Clinical management of sepsis

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ABSTRACT

Sepsis is a common cause of hospital admission worldwide and contributes significantly to morbidity and mortality. The definition of sepsis has evolved from the 1991 American College of Chest Physicians/Society of Critical Care Medicine definition based on the criteria of systemic inflammatory response syndrome, to the 2016 Sepsis-3 definition that incorporates the Sequential Organ Failure Assessment score. The landmark trial on protocolised early goal-directed therapy was published in 2001, but three subsequent multicentre randomised controlled trials (ProCESS, ARISE, and ProMISe) in 2014-2015 did not confirm a survival benefit with protocolised care. Over the years, there has been considerable improvement in sepsis outcome and management that hinges on early detection; timely source control; prompt, appropriate, and correctly dosed antibiotics; aggressive fluid resuscitation; and shock reversal. These are all directed by repeated bedside assessment. This article summarises recent developments and landmark trials that should guide current sepsis management.

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Introduction

Sepsis is a common cause of hospital admission worldwide. The annual incidence of sepsis has been reported to be approximately 300 to 1031 per 100 000 population in the US, and is increasing.[1] In-hospital mortality, however, decreased from 35% in 2000 to <20% in 2013.[2] Numerous studies have been performed or are ongoing in this field. The following discussion provides an update on the change to sepsis definition, three recent trials on protocolised early goal-directed therapy (EGDT), and individual components of sepsis management.

Defining and recognising sepsis: from systemic inflammatory response syndrome to Sequential Organ Failure Assessment score and the role of biomarkers

In 1991, sepsis was defined as fulfilling two or more than two systemic inflammatory response syndrome (SIRS) criteria in the presence of infection (Table 1).[3] Many seriously infected patients (eg old or immunocompromised), however, are unable to mount a SIRS. Using SIRS criteria to define severe sepsis will miss one in eight otherwise similar patients with substantial mortality.[2] In addition, the mortality risk has been shown to increase linearly with each additional SIRS criterion and there is no transition point noted at a threshold of two SIRS criteria.

To acknowledge the above shortcomings, the Sepsis-3 (Third International Consensus Definitions for Sepsis and Septic Shock) in 2016 redefined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[4] Organ dysfunction is identified as "an acute change in the total Sequential Organ Failure Assessment (SOFA) score of ≥2 points" (Table 1). In addition, a quick SOFA (qSOFA) score was introduced for bedside screening. Meeting two or more than two qSOFA criteria (respiratory rate ≥22/min, altered mentation with a Glasgow Coma Scale score of <15, systolic blood pressure ≤100 mm Hg) should prompt consideration of possible infection in undiagnosed patients, investigation for organ dysfunction that defines sepsis in infected patients, and initiation of sepsis management where appropriate.[4] Despite these recent changes in definition, clinicians should maintain a high index of suspicion and always consider sepsis as a possible explanation/diagnosis when faced with new-onset organ dysfunction in a patient.

Apart from clinical assessment, various serum biomarkers have been studied for their potential role in early diagnosis of sepsis. C-reactive protein is commonly used but it has a low specificity for sepsis. Procalcitonin (PCT) is a prohormone of calcitonin that is released into the circulation in response to severe systemic inflammation due to bacterial infection. A recent meta-analysis showed its clinical value in diagnosing sepsis in critically ill patients (an area under the receiver operating characteristic

curve of 0.85).[5] The meta-analysis, however, was limited by substantial heterogeneity across different studies, a wide range of cut-offs used, absence of a true reference diagnostic standard, and potential publication bias. It is noteworthy that PCT can be falsely elevated in inflammation due to other causes, such as trauma, rhabdomyolysis, surgery, severe pancreatitis, autoimmune disorders, cardiogenic shock, and following prolonged resuscitation. It cannot be solely relied on to discriminate sepsis from other causes of inflammation, but a plasma PCT level of ≥0.5 ng/mL is a helpful adjunct when interpreted along with additional clinical information and serial monitoring might have a role in guiding subsequent antibiotic treatment (see below). In case of doubt, it is advisable to initiate treatment for sepsis early, and adjust subsequent management and antibiotics according to the patient's clinical progress, results of investigations, and possibly serial PCT monitoring.

膿毒症的臨床治理

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膿毒症（敗血症）是很多國家一個最常見的入院原因，其發病率和死亡率很高。膿毒症的定義隨着這數十年的演變而有所修正。1991年美國胸科醫師學院與重症監護醫學學會共同商討，按全身炎症反應綜合症對膿毒症作定義。直至2016年第三次國際膿毒症共識會上，把器官衰竭評估分數納入定義中。2001年發表了一項有關早期目標導向的流程化治療，這項研究極具里程碑意義。可惜2014及2015年進行的三項多中心隨機對照研究，包括發起於美國的早期膿毒性休克流程化治療試驗（ProCESS）、發起於澳大利亞和紐西蘭的澳大拉西亞膿毒症復甦評估試驗（ARISE），以及發起於英國的膿毒症流程化管理試驗（ProMISe），均未確認流程化治療能提高病人生存效益。這些年來，膿毒症的治療結果有相當大程度的改善，這取決於早期發現、及時的病源控制、及時處方適當和正確劑量的抗生素、給予充分性液體復甦治療，以及休克逆轉。以上各項均透過不斷重複的床邊評估指導而成。本文總結有關治理膿毒症的最新發展，以及歸納對現行治療方法相關的具指標性臨床試驗研究。

Update on protocolised management: from early goal-directed therapy to ProCESS-ARISE-ProMISe

In 2001, Rivers et al[6] randomised 263 patients with severe sepsis or septic shock in an emergency department (ED) to EGDT or usual care. The sequential goals of EGDT were central venous pressure (CVP) achieved by fluid resuscitation, mean arterial pressure (MAP) with vasopressors, and central venous oxygen saturation ($ScvO_2$) with red cell transfusion and dobutamine. The result was an absolute reduction in in-hospital mortality of 16%.[6] The protocol was incorporated into the surviving sepsis campaign (SSC) 2004, 2008, and the 2012 Guidelines.[7]

Over the years, concerns have remained about the external validity of the original trial,

TABLE 1. Old and new definitions of sepsis[3]

	Definitions	Comments
Sepsis-1, 1991		
Sepsis	SIRS* with infection (presumed or proven)	SIRS can be non-infectious in aetiology. Only infection plus SIRS is termed sepsis. Not all patients with serious infection necessarily show SIRS features despite having organ dysfunction
Severe sepsis	Sepsis (as above) with evidence of acute organ dysfunction	Gives a false impression that infection must go through the three stages of sepsis, severe sepsis, and septic shock; or that organ dysfunction must have SIRS
Septic shock	Sepsis with persistent hypotension after fluid resuscitation	Emphasis placed on circulation (blood pressure) alone without considering the metabolic (lactate) component
Sepsis-2, 2001	Unchanged	The list of signs and symptoms associated with sepsis was expanded
Sepsis-3, 2016		
Sepsis	Life-threatening organ dysfunction† caused by a dysregulated host response to infection	To recognise the finding that infections can result in local organ dysfunction (reflected by the SOFA score) without triggering a dysregulated host response (the old SIRS criteria)
Septic shock	A subset of sepsis with persistent hypotension requiring vasopressors to maintain MAP of ≥65 mm Hg and a serum lactate level of >2 mmol/L despite adequate volume resuscitation	The term 'severe sepsis' is deleted, and both circulatory and metabolic abnormalities are considered. Whether the new Sepsis-3 criteria improves clinical outcomes remains to be validated

Abbreviations: MAP = mean arterial pressure; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment

* ≥Two of the following: (a) temperature >38°C or <36°C, (b) heart rate >90/min, (3) respiratory rate >20/min or $PaCO_2$ <32 mm Hg (4.3 kPa), (4) white blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands

† Defined by an acute change of ≥2 points in the SOFA score; 6 components including: respiratory (partial pressure of oxygen in arterial blood/fractional inspired oxygen [PaO_2/FIO_2] ratio), neurological (Glasgow Coma Scale score), cardiovascular (MAP and vasopressor use), renal (serum creatinine and urine output), hepatic (bilirubin level), and platelet count

haemodynamic goals, use of CVP and $ScvO_2$ monitoring, blood transfusion, dobutamine, and resultant higher costs of its implementation. Subsequently, three large-scale multicentre randomised controlled trials were published in 2014-2015: the ProCESS (Protocolized Care for Early Septic Shock) trial,[8] the ARISE (Australasian Resuscitation in Sepsis Evaluation) trial,[9] and the ProMISe (Protocolised Management in Sepsis) trial.[10] All three studies were negative; there was no survival benefit using protocolised care compared with usual care (Table 2).[6,8-10]

A lack of survival benefit of EGDT in the latest three trials may be the result of improved sepsis management since the original trial: nearly all patients received antibiotics within 6 hours of presentation, and a significant amount of fluid was already administered before randomisation (Table 2). Treatment in the usual care groups was guided by clinical assessment of volume and perfusion status, and achieved similar mean and systolic blood pressures at the end of the intervention period. These trials demonstrated that CVP and $ScvO_2$ goals confer no additional benefit for sepsis survival.

In response to the new evidence, the SSC Guidelines updated its 6-hour bundle in April 2015, and recommended reassessment in the event of persistent arterial hypotension with either physical examination or "two of the following (measure CVP, measure $ScvO_2$, bedside cardiovascular ultrasound, dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge)".[11]

TABLE 2. Comparison of the original EGDT trial, with the ProCESS, ARISE and ProMISe trials. (a) Study characteristics and (b) interventions and outcomes[6,8-10]

(a) Study characteristics

	Rivers et al, 2001[6]	ProCESS, 2014[8]	ARISE, 2014[9]	ProMISe, 2015[10]
Country (No. of centres)	United States (1)	United States (31)	Australia, New Zealand, Hong Kong, Finland, Republic of Ireland (51)	England (56)
Enrolment period	Mar 1997 to Mar 2000	Mar 2008 to May 2013	Oct 2008 to Apr 2014	Feb 2011 to Jul 2014
No. of patients	263	1341	1600	1260
Usual care	133	456	804	630
EGDT	130	439	796	630
Protocol-based standard therapy	N/A	446	N/A	N/A
No. of patients (% screened) eligible but not randomised due to study logistic issues or exclusion by clinicians	0	1191 (9.4)	797 (22.4)	1444 (23.3)

(b) Interventions and outcomes

	Rivers et al, 2001[6]		ProCESS, 2014[8]			ARISE, 2014[9]		ProMISe, 2015[10]	
	EGDT	Usual care	EGDT	Protocol-based standard therapy	Usual care	EGDT	Usual care	EGDT	Usual care
Baseline APACHE II score	20.4 ± 7.4	21.4 ± 6.9	20.8 ± 8.1	20.6 ± 7.4	20.7 ± 7.5	15.4 ± 6.5	15.8 ± 6.5	18.7 ± 7.1	18.0 ± 7.1
Baseline lactate level (mmol/L)	7.7 ± 4.7	6.9 ± 4.5	4.8 ± 3.1	5.0 ± 3.6	4.9 ± 3.1	6.7 ± 3.3	6.6 ± 2.8	7.0 ± 3.5	6.8 ± 3.2
Total intravenous fluid (mL)									
Before randomisation	N/A	N/A	2254	2226	2083	2515	2591	2100	2290
0-6 Hours	4981	3499	2805	3285	2279	1964	1713	2000	1784
Antibiotics within 6 hours (%)	86.3	92.4	97.5	97.1	96.9	100	100	100	100
Vasopressor (%)	27.4	30.3	54.9	52.2	44.1	66.6	57.8	53.3	46.6
Dobutamine (%)	13.7	0.8	8.0	1.1	0.9	15.4	2.6	18.1	3.8
Red cell transfusion (%)	64.1	18.5	14.4	8.3	7.5	13.6	7.0	8.8	3.8
Mechanical ventilation (%)	53.0	53.8	26.4	24.7	21.7	22.2	22.4	20.2	19.0
Mortality									
In-hospital (%)	30.5	46.5	N/A	N/A	N/A	14.5	15.7	25.6	24.6
60-Day (%)	44.3	56.9	21.0	18.2	18.9	N/A	N/A	N/A	N/A
90-Day (%)	N/A	N/A	31.9	30.8	33.7	18.6	18.8	29.5	29.2

Abbreviations: APACHE = acute physiology and chronic health evaluation; EGDT = early goal-directed therapy; N/A = not available/applicable

Clinical management: initial resuscitation and treatment

Source control

Source control includes drainage of any infected fluid collection, debridement of infected solid tissue, and removal of infected foreign bodies or devices. It should best be achieved within 12 hours of identification by imaging and/or diagnostic sampling of the infection foci. Minimally invasive intervention including percutaneous and endoscopic treatments should be considered, but surgery is indicated if control remains inadequate or if there is diagnostic uncertainty. Damage-control surgery for life-threatening peritonitis is associated with improved outcomes.[12] It involves an abbreviated initial laparotomy for haemorrhage and contamination control, followed by resuscitation before the final definitive repair and abdominal closure.

Antibiotics

Delay in antimicrobial treatment is associated with increased mortality, adverse clinical outcome, and longer intensive care unit (ICU) and hospital stay.[13] Effective intravenous antimicrobials should be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock.[14] One study showed that each hour delay reduces survival by 7.6% in the first 6 hours following the onset of septic shock.[15] Although a recent meta-analysis pooling data from 11 observational studies showed no survival benefit of early antibiotic therapy,[16] it failed to analyse all eligible studies and lacked microbiological considerations. Early therapy remains logical, especially in patients with severe infections, although the optimum time frame for administration remains unknown.[17] Delay in administration can occur anywhere, from ED triage, making a diagnosis, antibiotic order, drug dispensary to the actual administration, and should be addressed with clinical, administrative, and logistics measures to improve timeliness of treatment.

The choice of initial empirical antimicrobials should be broad enough to cover the likely pathogens, while also taking into account recent culture results, host factors, and susceptibility patterns. The EPIC II (Extended Prevalence of Infection in Intensive Care) study showed that in Asia, the common infective sources are the respiratory system, abdomen, blood stream, and renal/urinary tract, while the commonest organisms are *Streptococcus pneumoniae*, vancomycin-sensitive *Enterococcus*, *Klebsiella* spp, *Pseudomonas* spp, and *Acinetobacter* spp.[18] Local microbiologists can regularly provide antibiotic sensitivity patterns for reference.

Combination therapy, defined as administration of two or more different classes of antimicrobials with different mechanisms of action, has the advantages of broadening the spectrum of coverage, and possible additive or synergistic effects on pathogens. Meta-analyses showed that combination antibiotic therapy improves survival in the most severely ill patients with septic shock, but may be detrimental to low-risk patients and increases nephrotoxicity.[19,20] Once the causative pathogens and their susceptibility patterns are known, de-escalation of antimicrobial therapy should follow to prevent development of resistance, as well as reduce drug toxicity and cost. Discontinuing antibiotics can be considered when PCT is ≤0.5 ng/mL or serial monitoring shows a decline of ≥80% of its peak value.[21]

Appropriate antibiotic dosing to achieve effective bacterial killing while preventing toxicity and emergence of resistance is also important. This is particularly relevant in critically ill patients with substantial pharmacokinetic variability (Table 3), who are infected by pathogens with higher minimum inhibitory concentrations (MIC). Individualised dosing adjustment requires knowledge of pharmacokinetic targets and MIC for the organism. Readers can refer to published reviews for specific recommendations.[22,23] In general, changes to the volume of distribution will affect initial dosing, while changes in drug clearance will affect the maintenance dose. Killing by time-dependent antibiotics (eg β-lactams) correlates with the time fraction when serum drug concentration exceeds MIC. This can be achieved by frequent dosing and use of continuous infusion. Conversely, concentration-dependent killing (eg aminoglycosides) correlates with the ratio of peak drug concentration to MIC. A higher dosage with extended dosing intervals will maximise killing while minimising toxicity. Due to the complexity and variability of various factors at play, therapeutic drug monitoring has been advocated in the critically ill patients but remains to be available universally.[22-24] Therapeutic drug monitoring involves direct measurement of serum antibiotic concentrations and timely comparison with a therapeutic target to facilitate adjustments by the clinician or any dosing software.

Fluid

Type of fluid

Choice of non-blood product can be broadly divided into crystalloids and colloids. Crystalloids include normal saline or balanced solutions (eg lactated Ringer's solution [B Braun, US], Hartmann's solution [Fresenius Kabi, Australia], Plasma-Lyte 148 [Baxter, US]). Colloids include natural human albumin and semi-synthetic solutions (gelatin-like Gelofusine [B Braun, US] or Haemaccel [Sanofi, France], dextran, and hydroxyethyl starch). Normal saline has a high chloride content and may produce hyperchloraemic acidosis and renal vasoconstriction. Balanced solutions minimise these side-effects by using lactate

TABLE 3. Factors affecting antibiotic pharmacokinetics in critically ill patients

Factor	Cause/definition	Implication
Fluid overload	Capillary leakage and fluid extravasation from SIRS, compounded by fluid resuscitation	Increases volume of distribution for hydrophilic antibiotics (eg β-lactams, aminoglycosides, vancomycin, and linezolid). Reduces the time to reach effective therapeutic concentration
Hypoalbuminaemia	Serum albumin <25 g/L	Raises unbound fraction of protein-bound antibiotics (eg ceftriaxone, flucloxacillin, ertapenem, and daptomycin) resulting in: 1. raised antibiotic activity (unbound fraction) in the early dosing interval 2. increased volume of distribution reduces peak concentration 3. increased elimination in the later dosing interval
Microvascular failure	Sepsis and use of vasopressors	Impairs tissue penetration of antibiotics. Serum concentration becomes an imprecise guide
Augmented renal clearance	Vasodilation, increased cardiac output, and enhanced renal perfusion	Increases elimination of antibiotics predominantly excreted by the kidneys (eg β-lactams, aminoglycosides, vancomycin)
Acute kidney injury	Multi-organ dysfunction syndrome	Impairs elimination of antibiotics predominantly excreted by the kidneys (eg β-lactams, aminoglycosides, vancomycin). The effect of RRT on antibiotic dosing is dependent on the mode and dose of RRT, and the sieving or saturation coefficient of the antibiotic
Hepatic dysfunction	Multi-organ dysfunction syndrome	Impairs elimination of antibiotics predominantly cleared/metabolised by the liver (eg tigecycline)

Abbreviations: RRT = renal replacement therapy; SIRS = systemic inflammatory response syndrome

or acetate as buffers. Weak evidence suggests that balanced solutions compared with normal saline reduce acute kidney injury (AKI), the need for renal replacement therapy (RRT), and mortality in sepsis.[25,26] Nonetheless, the recent SPLIT trial did not find a difference in AKI among a heterogeneous group of ICU patients who received a balanced crystalloid or saline, although the study recruited predominantly postoperative patients at low risk who received small doses (median, 2 L) of fluid.[27]

Colloids theoretically maintain a higher oncotic pressure and hence intravascular volume but the CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) trial found no mortality difference among ICU patients with hypovolaemic shock who were resuscitated with either colloids or crystalloids.[28] Dextran has ceased to be a resuscitation fluid due to its high anaphylactoid potential, impact on platelet aggregation with resultant bleeding complications, and interference with erythrocyte cross-matching. Gelatins have the highest risk among the colloids for anaphylactoid reaction and the lowest intravascular persistence due to their rapid urinary excretion. Hydroxyethyl starch is not advisable for acute volume resuscitation because it deposits in the kidneys, liver, skin and other tissues, and is associated with increased mortality, AKI, new-onset hepatic failure, and higher incidences of pruritus and rash.[29-32] Concerning albumin, the SAFE (Saline versus Albumin Fluid Evaluation) trial[33] demonstrated no survival benefit among a general ICU population when either 4% albumin or normal saline was used for fluid resuscitation, but predefined subgroup analysis suggested a trend towards improved survival in patients with severe sepsis who received albumin solution. A decade later, however, the ALBIOS (Albumin Italian Outcome Sepsis) study of patients with severe sepsis could not confirm a survival benefit when albumin was used in addition to crystalloids compared with crystalloids alone to maintain a serum albumin level of ≥30 g/L, although there was a small haemodynamic advantage and post-hoc subgroup analysis showed a significantly lower 90-day mortality in patients with septic shock who received albumin.[34]

In summary, crystalloids (possibly balanced solutions) remain the initial fluid of choice in the resuscitation of sepsis. Routine use of albumin is not warranted given its higher cost, but it may be considered in patients with septic shock who do not respond to crystalloid. There is no evidence that gelatins are more beneficial, and dextran and hydroxyethyl starch should be avoided.

Assessment of fluid responsiveness

Both under- and over-hydration can be harmful.[35] It is therefore recommended that 30 mL/kg crystalloid be given with reassessment of fluid responsiveness (defined as >10%-15% increase in stroke volume in response to volume administration) or tissue perfusion afterwards. Static indices like CVP and pulmonary capillary wedge pressure are not good indicators of fluid responsiveness, and are not recommended for use to guide fluid therapy. Dynamic indices obtained by inducing a change in the preload and monitoring the corresponding change in cardiac output (CO) or its derivatives should be used instead (Table 4).

An arterial waveform pulse pressure variation (PPV) of >13%, induced by heart-lung interactions

TABLE 4. Assessment of fluid responsiveness

Technique	Setting	Device	Threshold values for fluid responsiveness
PPV	Mechanically ventilated with tidal volume ≥8 mL/kg, in the absence of spontaneous breathing activity and arrhythmias	Arterial blood pressure transducer and patient monitor	100 x (Ppmax - Ppmin)/[(Ppmax + Ppmin)/2] ≥13%
Passive leg raising	Validated in the presence of spontaneous breathing and arrhythmias	Device to measure cardiac output or surrogate (transthoracic echocardiography, oesophageal/ transthoracic Doppler, calibrated pulse contour analysis, bioreactance, pulmonary artery catheter, arterial blood pressure transducer)	Depending on index used Aortic or subaortic VTI increases ≥15%; accuracy drops if assessed by changes in pulse pressure instead of cardiac output or surrogate
Mini-fluid challenge	Mechanically ventilated at low-tidal-volume (<8 mL/kg ideal body weight) patients without spontaneous breathing or arrhythmias challenged with 100 mL 4% human albumin over 1 min	Arterial blood pressure transducer and patient monitor	ΔPPV_{100} ≥2%
Respiratory variation of inferior vena cava	Mechanically ventilated with tidal volume ≥8 mL/kg	Echocardiography	100 x (Dmax - Dmin)/Dmin ≥18% 100 x (Dmax - Dmin)/[(Dmax + Dmin)/2] ≥12%
	Spontaneously breathing	Echocardiography	100 x (Dmax - Dmin)/Dmax ≥40% AUC of ROC = 0.77 only: a value ≥40% more likely to be fluid responsive, but <40% cannot exclude fluid responsiveness

Abbreviations: AUC = area under curve; Dmax / Dmin = maximum / minimum IVC diameter; IVC = inferior vena cava; Ppmax / Ppmin = maximal / minimal pulse pressure; PPV = pulse pressure variation; ΔPPV_{100} = reduction in pulse pressure variation after 100-mL mini-fluid challenge; ROC = receiver operating characteristic curve; VTI = subaortic velocity time index

during mechanical ventilation, predicts fluid responsiveness with a high degree of accuracy in controlled settings.[36,37] Its accuracy, however, is lowered by arrhythmia, spontaneous breathing activity, low-tidal-volume ventilation (<8 mL/kg ideal body weight), low heart-rate-to-respiratory-rate ratio (<3.6), and right ventricular dysfunction (peak systolic velocity of tricuspid annulus <0.15 m/s). Raised intra-abdominal pressure (IAP) exaggerates PPV, and one study found that PPV/IAP of <1.41 could identify false-positive patients.[38] These confounders limit the application of PPV in routine clinical practice, in particular during protective ventilation for acute respiratory distress syndrome (ARDS).

A virtual fluid challenge test with passive leg raising can avoid the above caveats as it does not rely on mechanical ventilation to induce changes in preload and, unlike other methods, has been validated in patients with breathing efforts and arrhythmia. When coupled with CO monitoring, passive leg raising has an excellent predictive accuracy.[39] Accuracy drops when arterial pulse pressure instead of CO is used, as well as in patients with raised IAP of ≥16 mm Hg.[40]

A mini-fluid challenge (100 mL infused rapidly over 1 minute) is an alternative method and limits cumulative positive fluid balance in non-responders. Unlike PPV, it remains accurate at times of low-tidal-volume ventilation.[41]

Respiratory variation of the inferior vena cava diameter is another accurate marker of fluid responsiveness in patients who are mechanically ventilated,[42] but its use in spontaneously breathing patients is more controversial.

Vasopressors

Guidelines of SSC recommend maintaining MAP at a minimal of 65 mm Hg.[14] The SEPSISPAM (Sepsis and Mean Arterial Pressure) Investigators studied 776 septic shock patients, and found that targeting a MAP of 80-85 mm Hg rather than 65-70 mm Hg did not result in any difference in 28- or 90-day mortality.[43] A vasopressor should be considered when MAP of ≥65 mm Hg cannot be maintained despite adequate fluid resuscitation.

For the choice of vasopressors, studies that compared norepinephrine (with or without additional dobutamine in patients with low CO) with epinephrine found no difference in all-cause 28-day mortality,[44] or the time to achievement of a clinician-prescribed MAP goal.[45] Epinephrine use was associated with significant tachycardia and lactic acidosis that did not affect haemodynamic stabilisation or survival. The hyperlactataemia represents exaggerated aerobic glycolysis instead

of ongoing tissue hypoxia, but potentially interferes with interpretation of serial serum lactate measurements. The 2008 VASST (Vasopressin and Septic Shock Trial)[46] randomised 779 septic shock patients to receive either norepinephrine alone or norepinephrine plus low-dose vasopressin (0.03 U/min), and found no difference in all-cause 28-day mortality. The SOAP II Trial randomised 1679 patients with shock to receive either norepinephrine or dopamine, and found no difference in all-cause 28-day mortality but a significantly higher rate of arrhythmias in the dopamine group (the number needed to harm was 9). In their subgroup analysis, dopamine was associated with higher mortality in cardiogenic shock, but not septic and hypovolaemic shock.[47]

Norepinephrine is therefore recommended as the first-line vasopressor for septic shock. In refractory hypotension, epinephrine or low-dose vasopressin (0.03 units/min) may be added. Dopamine should be avoided except in highly selected patients who are bradycardic and at low risk of tachyarrhythmias.

Resuscitation endpoints

The optimal goal for sepsis resuscitation remains unknown. While under resuscitation is detrimental, achieving supranormal targets has also been shown to cause harm.[48] The MAP (perfusion pressure) of ≥65 mm Hg and urine output of ≥0.5 mL/kg/h are the recommended targets. The EMShockNet Trial showed that there was no difference in hospital mortality when using lactate clearance (>10%) or $ScvO_2$ (>70%) as goals of early sepsis resuscitation.[49] Hyperlactataemia in sepsis, however, can result from increased production driven by endogenous or exogenous epinephrine-stimulated aerobic glycolysis, endotoxin inhibition of pyruvate dehydrogenase, and decreased lactate metabolism due to liver and renal dysfunction. Thus, persistent hyperlactataemia does not necessarily indicate anaerobic metabolism and tissue hypoxia, and should not be solely relied on to guide therapy that aims to boost oxygen delivery in patients who are otherwise clinically improving. Conversely, normalisation of serum lactate is reassuring as it is associated with reduced hospital mortality in critically ill patients.[50]

Adjunctive therapy

Blood transfusion

In the original EGDT protocols, once $ScvO_2$ drops below 70%, blood transfusion to achieve a haematocrit level of ≥30% was recommended to boost oxygen delivery. The 1999 TRICC (Transfusion Requirements in Critical Care) trial demonstrated lower rates of in-hospital mortality with a restrictive rather than liberal transfusion strategy. This trial, however, excluded septic shock patients. The 2014 TRISS (Transfusion Requirements in Septic Shock) trial randomised 998 septic shock patients to either a liberal blood transfusion strategy with a transfusion threshold of haemoglobin of ≤90 g/L or a restrictive strategy with a threshold of ≤70 g/L.[51] Mortality at 90 days, rate of ischaemic events, and use of life support were similar. A transfusion threshold of 70 g/L is therefore recommended. For patients with ongoing acute coronary syndrome or chronic cardiovascular disease, targeting a higher haemoglobin level of 100 g/L might be beneficial but remains to be proven.[52]

Glucocorticoids

Glucocorticoids have anti-inflammatory and immunosuppressive effects. Despite the positive Annane Trial in 2002, the subsequently larger multicentre CORTICUS (Corticosteroid Therapy of Septic Shock) Trial[53] was negative. It randomised 499 patients with septic shock to receive 6-hourly 50-mg hydrocortisone or placebo, with the dose tapered over 11 days. Hydrocortisone did not improve 28-day survival in patients with septic shock, and should not be routinely used for septic shock before adequate fluid resuscitation and vasopressor therapy.[14] If used in refractory shock, early administration within 9 hours of commencement of vasopressor is advised.[54]

Glucose control

Tight glycaemic control (blood glucose, 4.4-6.1 mmol/L) was once commonly practised after the 2001 Leuven Surgical Trial. In 2009, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Surviving Using Glucose Algorithm Regulation) study randomised 6104 ICU patients, and showed that intensive glucose control (4.5-6.0 mmol/L) increased mortality compared with a target of <10 mmol/L.[55] Post-hoc analysis further demonstrated an association between hypoglycaemia and an increased risk of death in a dose-response relationship. This association was strongest for death from distributive, including septic shock.[56] Guidelines of SSC recommend targeting an upper blood glucose level of <10 mmol/L to reduce the risk of hypoglycaemia.[14]

Organ support

Kidney

The optimal timing of RRT in the absence of overt life-threatening complications (severe metabolic acidosis, hyperkalaemia, and/or fluid overload) is uncertain. Prior studies as well as the recent ELAIN (Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury[57]) and AKIKI (Artificial Kidney Initiation in Kidney Injury[58]) trials have yielded contradictory results, partly because of the heterogeneous

definitions of 'early' and 'late' initiation of RRT. It is hoped that the upcoming IDEAL-ICU (Initiation of Dialysis Early versus Delayed in Intensive Care Unit[59]) and STARRT-AKI (Standard versus accelerated initiation of renal replacement therapy in acute kidney injury[60]) trials will provide more evidence on the subject. Regarding the intensity of renal support in critically ill patients with AKI, an effluent rate of 25 mL/kg/h is considered adequate and high-volume haemofiltration is not superior.[61,62] Survival benefit of blood purification strategies has yet to be proven.

Lungs

Of note, ARDS is a frequent complication of sepsis. Optimal ventilatory support prevents further lung injury and the resultant biotrauma from cytokine release. A lung protective strategy with low tidal volume (6 mL/kg ideal body weight) remains the cornerstone of treatment.[63] A higher positive end-expiratory pressure should be reserved for patients with moderate-to-severe ARDS as defined by the latest Berlin definition.[64] Early (intubated for <36 hours) and sustained (≥16 consecutive hours per day) prone positioning in moderate-to-severe ARDS has proven survival advantage when practised in conjunction with lung protective ventilation.[65]

Conclusion

Optimal sepsis management involves both refinement of clinical interventions and administrative logistics for the timeliness of their delivery. Early recognition of sepsis, timely source control, prompt and effective antibiotic administration at the right dose, immediate fluid resuscitation as guided by bedside reassessment, and dynamic indices of fluid responsiveness remain the mainstay of sepsis management.

Declaration

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