or thrombotic thrombocytopenic purpura.

Improved understanding of the pathobiology of sepsis revealed that sepsis is caused by profoundly deranged host-microbial homeostasis with early activation of both pro and anti-inflammatory responses, along with major alterations in non-immunologic pathways such as the cardiovascular, neuronal, hormonal, metabolic and coagulation systems. Other factors such as the causative pathogen, initial site of infection, comorbidities and iatrogenic interventions also affect the host response.

As a result of these controversies and improved understanding of pathophysiology, a new, revised definition of sepsis was proposed in 2016: sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (Rhodes et al. 2017). This new definition accentuates the imbalanced host response to infection. It moves away from a focus on inflammation and emphasises the dysregulated and maladaptive response. It stresses the urgency of identifying patients at risk of clinical deterioration or death, prompting the clinician to institute adequate resuscitative measures rapidly (Singer et al. 2016). Under this revised definition, organ dysfunction is defined as an acute change in Sequential Organ Failure Asessment (SOFA) score ≥ 2 points due to infection and is associated with a ≥ 10% increase in mortality (Vincent et al. 1998). Note that the term “severe sepsis” is no longer in use.

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Organ dysfunction most commonly comprises the respiratory (Acute Respiratory Distress Syndrome (ARDS)) and cardiovascular (hypotension, myocardial dysfunction) systems (Angus and van der Poll. 2013). The central nervous system (septic encephalopathy, manifested by obtundation and delirium) and the kidneys (acute kidney injury) are also frequently affected. Other common manifestations of organ dysfunction are paralytic ileus, elevated aminotransferase levels, altered glycaemic control, disseminated intravascular coagulation and adrenal insufficiency. In this new terminology where organ dysfunction is part of the very definition of sepsis, the old term “severe sepsis” is redundant.

Table 1: Signs and Sympoms of Sepsis (adapted from Levy et al.)

General	• Fever (>38.3ºC) or Hypothermia (<36ºC) • Heart Rate > 90 bmp or >2 SD above the normal age value • Tachypnea • Significant oedema or positive balance (>20ml/Kg in 24h) • Hyperglycaemia >140 mg/mL (7,7 mmol/L)
Inflammatory Markers	• Leucocytosis (>12,000µ/L) or Leucopaenia (< 4000 µ/L) • >10% of immature forms in normal leucocytes • Raised CRP >2 SD above normal levels • Serum PCT >2 SD above normal levels
Haemodynamic Parameters	Hypotension (SAP <90 mmHg, MAP <70 mmHg, SAP drop >40 mmHg or <2 SD below normal range)
Organ Dysfunction Signs	• CNS: Altered mentation • Respiratory: Respiratory Index (PaO2/FiO2) < 300 • Renal: acute oliguria (urinary output <0.5ml/kg/h in 2 hours of adequate fluid therapy ot Creatinine Rise >0.5 mg/dL • Haematological: INR >1.5 or aPTT >60s; Thrombocytopaenia <100,000 / µl • GI: Ileus
Impaired Tissue Perfusion	• High lactate (>1 mmol/L) • Delayed capillary refill time • Mottled skin

Challenge

Write down five physiological or laboratory abnormalities that you believe to be most characteristic of sepsis. Now ask a colleague to do the same, and compare your lists. Are they the same? Is there a single clinical syndrome that we might call sepsis?

References

- Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Ber-nard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishim, Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016., 2017, PMID:28101605
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1. 3. Septic Shock

As with the 1991 and 2001 definitions, the new proposed Sepsis-3 terminology also indicates a subgroup of patients with septic shock. Under Sepsis-3, septic shock is defined as persistent hypotension despite adequate fluid resuscitation requiring vasopressors to maintain a mean arterial pressure ≥ 65 mmHg and having a serum lactate level ≥ 2 mmol/L. Perfusion is even more profoundly jeopardised in these patients, with vaso-regulatory mechanisms being overcome and tissues becoming ischaemic. When such profound circulatory and cellular abnormalities develop, hospital mortality may exceed 40%.

Some Concerns with Sepsis-3:

- Sepsis-3 did not involve low/ middle income countries (LMIC), where raising awareness and early detection are priorities
- Patients with isolated hypotension or a reduced level of consciousness will be classified as “uncomplicated infection”
- SOFA is a complicated score that is routinely calculated in some ICUs, but is not explicitly used in others (many ICUs use APACHE or SAPS II scores instead)
- The baseline SOFA score is assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection
- SOFA has the limitations characteristic of a categorical ordinal scale
- The use of the qSOFA score is potentially problematic, despite having predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) similar to that of the full SOFA score outside the ICU
- qSOFA has only been validated retrospectively, based on data from the USA and Germany
- qSOFA has not been demonstrated to be useful in the wide range of clinical settings that sepsis is encountered
- ‘New onset’ versus ‘established’ qSOFA points are unknown
- The authors of Sepsis-3 note that the addition of lactate measurement did not meaningfully improve predictive validity of qSOFA but may help identify patients at intermediate risk
- The data set of 148,907 patients that the definition is based on were those with suspected infection who had body fluids sampled for culture and received antibiotics – would mortality be higher if they had not received antibiotics? Can this be extrapolated to patients who are yet to receive antibiotics?
- It is unclear how to interpret previous studies (e.g. Rivers et al 2001, ProCESS, PROMISE, and ARISE) in light of the new definitions.

For more information about concerns with sepsis-3 see in Sepsis Definitions

Oxygen availability is compromised in patients with septic shock, normal oxidative metabolism at the cellular level is severely impaired and anaerobic metabolism occurs. This state is characterised biochemically by the release of lactate from cells, though elevated serum lactate levels are neither sensitive nor specific for shock. Altered cellular metabolism results in altered cellular function and even in cell death via necrosis or apoptosis. Apoptosis is a more physiologic and controlled process of programmed cell death, though these programmes may be heightened due to inflammatory stimulation.

In text References

(Singer et al. 2016)

References

- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC., The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)., 2016, PMID:26903338

1. 4. Biochemical Processes of Sepsis

The biochemical processes of sepsis are very complex – the consequence of the coordinated interaction of hundreds of host-derived mediator molecules including cytokines, the complement and coagulation cascades, vasoactive mediators such as kinins, prostaglandins, acute phase reactants and short-lived intermediates of oxygen and nitrogen. However, the resultant effects on blood flow and oxygen delivery to the tissue can be readily understood as the consequence of four key acute changes, described below.

1. 4. 1. Vasodilation

Vasodilation involving small arterioles and nutrient vessels reflects the presence of mediators and the dysfunction of compensatory mechanisms. A number of cytokines induce the expression of inducible nitric oxide synthase (iNOS) in vascular endothelial cells. iNOS catalyses conversion of the amino acid arginine to citrulline, generating a molecule of nitric oxide. Nitric oxide is a potent smooth muscle relaxing agent that causes

local vasodilatation – indeed this property accounts for the pharmacologic effects of such classical vasodilatory agents as nitroglycerin and nitroprusside. This may be a local process that directly opposes sympathetic stimulation. Vasodilatation reduces resistance, induces relative hypovolaemia (as the volume required to fill the cardiovascular tree is significantly increased) and therefore lowers the effective blood pressure10. Moreover, the loss of normal microvasculature resistance results in accelerated passage of blood through capillary beds, reducing the time available for the passive unloading of oxygen from saturated erythrocytes.

1. 4. 2. Loss of endothelial barrier function

Loss of integrity of the endothelial barrier – a consequence of disruption of the endothelial tight junctions and loss of endothelial cells – results in the loss of proteins and fluid into the interstitium. This further decreases the effective intravascular volume. Moreover, the resulting oedema aggravates cellular hypoxia by increasing the distance between the erythrocyte in the capillary and the adjacent cells, and so increases the distance that oxygen must diffuse to reach the cell.

1. 4. 3. Occlusion of capillaries

Occlusion of capillaries by thrombi, activated leukocytes, and aggregates of erythrocytes, whose capacity for deformation during passage through the microvasculature has been reduced, significantly impairs perfusion (Figure 2, Figure 3) (De Backer et al. 2002). Oxygenated blood bypasses these occluded capillaries, fails to unload oxygen and therefore results an increase in the local tissue oxygen deficit.

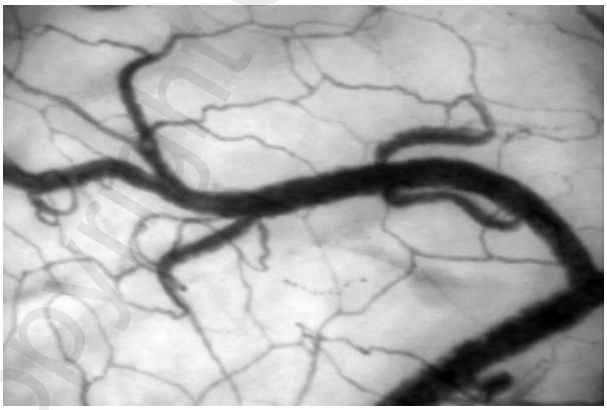


Figure 2:Intravital sidestream dark field (SDF) images of the sublingual microcirculation under normal conditions. Capillaries with red cells flowing(De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL., 2002).

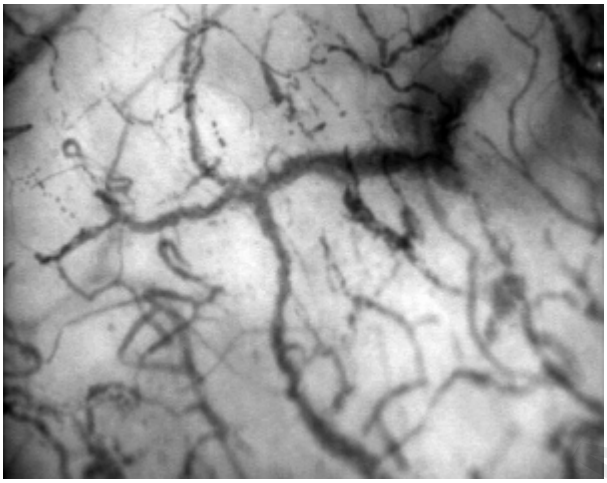


Figure 3:Intravital sidestream dark field (SDF) images of the sublingual microcirculation under septic conditions: Obstructed with minimal flow (De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL., 2002).

1. 4. 4. Impaired myocardial contractility

Impaired myocardial contractility occurs as a consequence of poorly characterised myocardial depressant factors and further affects physiologic compensation. Reduced myocardial contractility is readily demonstrable in animal models and in septic humans; its biologic basis is poorly understood and probably multifactorial. Moreover its significance is uncertain, since the cardiac output in sepsis is characteristically increased, and clinical evidence of impaired cardiac output commonly reflects inadequate fluid resuscitation. The net consequence of these abnormalities is the classical haemodynamic profile of resuscitated sepsis: tachycardia, peripheral oedema, a hyperdynamic circulation (assuming adequate fluid resuscitation), warm extremities, and tissue hypoperfusion characterised by an elevated mixed venous oxygen saturation (SvO_2).

1. 4. 5. Mitochondrial dysfunction in sepsis

There is significant evidence that implicates mitochondrial dysfunction in sepsis-induced organ dysfunction. Mitochondria are affected by systemic inflammation in a number of ways: insufficient oxygen at the mitochondrial level to allow function; the generation of excess amounts of NO, CO, H_2S and other reactive oxygen species that cause direct damage to mitochondrial structures; hormone induced alterations in function and efficiency; and the downregulation of mitochondrial gene transcription proteins. These processes lead to a bioenergetic-metabolic shutdown, similar to a state of hibernation, which manifests grossly as multi-organ dysfunction. Various preclinical and clinical studies have demonstrated an association between the degree of mitochondrial impairment and either clinical severity, organ dysfunction or poor outcomes.

However, whether this is a causal pathway to organ damage and death or simply “along

for the ride" is unclear. This cellular hibernation state that manifests as multi-organ failure may represent a mechanism through which eventual survival is enhanced in those tissues hardy enough to survive even overwhelming inflammation.

What is the pathologic basis for each of the following clinical features of sepsis?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

- Tachycardia
- Tachypnea
- Peripheral oedema
- A reduction in systemic vascular resistance
- An increase in central venous oxygen saturation

Think

The classical signs of local inflammation – rubor, tumor, calor, dolor, and functio laesa – have their systemic counterparts in patients with systemic inflammation. What are they? Are these beneficial or detrimental to the host?

In text References

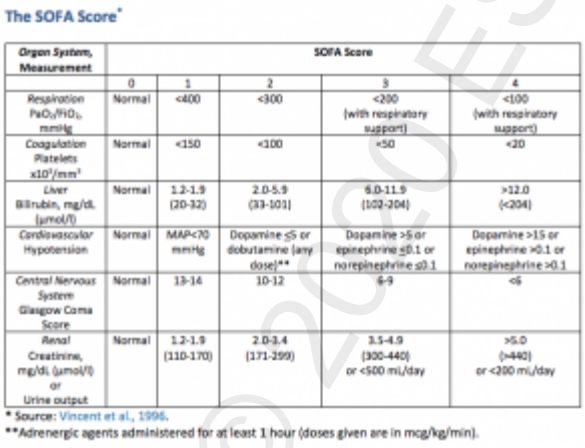
(Singer 2014)

References

- De Backer Daniel, Creteur J, Preiser JC, Dubois MJ, Vincent JL., Microvascular blood flow is altered in patients with sepsis., 2002, PMID:12091178
- Singer M, The role of mitochondrial dysfunction in sepsis-induced multi-organ failure., 2014, PMID:24185508

2. Recognising the Critically Ill patient with Sepsis

Early recognition is crucial in the treatment of sepsis. Previous consensus statements suggested that sepsis could be recognised by the relatively non-specific physiologic SIRS criteria (tachycardia, tachypnoea, hypo- or hyperthermia and leukopenia or leucocytosis) in the setting of suspected or confirmed infection. While each of these does reflect the physiologic abnormalities that accompany the onset of systemic inflammation, they are neither specific nor comprehensive in encompassing the acute derangements that signal sepsis. What is more important is the acute change in clinical status that denotes the systemic derangements of sepsis with organ dysfunction, which in the new sepsis definition is estimated by the SOFA score. Click here for a SOFA score calculator.



The SOFA Score*

Organ System, Measurement	SOFA Score				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (μmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

* Source: Vincent et al., 1996.
**Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

Figure 4: The SOFA Score. Vincent et al. 1996

In text References

(Vincent et al. 1996)

References

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2. 1. Use of qSOFA

The use of the SOFA score is less well established outside of the ICU setting and requires laboratory values that may not be readily available. In order to identify sepsis as soon as possible (usually in the Emergency Department, before the patient requires ICU-level care), the quick SOFA (qSOFA) was developed. The qSOFA is a simple, quick and easy to use risk stratification tool for non-ICU settings to recognise sepsis at an early stage.
It can be obtained without laboratory testing and requires ≥ 2 of the following 3 criteria:

1. Systolic Blood Pressure ≤ 100 mmHg
2. Respiratory Rate ≥ 22/min
3. Altered Mentation (e.g. confusion, lethargy, agitation, coma, etc.)

To identify patients with a significant risk of death from sepsis, prompting further assessment and rapid intervention. It urges the physician to consider the possibility of sepsis, to investigate for the presence of organ dysfunction and to escalate therapy as appropriate. However, qSOFA is not intended as a standalone assessment for sepsis, and it does not imply that patients with only one qSOFA criterion do not need timely appropriate escalation of care (Machado et al. 2017). In fact, any acute change in physiologic homeostasis may be an early sign of the sepsis clinical syndrome (Levy et al. 2003).

The qSOFA requires both prospective validation across different clinical settings and comparison with other risk stratification tools (such as the Modified Early Warning System score, the National Early Warning Score and the Mortality in Emergency Department Sepsis Score) before universal adoption can be recommended.

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2. 2. Use of Biomarkers

In the future, molecular diagnostic methods, including sepsis-specific biomarkers or assays, may provide the means to diagnose infection and sepsis with more speed and precision than current methods. Unfortunately, that future has not yet arrived, and biomarkers cannot be considered replacements for established diagnostic modalities. Traditional biomarkers of sepsis — such as total white cell count, neutrophil count and C-reactive protein — lack the specificity to discriminate inflammation due to burns, trauma or non-infectious inflammatory disorders such as vasculitis. Newer biomarkers, such as procalcitonin, polymorphonuclear CD64 index and sTREM-1 (soluble Triggering Receptor Expressed on Myeloid cells-1) do not have enough sensitivity or specificity and have not yet been adequately validated. Consequently, biomarkers, at present, do not play a role in the diagnosis, or exclusion, of sepsis.

2. 3. Finding the Causative Agent

Bacteraemia is presently defined by a positive blood culture. However, bacterial colonies can take up to 2-3 days to grow, so as a diagnostic test blood culture is slow and can delay appropriate treatment. Furthermore, the culture results may be falsely negative or falsely positive. Overall, positive blood cultures are found in only 30% of patients with sepsis (Calandra, Cohen and International Sepsis Forum Definition of Infection in the ICU Consensus. 2005). Molecular techniques, such as polymerase chain reaction/electrospray ionization-mass spectrometry (PCR-ESI-MS) have demonstrated higher rates of pathogen identification than standard blood culture and can provide results within 6 hours (Vincent et al. 2015). However, these assays still require broader clinical evaluation and are presently cost-prohibitive for many institutions.

Therefore, although several laboratory tests may contribute to the diagnosis of sepsis, and promising new laboratory techniques such as PCR/ESI-MS are emerging, at present the early identification of sepsis is still largely clinical.

Recognition of sepsis early is crucial, as immediate intervention is needed to:

- Restore haemodynamic stability and tissue perfusion
- Determine the cause and reverse or correct it
- Institute appropriate physiologic support to prevent further tissue injury.

Undertaking these steps is life saving and will be discussed next.

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3. Resuscitation and Haemodynamic Support of the Septic Patient

When oxygen supply falls short of tissue demand, cells fail to produce energy in adequate amounts, leading to cellular dysfunction and eventually cell death. Therefore, tissue survival depends on distribution of adequate amounts of oxygen and an adequate perfusion pressure (clinically represented by a normal blood pressure) to meet the needs of cellular oxygen consumption.

In order to evaluate the adequacy of blood pressure, it is important to search for signs of hypoperfusion, which include altered mentation, low urinary output, skin mottling/prolonged capillary refill time and lactacidemia. **Shock is defined as persistent hypotension (despite adequate fluid resuscitation requiring vasopressors to maintain a mean arterial pressure ≥ 65 mmHg) and a serum lactate level ≥ 2 mmol/L.**

Septic shock can be the result of a complex interaction between several haemodynamic abnormalities:

- Absolute hypovolaemia: due to insensible losses from fever and tachypnea, fasting, vomiting, diarrhoea and capillary leakage with extravasation of fluid into the interstitial tissues.
- Relative hypovolaemia due to vasodilation. Vasodilation may be present at the time of initial presentation or develop later in the course of hemodynamic decline. Vasodilation can coexist with zones of vasoconstriction, sometimes in the same organ.
- Myocardial dysfunction is often present, even at earlier stages. Clinical manifestation varies depending on the severity of shock and patient comorbidities.
- Imbalances between oxygen demand and supply and intracellular (probably mitochondrial) abnormalities of oxygen metabolism.

Rising levels of serum lactate represent cellular dysoxia and should be interpreted as an early marker of oxygen consumption impairment (VO_2) and tissue hypoperfusion. Lactate is poor prognostic indicator and should be actively normalised in the initial resuscitation in patients with septic shock (Rhodes et al. 2017).

In text References

(Perner et al. 2017)

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3. 1. Fluid Resuscitation

In the early phases of septic shock (within the first 3 hours), aggressive intravenous fluid infusion is recommended (at least 30 mL/kg of IV crystalloid), and the appropriateness of additional volume infusions should be carefully evaluated. Several methods are available to identify the degree of fluid responsiveness and the potential effects of fluid challenges on cardiovascular function. Static measurements such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) have been proven to be poor predictors of fluid responsiveness, and as such, their use as guides for fluid resuscitation can no longer be justified. Consequently, other parameters are now preferred (Tables 2 and 3). Additional tests have been proposed such as tidal volume challenges, recruitment manoeuvres, and micro (50 mL) fluid challenges, but these still require further evaluation.

How should fluids be administered?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

- The SSC guidelines recommend the administration of an initial fixed bolus of at least 30 mL/kg of fluid within the first 3 hours with frequent reassessments of hemodynamic status
- An alternative approach is giving 250-500 mL boluses followed by reassessment of the circulatory status after each bolus

- Fluid overload is strongly associated with an increase in mortality. After initial resuscitation additional fluid administration should be carefully weighed against detrimental effects, and guided by frequent reassessments of hemodynamic status

While fluid resuscitation can be life-saving, it is not an intervention without risk, particularly if misapplied. All of the following points should be considered:

- No predictor of fluid responsiveness has perfect sensitivity or specificity.
- Ancillary data points such as heart rate, urine output, improvement in tissue pallor, and lactate levels may also be useful in assessing the response to resuscitation.
- Fluid overload can be associated with a rise in mortality. Careful fluid management and “de-resuscitation” of septic patients (potentially as early as 24-48 hours following the success of early resuscitation efforts) can save lives and at a minimum, decrease the incidence of acute kidney failure and number of days in the ICU.

Table 2: Methods of Monitoring Response to Fluid Challenges

Method	Considerations
Pulse pressure variation (PPV) • 84% (75-90) sensitivity Stroke volume variation (SVV)	Patients must be deeply sedated and require paralysis. Not interpretable in the setting of: • cardiac arrhythmia • poor lung or thoracic wall compliance • low tidal volumes (=< 6 mL/kg) • spontaneous respiratory activity
Passive leg raising test (PLR) • 88% (80 -93) sensitivity	Preferably assessed by changes in cardiac output/index (CO/CI); changes in blood pressure secondary.
End-expiratory occlusion manoeuvre (EEOM)	Patients must tolerate a 15 second pause in ventilation. May be invalid at a tidal volume of 6 mL/kg.
“Mini” fluid challenge: infusion of 50-100 ml of fluid.	Not robustly validated
Ultrasonography of heart and inferior vena cava (tests respiratory variations)	Skill and experience is needed

Note

The first 3 tests are validated by many studies and meta-analyses. All parameters have sensitivity and specificity ranging from 75-95% under the proper clinical conditions.

Table 3: Cut-offs and "Grey Zones" for Parameters

Pulse Pressure Variation (PPV)	11% (4-15%)
Stroke Volume Variation (SVV)	13% (10-20%)
Passive Leg Raising (PLR)	• Δ in aortic blood flow (≈ CO) ≥10% • Δ in pulse pressure ≥15%
Inferior vena cava variation diameter (for patients receiving positive pressure ventilation)	12% ΔDIVC

In text References

(Marik and Cavallazzi. 2013; Angus et al. 2015; Rhodes et al. 2017; Hjortrup et al. 2016)

3. 1. 1. Type of Intravenous Fluid

Principles behind fluid selection are presented in Table 4. The superiority of colloids over crystalloids in terms of effectiveness is no longer accepted and initial resuscitation is now based on the use of crystalloids. The optimal crystalloid is not presently clear however. Concerns have been raised from observational studies and a meta-analysis over the association between the use of normal (0.9%) saline and hyperchloraemic renal injury (and potentially a rise in mortality). However, such concerns have yet to be borne out in a randomised trial.

Although the SSC guidelines presently do not recommend the use of balanced salt solutions (e.g. Ringer's lactate or Plasmalyte®) over normal saline, hyperchloraemia should be avoided and appropriate attention paid to serum chloride levels irrespective of the fluid solution selected. Two large trials are currently in progress to compare the safety profile of normal saline versus balanced salt solutions, the BRICNET Trial (Brazil - 11,000 patients) and the PLUS Trial (ANZICS - 8,800 patients). A combined meta-analysis is also planned.

Table 4: The Optimal Fluid in Sepsis

The Optimal Fluid in Sepsis
Crystalloids are preferred over colloids. The ratio of effectiveness is not 1:6 as previously thought, but 1:1 to 1:1.8
Irrespective of crystalloid solution selected, hyperchloraemia should be avoided
Human albumin can be considered for patients requiring substantial amounts of crystalloids
The place of gelatin solutions is presently unknown (quality studies on use in sepsis are lacking)
Hydroxyethyl starch (HES) should not be used due to higher rates of mortality and RRT as compared to crystalloid
If anaemia warrants correction, post-transfusion haemoglobin concentrations should be kept between 7-9 g/dL (i.e. there is no demonstrated benefit of transfusing to haemoglobin levels >9 g/dL).

The place of human albumin is still a matter of debate. However, when a colloid is considered in septic shock patients, albumin is the preferred choice and an albumin concentration target of 3 g/dL is usually used. The SSC guidelines suggest the addition of albumin to crystalloids for intravascular volume replacement when patients are requiring substantial volumes of crystalloids for resuscitation, though this is a recommendation with low quality of supporting evidence.

Table 5: Summary of the SSC recommendations regarding fluid therapy (SSC 2016)

Summary of the SSC recommendations regarding fluid therapy (SSC 2016)
We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve.
We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

In text References

(Finfer et al. 2004; Serpa Neto et al. 2017; Caironi et al. 2014; Holst et al. 2014; Rhodes et al. 2017)

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3. 2. Vasopressors

The correction of hypovolaemia alone will sometimes not result in the normalisation of blood pressure. One or more vasopressors, sometimes in combination with inotropes, are might be needed. However, the appropriate time to initiate vasopressor support is not clear. Presently, the SSC guidelines recommend the initiation of vasopressor therapy when fluid resuscitation has proven unsuccessful and there are some data to support norepinephrine initiation within 30 minutes of fluid resuscitation failure. An additional consideration for the early initiation of vasopressor therapy is diastolic arterial pressure (DAP) – a low DAP (i.e.: <40 mmHg) suggests a markedly depressed arterial tone, and these patients may benefit from the earlier initiation of vasopressor therapy, potentially as fluid resuscitation is ongoing. Studies to address the optimal timing of vasopressor initiation in relationship to fluid resuscitation are anticipated in the near future.

Recent systematic reviews and meta-analyses have established norepinephrine as the vasopressor of first-choice. Dopamine is now recommended as an alternative to norepinephrine only in a highly selected patient population (e.g. those with absolute or relative bradycardia and a low risk of tachyarrhythmia). Vasopressin and epinephrine are adjunctive agents to norepinephrine – either to decrease high norepinephrine dosages or to raise MAP to the targeted goal should norepinephrine alone prove insufficient. Terlipressin, where available, is an alternative to vasopressin.

The use of dobutamine, a β-adrenergic inotrope, is suggested in patients who show evidence of persistent tissue hypoperfusion despite adequate volume resuscitation and vasopressor support, particularly if cardiac output is appears inadequate. Alternative inotropic agents, such as milrinone or levosimendan, can be considered for the treatment of septic cardiomyopathy (see section on Septic Cardiomyopathy).
Vasoactive therapies are implemented to target a MAP of 65 mmHg. There are no data to support a mortality benefit of targeting higher MAP targets. However, MAP targets should be individualised to a given patient's condition and pre-existing normal blood pressure or

co-morbidities (lower values may be acceptable for younger patients with no prior medical history, while higher targets may be required in older, formerly hypertensive patients). Lactate-guided resuscitation may be considered as an alternative to resuscitation based upon hemodynamic targets and may confer survival benefits over resuscitation strategies without lactate monitoring.

All patients requiring vasopressor therapy should have an arterial catheter placed as soon as possible in order to more accurately measure MAP.

Table 6: Suggested Initial and Maximum Dosage of Vasopressors/Inotropes. It recommended to the guidelines in your local institution.

Vasopressor/Inotrope	Initial Dose	Maximum Dose
Dobutamine	2-5 mcg/kg/min	50-200 mcg/kg/min
Dopamine	2 mcg/kg/min	20-50 mcg/kg/min
Epinephrine	0.1 mcg/kg/min	1 mcg/kg/min
Norepinephrine	0.1 mcg/kg/min	3 mcg/kg/min
Milrinone	0.375 mcg/kg/min	75 mcg/kg/min
Phenylephrine	0.4 mcg/kg/min	9 mcg/kg/min
Vasopressin	0.01 units/min	0.06 units/min
Methylene Blue		2 mg/kg/hour

Table 7: Controversial or Alternative Vasopressors for Septic Shock

Controversial or Alternative Vasopressors for Septic Shock
Dopamine: an alternative to norepinephrine only in selected patients (those with absolute or relative bradycardia and low risk of tachyarrhythmia). Low-dose dopamine (1-5 mcg/kg/min IV) for “renal protection” is not recommended.
Epinephrine: is an adjunct to norepinephrine. Its use makes it difficult to use lactate clearance to guide resuscitation.
Phenylephrine: is a weak agonist of alpha receptors and will not work if other catecholamines fail. Its use is discouraged.

Methylene Blue: Inhibits nitric oxide (NO) mediated peripheral vasodilation. Should not be used in the setting of G6PD deficiency, ARDS or pulmonary hypertension.
Vasopressin and Terlipressin: are alternative vasopressors when adrenergic receptors are down-regulated. They are also adjuncts to norepinephrine. They mobilise intra-cellular Ca++ through a different pathway (AVP receptors).
Angiotensin II: a potential new addition to the vasopressor repertoire (though not yet widely available). LJPC-501 is a synthetic human angiotensin II recently evaluated in a Phase III study in which 70% catecholamine resistant patients responded with a significant increase in arterial pressure.

Table 8: Summary of the SSC recommendations regarding the use of vasoactive medications:

Summary of the SSC recommendations regarding the use of vasoactive medications:
We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).
We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.
We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g. patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).
We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

Remarks: If initiated, vasopressor dosing should be titrated to an end point reflecting

perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.

3. 3. Septic Cardiomyopathy

Myocardial dysfunction consequent to infection occurs in a subset of patients with septic shock but cardiac output is usually maintained by tachycardia, ventricular dilatation and reduced vascular resistance. Some patients may, however, have a diminished cardiac reserve resulting in poor oxygen delivery. Vasopressor treatment options in this case are outlined in Figure 2. From a clinical point of view, the use of dobutamine for the correction of systolic dysfunction should be titrated to a target cardiac index. Targeting a cardiac index of 3.0-3.5 L/min/m^2 is reasonable, but has no evidence base. Targets should be assessed in the hemodynamic/perfusion context, integrating additional data such as lactate levels and the $ScvO_2$. Of note, markedly elevated cardiac indices or $ScvO_2$ are associated with poor outcomes and should be avoided when possible. Consequently, dobutamine is best used with a continuous assessment of cardiac index and continuous (or intermittent) measurements of $ScvO_2$. Beta-blockade (i.e.: esmolol infusion) can be considered in patients with markedly hyperdynamic cardiac indices, though additional evidence is required before this practice can be broadly recommended.

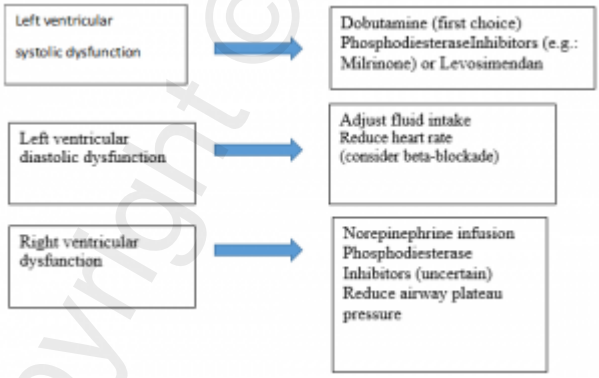

Figure 5: Cardiac Dysfunction

3. 4. Treatment Options in Refractory Septic Shock

When septic shock remains refractory to standard therapies, several options are presented in Table 9. Aside from corticosteroid therapy and Angiotensin II, however, the use of these agents is not supported by robust evidence.

Table 9: Potential Options for Refractory Septic Shock

Potential Options for Refractory Septic Shock
1)Consider hydrocortisone (200-300mg IV/day)
2)Consider calcium-sensitizing agent (i.e.: levosimendan)
3)Consider methylene blue
4)Consider angiotensin II infusion (if available)
5)Consider ECMO, depending on mechanism of hemodynamic compromise

After 12 to 24 hours, if hemodynamic stabilisation has been achieved, catecholamine weaning should be considered.

In text References

(Rhodes et al. 2017; De Backer et al. 2010; Russell et al. 2008; Asfar et al. 2014; Jones et al. 2010; Morelli et al. 2013; Khanna et al. 2017)

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4. Identification and Control of the Source of Infection

Sepsis is a life-threatening medical emergency. Timely identification and early treatment initiation is crucial for the patient's survival. Source control is one of the cornerstones of the treatment of septic patients.

In the famous Kumar study, only 50% of patients with septic shock had received antibiotics 6 hours after the recognition of hypotension. In this group of patients, mortality increased 7.6% for every hour that antimicrobial therapy was delayed. A retrospective analysis of the SSC database showed that mortality rose linearly for every hour where antimicrobial therapy administration was delayed. Therefore, the administration of appropriate antibiotics, as early as possible, is the main pillar of the management of patients with sepsis.

The diagnosis of sepsis is based upon the criteria for sepsis and septic shock as previously discussed (link). However, the identification of the underlying focus of infection can be difficult because specific signs are often missing. Furthermore, multiple foci can be present and clinical signs are often non-specific and can mimic other diseases.

Patients with impaired organ function should always be promptly examined for infection. This is very important, as the initiation of antimicrobial therapy and source control are life saving.

If the clinical situation is complex and infection cannot be ruled out, empirical antibiotics should be started without delay, especially if organ dysfunction is present. Depending on the clinical course, management can be re-evaluated subsequently.

Important

Sepsis is a medical emergency. Consider it present in every critically ill patient until proven otherwise

4. 1. Clinical Recognition of Infection

Suspected infection merits prompt and comprehensive evaluation, as the clinical signs are diverse and can be misleading. Non-specific symptoms such as **alterations in mental state** and **general deterioration** are frequently observed by relatives and medical

staff. Patients can report nausea, pain and thirst. Such symptoms should trigger further assessment.

To address the challenges of recognition, current guidelines recommend screening critically ill patients who are at risk for sepsis. See Sepsis and Septic Shock Part 1.

> ★ **Important**
>
> Awareness, active investigation and further diagnostics are essential for the recognition of infection and sepsis

4. 1. 1. Summary

1. Patients suspected of having an infection, especially with impaired organ function, need to be immediately diagnosed and treated.
2. Patient´s history, clinical examination and laboratory values can point to the source of infection. Consider:
    1. Age
    2. Comorbidities
    3. Previous treatments and surgery
    4. Presence of foreign material, e.g.: prosthetic valves
    5. Social history and habits
    6. Location where infection was acquired, e.g.: community, hospital, institution, abroad, etc.
3. Treat a patient with suspected infection the same as you would a patient with proven infection.
4. Whenever possible, obtain blood cultures (at least 2 pairs) prior to antimicrobial therapy. DO NOT delay treatment if unable to obtain adequate samples in a timely manner.
5. Start antimicrobial therapy with broad-spectrum coverage without delay.
6. Search for the focus of infection. Use clinical examination, imaging, and laboratory and microbiological studies (e.g. urine, bronchial secretions, pleural effusion, cerebrospinal fluid, swabs, tissue samples).
7. Evaluate interdisciplinary possibilities of source control as soon as possible – Involve the surgeon!
8. Re-evaluate the patient frequently. Once the source is identified, target (escalate or deescalate) therapy in accordance with microbiological findings and susceptibility results. This should occur within 72h.

Do not continue antimicrobial therapy without justification or for unnecessarily long durations.

4. 2. Sites of Infection

Table 10 represents an overview of the foci and types of infection.

Table 10: Specific types of infection

Bone and Joint Infection	Osteomyelitis, Disc space infection, Joint or bursa infection, Prosthetic joint infection, Spondylodiscitis
Central Nervous System Infection	Intracranial infection, Meningitis or ventriculitis, Cerebritis, Spinal abscess
Cardiovascular System Infection	Endocarditis, Mediastinitis, Arterial or venous infection
Dental, Ear, Upper Respiratory Tract Infection	Dental infection, Mastoiditis, Oral cavity infection, Sinusitis, Upper respiratory tract infection, Pharyngitis, Laryngitis, Epiglottitis
Gastrointestinal System Infection	Gastritis, Enteritis, Colitis, Intraabdominal abscess, Clostridium difficile Infection, Necrotizing enterocolitis, Cholecystitis, Cholangitis, Pancreatitis
Lower Respiratory System Infection	Pneumonia, Pleural empyema
Reproductive Tract Infection	Male or female reproductive tract, Endometritis, Episiotomy infection, forgotten tampons
Skin and Soft Tissue Infection	Breast abscess or mastitis, Burn super-infection, Decubitus ulcer infection, Skin infection, Soft tissue infection
Renal and Urinary System Infection	Cystitis, Pyelonephritis, Urinary tract infection (UTI)
Sepsis of the newborn	Early onset neonatal sepsis, Late onset neonatal sepsis

Heath care associated infections	Central line-associated bloodstream infection (CLABSI), Catheter-associated urinary tract infections (CAUTI), Surgical site infection (SSI), Ventilator-associated pneumonia (VAP), Implant infection (artificial joints, artificial heart valves)

4. 3. Clinical Examination, Laboratory Investigations, Microbiological Testing and Imaging

Finding the focus of infection can require extensive diagnostic measures. The **patient's history** (comorbidities, recent medical interventions/operations) and a **physical examination** (altered mental status, temperature, respiratory rate, heart rate, blood pressure, the presence of purulent sputum, abdominal pain, indwelling catheters, foreign bodies or material, oliguria/anuria) are always necessary and can provide important information.

Laboratory investigations should always be performed. They should include a full blood count, tests of organ function and particularly infection-associated markers. Table 10 describes laboratory values useful for the identification of infection. Procalcitonin in particular has been widely used to discriminate infectious from non-infectious conditions. However, procalcitonin levels vary depending on the source of infection, and false negative results can occur, some caution should therefore be exercised in its interpretation.

Important

Many types of infection are possible and often not readily visible. Finding the focus of infection can be challenging. Extensive investigation, including laboratory testing and imaging are often necessary.

Table 11: Potential laboratory values for the detection of infection

	Threshold value	Sensitivity	Specificity
White blood cell count	>12 Gpt/L or <4 Gpt/L		
Immature (band) forms	>10%		

C-reactive protein (CRP)	>10 mg/L	55-75%	55-75%
Procalcitonin (PCT)	>0.5ng/mL	80-90%	65-90%
Interleukin-6	>25ng/mL		

n.b.: In our opinion, TREM-1 testing has not been sufficiently validated to justify its use at this time.

Table 12: Specific Pathogen Tests/Assays

Test	Pathogen	Threshold value	Sensitivity	Specificity
Legionella antibodies	Legionella spp			
Beta-D-Glucan (BDG)	Pneumocystis jirovecii, Aspergillus spp., Candida spp	> 80 pg/mL	50-70%	80-90%
Galactomannan	Aspergillus spp.	>1 ng/mL	50-100%	80-100%
Quantiferon	Mycobacterium tuberculosis			
Influenza Antigen	Influenza A, Influenza B		80%	85%

4. 3. 1. Microbiological Testing

Appropriate routine microbiologic cultures (including blood) should be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock but should not delay the start of antimicrobials.

Positive blood cultures provide objective evidence of the systemic dissemination of a microorganism. Fever has poor positive predictive value, whereas elevated Procalcitonin (PCT) levels are predictive of blood culture positivity. However, blood culture positivity is variable, depending on the nature of the infection as well as the method of sampling. Following adequate skin preparation, at least two blood culture pairs (aerobic and anaerobic bottles) should be taken from peripheral sites, inoculating at least 10 mL of

blood into each specimen bottle. Positive cultures of normally sterile fluids (e.g. pleural or peritoneal fluid) obtained using sterile technique also provide conclusive evidence of infection.

Cultures obtained from surfaces are less reliable, as the differentiation of colonisation from infection is difficult. Positive sputum or urine cultures in intubated or catheterised patients may simply reflect colonisation of the tracheobronchial tree or lower urinary tract respectively. The use of quantitative culture techniques and more invasive interventions such as bronchoalveolar lavage to obtain specimens can improve the reliability of culture data.

> ★ **Important**
>
> Microbiological sampling, especially blood cultures, is essential for pathogen identification. Pathogen identification is a necessary prerequisite for directing and de-escalating antimicrobial therapy.

Microbiological Samples:

- Blood cultures (at least 2 pairs of an anaerobic and anaerobic culture)
- Urinalysis and culture
- Tracheal aspirates
- Bronchoalveolar lavage fluid
- Cerebrospinal fluid
- Tissue swabs
- Fluid/aspirates from abscesses and body cavities (pleural effusions, articular effusions)

Definitive identification of the isolated microbial species, and evaluation of their sensitivity profiles to common antibiotics are not typically available for two or three days after specimen collection. Earlier presumptive microbial diagnosis can be made using a Gram stain (particularly of blood, cerebrospinal fluid or urine samples), which can provide information on the class of organism within an hour.

4. 3. 2. Imaging

Imaging is usually necessary to supplement and refine the clinical examination. Imaging informs the determination of whether source control measures (surgical or interventional) are indicated. Imaging studies are typically needed to document the precise site of infection origin and the extent of spread.

- **Ultrasonography** is inexpensive, rapid, and widely available. Its greatest utility lies in detecting infections arising from an obstructed abdominal hollow viscus – for example, the gall bladder and biliary tree leading to acute cholecystitis or cholangitis, respectively, or from the urinary tract in the case of pyelonephritis.

- **Transthoracic or transoesophageal echocardiography (TTE or TEE)** is essential for diagnosing endocarditis.
- **Computerised tomography (CT)** scanning is the most useful diagnostic modality for patients with deep space infections in the abdomen or thorax. It is also useful in evaluating the extent of complex soft tissue infections. Oral or rectal contrast aids in CT interpretation by delineating the lumen of the gastrointestinal tract and by demonstrating leaks from the GI tract when these are present. Intravenous contrast permits the identification of major vascular structures and can demonstrate areas of tissue non-perfusion which are suggestive of ischaemia or infarction.
- **Magnetic resonance imaging (MRI)** can be useful for the diagnosis of soft tissue infections or spondylodiscitis. However, it is time consuming and not readily available.

> ★ **Important**
>
> A whole body computerised tomography scan can be considered in patients with an unknown focus of infection.

See ESICM e-Academy module on Clinical imaging

5. Treatment of Infection

5. 1. Antimicrobial Therapy

If the initial clinical assessment, augmented by the results of rapidly available diagnostics, suggests that infection is likely to be present, then empiric therapy should be started at once. Especially in patients with sepsis and septic shock, intravenous, broad spectrum antibiotics to cover potential pathogens should be started within 1 hour of recognition.

Table 13: Definition of antimicrobial terms

Name	Definition
Empiric therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification. Empiric therapy may be monotherapy, combination, or broad-spectrum.
Targeted/definitive Therapy	Therapy targeted to a specific pathogen (usually after microbiological identification). Targeted/definitive therapy may be monotherapy or combination therapy, but it is not intended to be broad-spectrum.
Broad spectrum therapy	The use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, usually during empiric therapy (e.g. piperacillin/tazobactam, vancomycin and anidulafungin; each is used to cover a different group of pathogens). Broad-spectrum therapy is typically empiric since the usual purpose is to ensure antimicrobial coverage with at least one drug when there is uncertainty about the possible pathogen. On occasion, broad-spectrum therapy may be continued into the targeted/definitive therapy phase if multiple pathogens are isolated.

Multidrug therapy	Therapy with multiple antimicrobials to deliver empirical broad-spectrum therapy or to potentially accelerate pathogen clearance (combination therapy) with respect to a specific pathogen where the pathogen is known or suspected. This term therefore includes combination therapy.
Combination therapy	The use of multiple antibiotics (usually in different mechanistic classes) with the specific intent of covering the known or suspected pathogen with more than one antibiotic (e.g., piperacillin/tazobactam and aminoglycoside or fluoroquinolone for gram negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with ß-Lactams for streptococcal toxic shock) or potentiate immune modulatory effects (macrolides with a ß-lactam for pneumococcal pneumonia)

★ **Important**

In critically ill patients with suspected infection, broad spectrum antimicrobial therapy should be initiated without any delay. Subsequent modification based on the clinical situation, microbiological findings and sensitivity results is recommended.

Antimicrobial therapy and dosing should be selected based on the presumptive focus of infection (e.g. pneumonia, intra-abdominal infection, prosthetic device-related infection), the mode of acquisition (community-acquired or nosocomial), patient related factors (comorbidities, renal elimination, renal replacement therapy, volume of distribution) and the local/institutional microbial resistance patterns.

Specific characteristics (tissue penetration), pharmacokinetics and pharmacodynamics (PK/PD) should also be considered. Therapeutic drug monitoring may be required to optimise antimicrobial dosing.

Empiric broad-spectrum antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established and/or clinical improvement is observed. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy. In the case of clinical deterioration, other organisms (fungi, viruses, parasites) should be considered and therapy escalated if appropriate.

The ongoing need for antimicrobial therapy should be evaluated daily.

Systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g. severe pancreatitis, burn injuries) is not recommended. In most cases, an antimicrobial treatment duration of 7–10 days (or shorter) is adequate. Longer courses are appropriate in patients who demonstrate slow clinical responses, have undrainable foci of infection, bacteraemia with Staphylococcus aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia.

Daily assessment for de-escalation of antimicrobial therapy is recommended to avoid unnecessarily long treatment courses. Procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appear to have sepsis, but subsequently have limited clinical evidence of infection.

Table 14: Summary of recommendations for antimicrobial therapy SSC 2016

Summary of recommendations for antimicrobial therapy SSC 2016
We recommend that administration of IV antimicrobials is initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).
We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).
We recommend that empiric antimicrobial therapy is narrowed once pathogen identification and sensitivities are established and/or clinical improvement is observed .
We do not recommend sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury).

We recommend that dosing strategies of antimicrobials are optimised based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock.
We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).
We suggest that combination therapy is not routinely used for ongoing treatment of most other serious infections, including bacteraemia and sepsis without shock (weak recommendation, low quality of evidence).
We do not recommend combination therapy for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence).

If combination therapy is initially used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy.

- We suggest that an antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
- We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable focus of infection, bacteraemia withS. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).
- We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).
- We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

5. 2. Source Control

Source control is as important as antimicrobial therapy. A specific anatomic focus of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis. Appropriate source control interventions should be

implemented as soon as medically and logistically feasible after the diagnosis is made. Imaging of anatomic sites may facilitate image-guided minimally invasive management using percutaneously placed drains.

Table 15: Incubation periods of common travel-related infections

Intervention	Sources
Catheter removal	Catheters (central line, urinary catheter) suspected as a possible source of infection
Surgical removal/drainage (Surgical/interventional specialists where available)	Abscesses, intestinal perforations, anastomotic leaks, cholecystitis, appendicitis, osteomyelitis, dental infections, Implants (artificial joints, heart valves, pacemakers), joint infections
Debridement	Skin and soft tissue infections, decubitus ulcer infections
Percutaneous drainage	Abscesses, pleural effusions

Table 16: Summary of recommendations for Source Control of the SSC 2016

Summary of recommendations for Source Control of the SSC 2016
*We recommend that a specific anatomic diagnosis of infection requiring emergent source control is made or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention is implemented as soon as medically and logistically practical after the diagnosis is made.
*We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.

In text References

(Rhodes et al. 2017; Singer et al. 2016; Baron et al. 2013; Martínez et al. 2017; Horan, Andrus and Dudeck. 2008)

References

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5. 1. Adjuvant Therapies for Sepsis

Despite advances in our understanding of sepsis, mortality rates remain about 40% in the presence of shock, even with treatment. Earlier in this module, the importance of prompt diagnosis, early resuscitation and directed therapies for sepsis were emphasised. It is, however, important to appreciate that several other aspects of the disease and its treatment can also influence outcomes in sepsis. This section will highlight adjunctive interventions, based on available evidence, that may be considered part of a comprehensive therapeutic approach.

Warning

> Many therapeutic interventions have been investigated for sepsis in an attempt to reduce morbidity and mortality. We will only discuss those with some evidence base.

In text References

(Rhodes et al. 2017; Singer et al. 2016)

References

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5. 1. 1. Corticosteroids

A French RCT showed that administration of hydrocortisone in patients with vasopressor-unresponsive septic shock was associated with shock reversal and lower mortality rates. However, the large European multicentre CORTICUS trial, demonstrated that in septic patients with systolic blood pressure <90 mmHg unresponsive to fluid resuscitation and vasopressors, steroid therapy did not lead to a survival benefit. The Surviving Sepsis Campaign (SSC) guidelines presently recommend against the use of in hydrocortisone in septic shock patients if hemodynamic stability has been restored with fluids and vasopressors. If the restoration of hemodynamics cannot be achieved, SSC suggests hydrocortisone administration at 200 mg/day.

ACTH testing is no longer recommended before the use of hydrocortisone in septic patients. In addition, while random cortisol levels may assist in the diagnosis of absolute adrenal insufficiency, they are much less useful in the diagnosis of relative adrenal insufficiency, a condition frequently observed in sepsis. There is no robust current evidence to favour either tapering or abruptly stopping steroid therapy. However, a crossover study showed that abrupt cessation of steroid therapy did result in a

hemodynamic decline. Therefore, it is generally recommended to taper corticosteroids, and to start this taper when there is no longer a need for vasopressor support. It should be noted that steroid administration does not prevent the evolution of sepsis to septic shock, and hyperglycaemia and hypernatremia common may develop. Early steroid therapy should be considered in cased of known prior steroid therapy or suspected impaired adrenal function.

In text References

(Sprung et al. 2008; Annane et al. 2009; Keh et al. 2016)

References

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5. 1. 2. Blood products

5. 1. 2. 1. Red Blood Cells

Transfused red blood cells (RBCs) increase the oxygen carrying capacity of blood but may not readily release bound oxygen and consequently, may not result in increased oxygen delivery. In addition, increases in the RBC concentration may adversely affect blood rheology or cause microthromboses, further reducing tissue oxygen delivery. According to the Transfusion Requirements In Septic Shock (TRISS) trial, a restrictive transfusion threshold of 7 g/dL resulted in similar rates of ischemic events, usage of life support modalities, and 90-day mortality as the liberal threshold of 9 g/dL. Further, the

lower-threshold group received significantly fewer transfusions. According to the SSC guidelines, RBC transfusion is not recommended for patients with haemoglobin levels of >7 g/dL in the absence of myocardial ischemia, severe hypoxemia or acute haemorrhage.

5. 1. 2. 2. Fresh Frozen Plasma (FFP)

The transfusion of fresh frozen plasma is indicated in the case of a documented deficiency of coagulation factors in the setting of active haemorrhage or prior to a haemostatic challenge such as surgery or other invasive procedures. Mild clotting abnormalities in non-bleeding patients are usually not corrected with FFP transfusion. Therefore, the SSC guidelines do not recommend the transfusion of FFP if the patient is not bleeding and an invasive procedure is not anticipated (weak recommendation).

5. 1. 2. 3. Platelets

According to the SCC guidelines, prophylactic platelet transfusion is indicated when the concentration is <10,000/mm3 in the absence of apparent bleeding. If there is a significant risk of haemorrhage and platelet counts are <20,000/mm3, platelet transfusion can be considered (weak recommendation). In the case of active bleeding, surgery or invasive procedures, which are frequently performed in septic patients, higher platelet goals are suggested (30-50,000/mm3).

5. 1. 2. 4. Erythropoietin

Erythropoietin administration in critically ill patients has been associated with a slight reduction in RBC transfusion frequency, but no impact on mortality rates and an increased incidence of thrombotic events. Therefore, erythropoietin is not recommended for sepsis-associated anaemia (strong recommendation).

In text References

(Rygård et al. 2016; Liumbruno et al. 2009; Corwin et al. 2002)

References

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5. 1. 3. Analgesia and Sedation

Limiting the use of sedatives in critically ill patients is associated with a reduction of the duration of mechanical ventilation, ICU and hospital length of stay. Several nurse-directed protocols utilise standardised sedation scores in order to facilitate reductions in sedative use. Moreover, a landmark RCT proved that intermittent sedation with daily interruptions led to improved outcomes. Several studies have shown that the use of opioids or short acting drugs, such as propofol and dexmedetomidine, results in better outcomes and faster weaning from mechanical ventilation than the use of benzodiazepines. According to the SSC guidelines, continuous or intermittent sedation should be minimised in septic patients, regardless of the administered drug.

In text References

(Shehabi et al. 2012; Kress et al. 2000; Fraser et al. 2013)

References

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5. 1. 4. Glucose Control

The NICE-SUGAR study demonstrated an increase in mortality rates with intensive insulin therapy in medical and surgical ICU patients. Moreover, a meta-analysis by Song et al., confirmed that intensive insulin therapy did not lead to a survival benefit in septic patients, while it did result in increased incidence of hypoglycaemia. Consequently, it is presently recommended to start insulin therapy after two blood glucose levels >180 mg/dL (10 mmol/l), with the target of a blood glucose level ≤180mg/dL(10 mmol/l). Blood glucose levels should be monitored every 1-2 hours until stabilisation, and every 4 hours therafter if the patient receives an insulin infusion. Glucose levels obtained by point of care testing of capillary blood should be evaluated with caution, as they can overestimate arterial blood or plasma values. Therefore, for point of care measurements of glucose, it is recommended to use arterial blood rather than capillary blood samples.

In text References

(Finfer et al. 2009; Song et al. 2014)

References

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5. 1. 5. Thromboembolism Prophylaxis

The incidence of deep vein thrombosis (DVT) in critically ill patients is 10%, while the incidence of pulmonary embolism (PE) is 2-4%. Risk factors associated with DVTs in ICU are sepsis, septic shock and vasopressor use. Thromboembolism prophylaxis with UFH or LMWH in ICU patients results in a significant decrease in DVT and PE incidence, as confirmed in a meta-analysis. Therefore, the SSC guidelines strongly recommend pharmacologic prophylaxis with LMWH (preferably) or UFH in septic patients in the absence of any contra-indications. Another meta-analysis demonstrated that prophylaxis

with LMWH compared to UFH was associated with lower rates of DVT and a lower mortality rates. Based on this, LMWH is recommended over UFH, with some caveats. LMWH is renally excreted, thus the dose should be reduced to avoid accumulation in patients with renal dysfunction. Monitoring of anti-Xa levels, and subsequent modifications in LMWH dosing, is recommended in patients with a creatinine clearance of <30 ml/minute. In septic patients, a combination of pharmacologic prophylaxis with intermittent pneumatic compression (IPC) or graduated compression stockings (GCP) may be more effective than either method alone. Finally, if pharmacologic prophylaxis is contraindicated, mechanical thromboembolism prophylaxis is recommended.

In text References

(Alhazzani et al. 2013)

References

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5. 1. 6. Stress Ulcer Prophylaxis

Gastrointestinal stress ulcers are common in ICU patients. Clinically significant bleeding has been observed in 2.6% of the critically ill. Mechanical ventilation for >48 hours and coagulopathy are the most common risk factors for gastrointestinal (GI) bleeding. A meta-analysis of 20 RCTs demonstrated that the risk of GI bleeding was reduced when prophylaxis with histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) was used as compared to no prophylaxis. However, prophylaxis was associated with a (non-statistically significant) higher risk of pneumonia. Overall, there is a strong recommendation for patients with sepsis or septic shock to receive stress ulcer prophylaxis, with either H2RAs or PPIs. The need for stress ulcer prophylaxis should regularly be re-evaluated, depending on the presence of risk factors for haemorrhage.

In text References

(Krag et al. 2014)

References

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5. 1. 7. Anticoagulants

In the SSC 2016 guidelines, there is a strong recommendation against the use of antithrombin, based on several reviews and a phase III clinical trial, which failed to show any effect on mortality rates. Furthermore, the use of antithrombin was associated with an increase in bleeding risk. However, post hoc analyses of these studies did demonstrate a survival benefit in septic patients with DIC. Nevertheless, its use cannot be recommended at this time until further testing is completed.

There are several RCTs regarding the use of recombinant soluble thrombomodulin in DIC associated with sepsis that appear promising. The SCARLET study, a Phase II study of thrombomodulin administration to surgical and non-surgical septic patients, demonstrated a trend towards improved survival without an increase in the risk of bleeding. As the results of a Phase III trial are pending, there was no recommendation for or against thrombomodulin in the SCC 2016 guidelines.

Heparin administration in patients with sepsis may improve survival, as demonstrated in two recent reviews. However, further RCTs are required in order to confirm the survival benefits.

The PROWESS-SHOCK trial proved that recombinant activated protein C, previously recommended in the SSC guidelines of 2004 and 2008, did not provide any benefit in patients with sepsis. It has consequently been withdrawn from the market.

In text References

(Allingstrup et al. 2016; Hagiwara et al. 2016; Ranieri et al. 2012)

References

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5. 1. 8. Intravenous Immunoglobulin

Several studies have suggested the use of intravenous immunoglobulin (IVIG) as an adjunctive intervention in patients with sepsis. The rationale for its use is based on the augmentation of the immune response to infection, but results of trials of IVIG use in patients with sepsis have been conflicting. A recent meta-analysis demonstrated that the use of immunoglobulins in septic shock led to anti-microbial, anti-inflammatory and anti-apoptotic effects on immune cells and might be associated with reduction in mortality. The current recommendation of the SSC is, however, against the use of IV immunoglobulins in patients with sepsis (weak recommendation).

In text References

(Werdan et al. 2007; Busani et al. 2016)

References

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5. 1. 9. Adrenomedullin as a Target in Sepsis

Adrenomedullin is a vasoactive peptide that can hinder the progression of sepsis and help maintain hemodynamic homeostasis. In a large cohort of patients with septic shock, it was shown that adrenomedullin levels were high, while the biologically active form was associated with hemodynamic stability, with reduced organ failure and 90-day mortality. As such, it is a potential therapeutic target in septic shock. AdrenOSS-2 is an ongoing Phase II RCT to investigate the efficacy of adrecizumab, a monoclonal antibody against adrenomedullin in septic patients. At present, however, there are no recommendations for or against its use.

In text References

(Caironi et al. 2017)

References

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5. 1. 10. Blood Purification

Blood purification techniques include high-volume haemofiltration and haemoadsorption (the use of adsorbents to remove endotoxin and/or cytokines), plasma exchange/filtration, or coupled plasma filtration adsorption (CPFA, a hybrid of the two methods).

Hemoadsorption with polymixin B-immobilized polystyrene-fibers in order to remove endotoxin is the technique most widely investigated to date. The data on this technique are limited and contradictory, however, and the largest RCT to date (the EUPHRATES trial) was terminated early due to a failure to achieve the primary endpoint.
Plasma filtration and CPFA techniques presently lack robust RCTs to support their use, and data on clinical outcomes are still awaited.

Overall, while the removal of endotoxin or cytokines may have theoretical benefits, detrimental effects may also develop – as both pro- and anti-inflammatory cytokines and cell-signalling molecules will be decreased, the net effect on inflammation and organ

injury is uncertain. In addition, nutrients and therapeutic drugs, including antibiotics, may also be removed from the circulation.

In light of this uncertainty, the SSC made no recommendation for or against the use of blood purification techniques.

In text References

(Klein et al. 2014; Pickkers and Payen 2017)

References

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