



Improving Outcomes in Sepsis: What Works?



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Management of Sepsis: What Works and What Doesn't?

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection that is most often seen in the context of bacterial infection. The results of several recent studies have suggested that outcomes for patients with sepsis have improved over the years (Vincent 2020).

However, both morbidity and mortality from sepsis remain significant. In order to improve outcomes, it is imperative that at-risk patients are detected as early as possible and that during initial assessment of an acutely ill patient, a determination of the severity of illness, cause of illness, and prioritization of early treatment be established (Inada-Kim 2022).

The aim of this short review is to present current knowledge of factors that are known to improve outcomes in patients with sepsis, and also to present those that have not improved outcome, with the goal of clarifying and prioritising appropriate and potentially life-saving treatment.

What Has Not Worked?

Our understanding of sepsis has improved to the point where many of the complex responses to infection and severe inflammation are well understood. This has led to the targeting of many signaling molecules and inflammatory pathways for amplification or inhibition, with the goal of altering the dysregulation of the inflammatory pathways involved in sepsis (Vincent 2020).

However, over 100 randomised clinical trials evaluating sepsis-modulating therapies based on inhibition or enhancement of inflammatory chemicals failed to demonstrate improvement in survival or illness severity.

Whilst the outcomes of clinical trials may suggest that sepsis-modulating therapies are ineffective in the management of sepsis, there may be some confounding factors, that, when addressed, may lead to improved understanding of the role - if any - of these therapies in patient management, including (Vincent 2020):

1. Studies have been carried out in disparate groups of patients with differing underlying disease, and severity of sepsis
2. Doses of disease-modulating factors vary, with effective doses being largely undetermined in the clinical setting
3. Multicenter studies involve patients with different standards of care and interventions, which can confound result interpretation
4. Patients with sepsis can present with hyperdynamic or hypodynamic cardiovascular responses, which can alter responses to given medications designed to modulate the inflammatory response
5. Patients with sepsis can present simultaneously with pro-inflammatory and anti-inflammatory responses to systemic disease, which can confound a response to medications directed at one or more inflammatory mediators

The conclusion regarding single interventions, such as anti-inflammatory or immunomodulatory agents in patients with sepsis, is that because patients with sepsis encompass such a wide spectrum of disease severity, aetiology and patient response, that it is unlikely that a specific agent therapy will be clinically relevant or useful across the spectrum of patients with sepsis.

Anti-inflammatory Therapy in Sepsis

Despite the large number of pro-inflammatory cytokines produced in severe illness and sepsis, anti-inflammatory therapies have not shown to decrease overall mortality in patients with sepsis (Remy et al 2020). Anti-inflammatory therapies that have been investigated include:

- Tumour necrosis factor-alpha antagonists
- Interleukin-1 receptor antagonists
- Anti-endotoxin antibodies
- Corticosteroids

Potential reasons for the lack of improvement in mortality with the use of anti-inflammatory agents include:

- Many deaths in sepsis occur during the anti-inflammatory, or immune-suppressive phase of systemic inflammation and infection, rather than during the pro-inflammatory phase.
- Due to the broad range of pro-inflammatory cytokines produced in the pro-inflammatory phase of sepsis, targeting a single cytokine or inflammatory pathway seems unlikely to affect significant alteration in the host response.

What Has Worked?

As mentioned previously, reviews of published literature show improved survival rates in sepsis. If single-agent therapy directed at components of sepsis do not have an effect on survival, what has? Causes of improvement in survival from sepsis fall into 2 general categories (Vincent 2020):

1. Increased awareness of sepsis, meaning patients are diagnosed earlier, and are therefore able to receive early treatment (Young 2021)
 - a. Early antibiotic therapy
 - b. Early source control
 - c. Fluid resuscitation
 - d. Early inotrope and pressor support
 - e. Early organ support
2. Improved standards of care for patients with sepsis (Landoni et al 2015)
 - a. Avoidance of fluid overload
 - b. Judicious transfusion therapy
 - c. Lung-protective ventilation strategies
 - d. Avoidance of excess calories and illness factor application in nutritional formulae
 - e. Standardised check-lists to avoid overlooking crucial patient support parameters
 - f. Early recognition of complications, and development of action standards when detected

Increased awareness of sepsis:

The ability to identify a patient with sepsis is directly related to the potential to begin effective treatment and to reduce mortality and morbidity.

Over recent years, the traditional concepts of SIRS criteria in humans (tachycardia, elevated respiratory rate, elevated or decreased white blood cell count, and hyperthermia or hypothermia) have been replaced with the "Sepsis 3" definitions of sepsis, outlined by the Sepsis-Related Organ Failure Assessment (SOFA) score (Coopersmith et al 2020). This score facilitates an objective scoring system for clinical illness, based on the following:

SOFA Score	1	2	3	4
Respiration: PaO ₂ /FiO ₂ (mm Hg)	<400	<300	<200	<100
Coagulation: Platelets x 10 ⁹ /L	<150	<100	<50	<20
Liver: Bilirubin µmol/L	20-32	33-101	201-204	>204
Cardiovascular: MAP (mm Hg)	< 70 mm Hg	Dopamine < 5 µg/kg/min or dobutamine	Dopamine > µg/kg/min or noradrenaline < 0.1 µg/kg/min	Dopamine > 15 µg/kg/min or noradrenaline > 0.1 µg/kg/min
CNS: Coma Score	>13	10-12	6-9	<6
Kidney: Creatinine µmol/L	110-170	171-299	300-440	>440

The value of the SOFA scoring system is that it identifies patients in need of urgent care - with the goal of shortening the time between diagnosis and care provision.

An abbreviated screening system for systemically ill patients has also been developed, that prompts clinicians to conduct further diagnostic work-up in order to diagnose sepsis, and to begin prompt therapy. This screening test is termed the qSOFA, and includes 3 clinical parameters that should prompt action on part of the clinician:

- Hypotension: systolic arterial blood pressure <100 mm Hg
- Tachypnoea
- Coma score < 13

The value of qSOFA is that it allows early clinical identification of at-risk patients that should receive additional work-up and early treatment for sepsis. A 2018 meta-analysis of 9 studies of qSOFA in humans showed that qSOFA identified patients at risk of death, and was superior to traditional SIRS criteria in sensitivity and specificity.

In dogs and cats, SOFA and qSOFA have not been found to improve sepsis and severe disease recognition, and subsequent mortality, owing to low specificity and sensitivity. The canine and feline APPLE scoring systems developed in 2010 have been validated for this purpose, and are recommended in veterinary medicine.

Immune Suppression Modulation in Sepsis

Immune suppression occurs in sepsis as a bi-product of the acute pro-inflammatory phase of severe illness and tissue injury (Remy et al 2020), and results in:

- Reduced leukocyte chemotaxis
- Reduced ability of neutrophils to kill bacteria due to reduced production of reactive oxygen species, and reduced phagocytic ability
- Reduced cytokine production by monocytes
- Increased release of incompletely differentiated myeloid suppressor cells from the bone marrow, which results in suppressed T-cell activation, and increased production of interleukin-10, an immunosuppressive interleukin, that reduces activation of macrophages.
- Increased rates of lymphocyte and gastrointestinal epithelial cell apoptosis

Interestingly, it does appear that the phagocytic capacity of monocytes is preserved, despite these anti-inflammatory effects, and that production of some cytokines and metalloproteinases actually increases during sepsis (Cavaillon et al 2020). In addition, following injury or hypoxia, many tissues increase production of inflammatory cytokines, including TNF-alpha. Interleukin-1 and interleukin-6, along with anti-inflammatory cytokines (Cavaillon et al 2020). However, it does appear that the anti-inflammatory effects persist in patients with sepsis beyond the early phase of tissue inflammation and infection, and that eventually, immune suppression becomes a more significant problem in patients with sepsis.

The diagnosis of immune suppression in sepsis is generally based on the following:

- Increased initial or sustained interleukin-10 serum levels
- High interleukin-10: TNF-alpha ratios

Treatment of immune-suppression in sepsis has been attempted using immune-stimulants including granulocyte colony stimulating factor, interferon-gamma, and a number of other inhibitory cytokine receptor-blocking agents, including T-cell stimulators, and interleukin-7. To date, only granulocyte colony stimulating factor and interferon-gamma have been studied extensively enough to offer recommendations:

- Granulocyte colony stimulating factor, when administered to patients with immune-suppression and sepsis, resulted in fewer ICU days and decreased illness severity scores, compared to controls
- Interferon-gamma administration to patients with severe infection and sepsis resulted in improved outcomes
- Interleukin-7 trials in animals resulted in improved lymphocyte function, lymphocyte numbers and resulted in improved survival rates in an animal model of sepsis.

The difficulty in applying these results across all patients with sepsis, is that immune-suppression - and hence the requirement for, or response to, immune stimulants, is not universal

Early Antibiotic Therapy

Large-scale observational and clinical studies have determined that early antibiotic therapy is independently associated with improved outcome in patients with sepsis.

One study (Kumar et al 2006) showed that mortality increased by 7.6% for every hour that elapsed between the diagnosis of septic shock (hypotension requiring vasopressors) and the onset of antibiotic therapy.

Another study of 2796 patients with sepsis found the odds of mortality were 49% higher among patients who had antibiotics started > 6 hours vs. <1 hr following presentation (Ferrer et al 2009).

A study of over 35,000 emergency patients with sepsis found a 9% increase in mortality with each hour antibiotic therapy was delayed following hospital admission in the first 6 hours (Liu et al 2017).

Finally, in a study of 49,331 patients with sepsis admitted to an emergency department, the odds of mortality increased 4% for each hour antibiotic therapy was delayed from the time of patient evaluation.

Notwithstanding the potential adverse effects of administering empirical antibiotic therapy (microbial resistance, anaphylaxis, liver failure, gastrointestinal and kidney-related side effects etc.), it appears that early antibiotic therapy is likely associated with improved survival in patients with sepsis (Peltan et al 2020).

Early Source Control

Source control is a key step in early sepsis treatment. Source control may be defined as abscess drainage, infected or necrotic tissue debridement, microbial contamination control, or infected device removal. The timing of source control has been an area of controversy, owing principally to a lack of strong evidence (Martinez et al 2017).

It is difficult to determine the best time to initiate surgery for GI perforation with associated septic shock. It is common to stabilise circulatory dynamics before surgery - however delaying initiation of surgery may result in death from sepsis. The question of surgical timing becomes even more challenging to answer if circulatory dynamics are not stabilised (Reitz et al 2022).

Recent studies reveal that early source control is associated with improved survival (Martinez et al 2017; Reitz et al 2022, Azuhata et al 2014), with the odds of survival following diagnosis of sepsis improving if source control was established within 6 hours.

Of particular note, one study (Reitz et al 2022) found that source control within 6 hours was associated with reduced mortality. These odds were significantly improved in patients who received source-control surgery for soft tissue injury or infection, gastrointestinal perforation or disease, and abdominal disease, and somewhat

Collectively, these data suggest that surgical intervention is a crucial component of patient therapy, and that timing should not be delayed in patients in which lack of source control is associated with adverse outcomes.

Vasopressor and Inotrope Use in Septic Shock

Vasopressors have a crucial role in the management of sepsis and septic shock, given that the presence of hypotension is associated with worse clinical outcome and higher mortality. The choice of vasopressor agent and inotrope has been researched in several studies (Devlin et al 2020), with the following conclusions:

1. Vasopressors:
 - a. Noradrenaline
 - i. Is the agent of choice for management of hypotension in septic shock
 - ii. Increases myocardial contractility due to beta-1 effects
 - iii. Vasoconstriction prevents beta-1 mediated tachycardia
 - iv. Less arrhythmogenic than dopamine
 - v. Lower hospital mortality rates in people treated with noradrenaline vs. dopamine
 - vi. Early treatment with noradrenaline is associated with better outcomes than delayed-onset noradrenaline in septic shock patients. A study of 213 patients with septic shock found that each hour delay in noradrenaline initiation in the first 6 hours of diagnosis of septic shock as associated with a 5.3% increase in mortality (Martin et al 2000)
 - b. Dopamine
 - i. There is little benefit in using dopamine over noradrenaline for blood pressure support in septic patients, as eluded by research comparing both agents outlined above.
 - ii. Dopamine Is a potent chronotrope, and is more arrhythmogenic than noradrenaline
 - iii. Dopamine use is associated with higher mortality than noradrenaline
 - c. Vasopressin
 - i. Endogenous vasopressin concentrations are known to reduce in sepsis
 - ii. The combination of vasopressin with noradrenaline increases gut and kidney blood flow, as well as urinary output, and does not increase myocardial oxygen demand, Additionally, the combination reduced dose requirement for noradrenaline to achieve target blood pressure.
 - iii. The combination of noradrenaline and vasopressin may reduce 28-day mortality in sepsis
2. Inotropes
 - a. Dobutamine
 - i. Is a potent positive inotrope. It also has bronchodilator effects and is a mild vasodilator
 - ii. Dobutamine is associated with lower risk for mortality compared to dopamine
 - iii. Dobutamine use is associated with lower blood lactate compared to epinephrine use
 - b. Epinephrine, phenylephrine
 - i. Currently no evidence to support use in septic shock
 - c. Phosphodiesterase inhibitors
 - i. Theoretically may improve myocardial function in septic shock, but the vasodilatory effect may have adverse effects on blood pressure
 - ii. Currently no studies exist to support or refute their use in septic shock

Surviving Sepsis Guidelines

The surviving sepsis guidelines were established in 2004, following a 2002 meeting to establish the "Surviving Sepsis Campaign" to improve outcomes in sepsis. The guidelines had been revised several times since their initial publication, to reflect updates in scientific literature and clinical understanding of sepsis and its effective treatment (Evans et al 2020).

The guidelines themselves promote the use of so-called "care bundles" - essentially groups of recommendations for diagnostic and therapeutic steps, organised in a temporal fashion, to assist clinicians in guiding management of a patient with sepsis, in order to achieve optimum outcome, based on scientific evidence.

Over fifty large-scale, multicenter studies have evaluated the outcome of sepsis patients when exposed to various levels of compliance with the surviving sepsis campaign bundle recommendations. Results are summarised as follows:

- The greater the number of bundles applied to sepsis patients, the lower the mortality rate
- In one study, mortality rate was halved in patients in which bundle compliance was high, compared to those patients in which bundle compliance was low.
- In another study, bundle compliance at 3 hours was associated with a 40% reduction in mortality
- Higher bundle compliance is associated with improved survival and reduced hospital and ICU stay duration

Judicious Transfusion Therapy:

Over the past 25 years, the use of plasma in patients with sepsis has been reviewed and studied extensively. Despite beneficial effects of plasma transfusion being reported in several studies, the overall effect of plasma transfusion therapy in patients with sepsis appears to be minimal, and has been shown to be detrimental in many patient groups. Plasma transfusion is associated with the following observations:

- Immune suppression
- Increased release of pro-inflammatory cytokines
- Transfusion-related infection
- Transfusion-related sepsis
- Transfusion-related acute lung injury
- Increased complication rates following gastrointestinal and cancer surgery
- Increased risk of volume overload
- Increased risk of hypersensitivity reactions
- Increased 30- and 90-day mortality rates

Despite these findings, there is still controversy on the benefits of albumin or plasma transfusion in both humans and in companion animals. Where coagulopathy exists in the context of potentially life-threatening haemorrhage, or planned emergency surgical intervention, plasma transfusion is warranted to prevent bleeding.

The non-haemorrhagic patient with hypoalbuminaemia presents a distinct therapeutic challenge, as it appears, based on much of the recent literature, along with systematic reviews, that there is a lack of clear evidence of improved outcomes following administration of albumin. In the critical patient, hypoalbuminaemia is associated with worse outcome. However, it seems transfusion of hypoalbuminaemic patients does not always correlate with improved outcome.

Additionally, whilst there may be some theoretical benefit to transfusion of albumin to patients with clinical syndromes associated with endothelial glycocalyx shedding (sepsis, acute trauma, haemorrhagic shock etc.) there is currently no available study to provide evidence for a recommendation in this setting.

Human serum albumin use in dogs is associated with at-times severe adverse reactions in dogs, and its use cannot be recommended.

Regarding species-specific albumin transfusions (either concentrated albumin or cryopoor plasma), transfusion does appear to result in elevated albumin concentrations. However, there is insufficient evidence to document an improved outcome.

There may be cause to administer albumin-containing solutions in selected patients - for example, those with sepsis and septic shock - in which low-volume colloid resuscitation may be preferable to crystalloid solutions - particularly in those patients in which there is significant third space fluid accumulation/oedema. Research in this setting would provide clarity on the value of such an intervention.

Avoid Fluid Overload

Fluid overload is classically defined as a positive fluid balance in a patient that has received intravenous fluid therapy. Fluid overload, which is also described as volume overload or hypervolemia, is a potentially serious complication of intravenous fluid therapy in both hospitalized animals and humans.

Adverse effects of fluid overload include:

- CNS dysfunction
- Gastrointestinal dysmotility and increased intestinal wound infection rate
- Impaired liver function
- Cardiac arrhythmias
- Increased requirement of inotrope and vasopressor support
- Acute kidney injury
- Pulmonary oedema and pleural effusion
- Delayed wound healing rates

Fluid overload is associated with worse clinical outcomes across a wide spectrum of medical and surgical conditions. Avoidance of fluid overload potentially carries significant advantage for patients.

Strategies for avoiding fluid overload include:

1. Limiting high-volume resuscitation volumes of intravenous fluids beyond clear physical and ultrasound evidence of responsiveness.
2. Following obtaining haemodynamic stability, fluid rates should be reduced to appropriate maintenance rates, based on caloric requirements, to avoid excess fluid administration rates
3. Avoid placing patients on supra-normal maintenance rates in anticipation of ongoing fluid losses secondary to underlying disease e.g. vomiting and diarrhoea. Rather, these excess losses should be calculated or measured, and replaced as they occur.

Fluid overload, when diagnosed, should be managed as follows:

1. Sodium and water restriction (including temporary cessation of intravenous fluids, if necessary)
2. Administration of diuretic therapy to reduce excess fluid e.g. furosemide 0.66 mg/kg/hr for 6 hours

Volume overload is a common complication of fluid therapy, particularly in critically ill patients, and can lead to significant increases in both morbidity and mortality. The available literature suggests that a more conservative approach to fluid administration may be beneficial in many disease conditions, particularly in those with critical illness.

Furthermore, close monitoring of fluid balance, and timely intervention in patients diagnosed with volume overload, may improve outcomes in affected patients.

Conclusion:

Sepsis remains a challenging and potentially life-threatening condition in both humans and veterinary patients. Whilst several interventions have currently proven of little benefit in improving outcome, improvements in our understanding of the pathophysiology of sepsis, have led to the development of several interventions that have reduced both illness severity and mortality.

Key among these is early syndrome recognition, and early treatment – including early use of antibiotics, care bundles, and vasopressors +/- inotropes. Additionally avoidance of potentially harmful interventions, including the use of synthetic colloids, excessive fluid rates and volumes, the use of lung-protective ventilation strategies, and judicious, early resuscitation with blood products have also reduced complication rates.

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Surviving Sepsis Campaign

Vasoactive Agent Management



Use norepinephrine as first-line vasopressor

For patients with septic shock on vasopressor



Target a MAP of 65mm Hg



Consider invasive monitoring of arterial blood pressure

If central access is not yet available



Consider initiating vasopressors peripherally*

If MAP is inadequate despite low-to-moderate-dose norepinephrine



Consider adding vasopressin

If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure



Consider adding dobutamine or switching to epinephrine



Strong recommendations

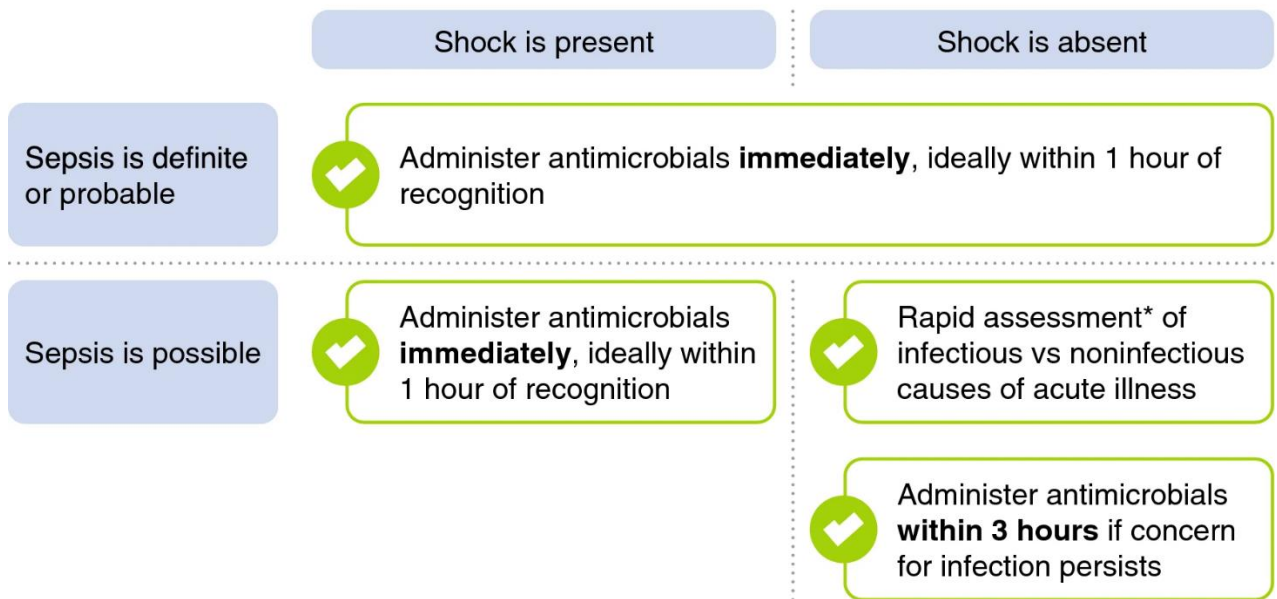


Weak recommendations

*When using vasopressors peripherally, they should be administered only for a short period of time and in a vein proximal to the antecubital fossa.

Surviving Sepsis Campaign

Antibiotic Timing



*Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.

Surviving Sepsis Campaign

Surviving Sepsis Campaign

BUNDLE

HOURLY-1 BUNDLE: INITIAL RESUSCITATION FOR SEPSIS AND SEPTIC SHOCK:

- 1) Measure lactate level.*
- 2) Obtain blood cultures before administering antibiotics.
- 3) Administer broad-spectrum antibiotics.
- 4) Begin rapid administration of 30mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.
- 5) Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure ≥ 65 mm Hg.

* Remeasure lactate if initial lactate elevated (> 2 mmol/L).

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