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Surviving the first hours in sepsis: getting the basics right (an intensivist's perspective)

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Severe sepsis is a major cause of morbidity and mortality, claiming between 36000 and 64000 lives annually in the UK, with a mortality rate of 35%. International guidelines for the management of severe sepsis were published in 2004 by the Surviving Sepsis Campaign and condensed into two Care Bundles. In 2010, the Campaign published results from its improvement programme showing that, although an absolute mortality reduction of 5.4% was seen over a 2 year period in line with increasing compliance with the Bundles, reliability was not achieved and Bundle compliance reached only 31%. This article explores current challenges in sepsis care and opportunities for further improvements. Basic care tasks [microbiological sampling and antibiotic delivery within 1 h, fluid resuscitation, and risk stratification using serum lactate (or alternative)] are likely to benefit patients most, yet are unreliably performed. Barriers include lack of awareness and robust process, the lack of supporting controlled trials, and complex diagnostic criteria leading to recognition delays. Reliable, timely delivery of more complex life-saving tasks (such as early goal-directed therapy) demands greater awareness, faster recognition and initiation of basic care, and more effective collaboration between clinicians and nurses on the front line, in critical care and in specialist support services, such as microbiology and infectious diseases. Organizations such as Survive Sepsis, the Surviving Sepsis Campaign and the Global Sepsis Alliance are working to raise awareness and promote further improvement initiatives. Future developments will focus on sepsis biomarkers and microarray techniques to rapidly screen for pathogens, risk stratification using genetic profiling, and the development of novel therapeutic agents targeting immunomodulation.

Keywords: antibiotics, bundles, critical, cultures, lactate

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Introduction

Sepsis is a common condition with a major impact on healthcare resources and expenditure. The incidence of severe sepsis (sepsis-induced organ dysfunction) in the European Union has been estimated at 90.4 cases per 100000 population, as opposed to 58 per 100000 for breast cancer.[1] The documented incidence of sepsis worldwide is 1.8 million cases annually, but this figure reflects low rates of recognition and diagnosis. Recent estimates give an incidence of sepsis requiring intensive care admission of 0.25–0.38 per 1000 population, suggesting ~2 million admissions to intensive care units (ICUs) alone.[2,3] In 1992, it was estimated that 1400 people worldwide were dying each day from severe sepsis,[4] although the true figure is likely to be much higher and rising. A more recent US study estimated 3.0 cases to occur per 1000 population per year,[5] or ~20 million cases per year. With a mortality of 35%, this would mean ~20000 deaths per day worldwide and 64000 deaths annually in the UK.

Data from the UK Intensive Care National Audit and Research Centre (ICNARC) covering the last 6 months of 2005 showed that 8300 patients died from severe sepsis on ICUs.[6] Between 65% and 70% of eligible ICUs in the UK contribute data to ICNARC, and only ~70% of patients with severe sepsis are treated on an ICU.[7] This gives an estimated 36800 deaths annually in the UK (Figure 1). The mortality rate from severe sepsis has been estimated in a number of studies as between 28% and 50%.[5,8,9] More recently, the Sepsis Occurrence in Acutely ill Patients (SOAP) study in Europe observed an overall hospital mortality of 36%.[10] Data from the Surviving Sepsis Campaign (SSC) showed a mortality of 34.8%[11] among 15022 patients, and ICNARC data show that 39.8% of those admitted to critical care in England and Wales die in hospital. There are few disease processes with such a high mortality. An admission with severe sepsis places the patient at a level of risk ~6–10-fold greater than if he were admitted with an acute myocardial infarction and 4–5 times greater than if he had suffered an acute stroke.

There has been considerable debate around treatment guidelines, particularly those relating to invasive management and critical care. The most widely discussed guidelines are those from the SSC. This article aims to set the background and to offer discussion on the most important issues facing clinicians in the UK: those of early recognition and immediate, basic management.

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The SSC

In 2002, critical care experts agreed that concerted action was needed to reduce the mortality from severe sepsis. The SSC was developed as a collaboration between the European Society of Critical Care Medicine, the International Sepsis Forum and the Society of Critical Care Medicine. A desire to reduce the mortality from sepsis by 25% over a 5 year period became known as the Barcelona Declaration.[12] In March 2004, the SSC guidelines for the management of severe sepsis and septic shock were published—these were subsequently updated in 2008.[13,14] Care Bundles were created in collaboration with the Institute for Healthcare Improvement. The first (the Resuscitation Bundle) comprised a set of tasks to complete within the first 6 h following the identification of sepsis (Figure 2).

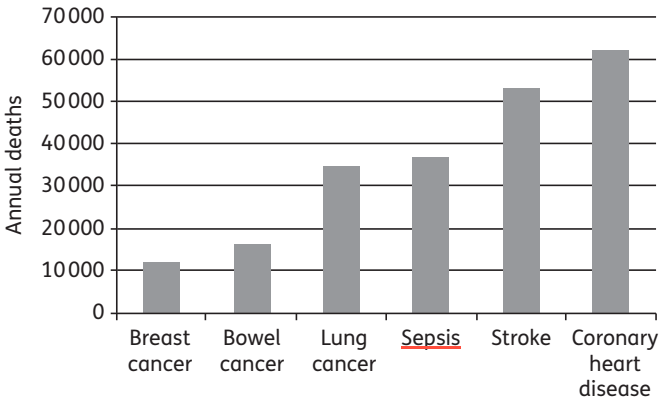

Figure 1. Chart showing relative mortality figures in 1 year for the UK for common conditions. Sources: sepsis, ICNARC data 2006. For all others: for England and Wales, Office for National Statistics 2008; for Scotland, General Register Office Registrar General Annual Report 2008; and for Northern Ireland, Statistics and Research Agency Registrar General Annual Report 2008.

In 2010, the SSC published results from its improvement programme, which concluded in December 2008.[11] Data were reported for 15 022 patients from 165 sites across 30 countries and showed that 71.5% of patients presented with septic shock. Compliance with the Resuscitation Bundle rose over a 2 year period from 10.9% to 31.3%, with mortality reducing over the same period from 37.0% to 30.8% ($P<0.001$). Adjusted mortality was reduced by 0.8% for each quarter that a site was in the SSC, with an absolute mortality reduction of 5.4% over 2 years [95% confidence interval (CI) 2.5%–8.4%]. The delivery of early antibiotics and sampling for culture prior to antibiotics were each found to be independently associated with survival, as was the maintenance of tight glycaemic control over the first 24 h [odds ratios (OR) for mortality 0.86, 0.76 and 0.67, respectively; upper 95% CI limits <1.0, $P<0.001$, for each]. These results, although limited by voluntary contribution of data, demonstrated that the use of a multifaceted improvement initiative was successful in changing sepsis treatment behaviour as demonstrated by a significant increase in compliance with performance measures. However, the SSC has not been universally acclaimed, and was fiercely criticized by some, due to its links with industry during the second phase.[15] This criticism has largely been levelled at the inclusion of activated protein C (Xigris®; Eli Lilly and Co.) in the second of the two Care Bundles (the Management Bundle). This recommendation was downgraded to Level 2 in the 2008 revisions. More scientifically solid criticism has arisen surrounding a number of other

Measure serum lactate

Obtain blood cultures prior to antibiotic administration

From the time of presentation, broad-spectrum antibiotics to be given within 1 h

Source of infection to be identified and drained within 6 h

In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL):

- deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
- give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure ≥65 mmHg

In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/L (36 mg/dL):

- achieve central venous pressure of ≥8 mmHg
- achieve central venous oxygen saturation of ≥70%

Figure 2. The Surviving Sepsis Campaign Resuscitation Bundle. Source: www.survivingsepsis.org.

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recommendations, including that for early goal-directed therapy (EGDT), discussed below.

Debate aside, these recommendations for immediate care are endorsed by the European Society of Intensive Care Medicine, the Intensive Care Society and the College of Emergency Medicine, among others.[16] It is likely and appropriate that sepsis resuscitation will increasingly occur prior to admission to critical care. Much of the published work linking quality of sampling and antimicrobial administration is drawn from the strong working relationships forged between intensivists and microbiologists over recent years: the future, as sepsis resuscitation moves closer to the front line, will demand new relationships and cohesive working.

The Resuscitation Bundle

This comprises a set of tasks to be completed for all patients within the first 6 h following the onset of severe sepsis. Some tasks are within the scope of practice of most healthcare workers, while others—together termed 'early goal-directed therapy'—require specialist skills. This leads to a complexity for the Bundle that makes it difficult to achieve outside well-resourced units,[7,17,18] and demands effective collaboration between point-of-access, admitting and critical care teams, with advice and clinical support from radiology, microbiology and infection control personnel. Even in emergency departments, resources to complete the invasive aspects of the Bundle are rarely accessible in the UK.[18]

Challenges in identification

A key difficulty for any organization attempting to implement a project to improve compliance with the Resuscitation Bundle is that the tasks require completion within a narrow time frame: for sampling and antibiotic administration, 1 h. The internationally accepted definition of severe sepsis (Figure 3) is drawn from a consensus definitions conference in 2001.[19] This requires a battery of physiological and laboratory indices together with a clinical suspicion of a new infection as the source of the abnormalities, in addition to maintaining an awareness of sepsis while completing other, co-existing care pathways, such as for pneumonia. The challenges in reliably identifying severe sepsis at the outset remain the greatest barrier to implementing the guidelines.[20]

To reliably identify severe sepsis demands a degree of awareness, vigilance and knowledge among individual healthcare workers and within the organization itself. A number of multiprofessional education programmes are available to achieve this, such as Survive Sepsis.[21] Systems need to be well-designed and implemented to ensure that appropriate investigations (e.g. lactate measurement), equipment (e.g. blood culture bottles) and treatments (including all first-line antibiotics) are available at the point of care, and that lines of communication are clear and effective. Without a 'whole systems' approach, improvements will be limited.

Individual recommendations

Measurement of serum lactate

There is some evidence that lactate levels carry prognostic value, with at least one study demonstrating the ability to risk-stratify patients according to their serum lactate at presentation.[22] Patients with a lactate of >4 mmol/L had a mortality of ~40%, compared with under 15% for patients with a lactate of <2 mmol/L. Other studies have shown lactate to be predictive of critical care admission.[23] Lactate levels are particularly useful when measured serially, to guide response to resuscitation and fluid therapy.

There is certainly debate surrounding the validity of lactate measurement and its interpretation—some studies have shown a relatively low incidence of hyperlactataemia in septic patient populations, and the SSC found lactate measurement not to impact on survival.[11] It should be noted that lactate is not specific to organ hypoperfusion secondary to severe sepsis. Indeed, some units prefer serum procalcitonin as a more specific marker.[24] Evidence suggests that the prognostic value of procalcitonin may occur later than that of lactate, although changes in both markers combined are highly predictive of outcome between 24 and 48 h.[25] Studies in trauma patients have evaluated lactate levels against Acute Physiology and Chronic Health Evaluation (APACHE) scores and lactate clearance rates, and found lactate levels to be inferior.[26] In patients with sepsis, the rate of lactate clearance over the first 6 h has been shown to be predictive of mortality.[27]

Determination of APACHE scores and lactate clearance require a period of observation prior to their potential use as prognostic indicators. To apply these indicators in a busy UK emergency department (particularly in the context of targets for 4 h trolley waits) is a challenge. There is a potential danger that referral to critical care may be delayed for several hours if prognostic indicators are not available for some hours after presentation: this is clearly not in the best interests of our patients. However, the ideal biomarker for prognostication at presentation has not yet been identified.

The term 'cryptic shock' has been used to describe patients with hyperlactataemia in the presence of normal blood pressure,[28] with hyperlactataemia suggestive of hypoperfusion existing in up to 25% of normotensive patients. While it has not been demonstrated that patients with cryptic shock fare as poorly as those with overt shock, these data do suggest that reliance on haemodynamic indices alone does not reliably identify hypoperfusion. It is reasonable to assume that lactate, while non-specific, may prompt aggressive treatment in a subgroup of septic patients who are normotensive and who otherwise may not be aggressively treated with fluid resuscitation. Lactate is associated with a degree of prognostic value. It seems appropriate, therefore, to continue to promote the use of this relatively inexpensive, minimally invasive assay. Further work is required to evaluate stand-alone lactate measurement against procalcitonin and lactate clearance rate in prognostication for these patients.

Microbiological sampling

The SSC recommends at Level 1 the taking of at least two blood cultures prior to the administration of antibiotics, with one drawn percutaneously and one from each vascular access device in place for >48 h, with the proviso that sampling does not significantly delay the administration of antibiotics. Sampling of other fluids based on clinical suspicion is also recommended. These recommendations are based upon retrospective work from the

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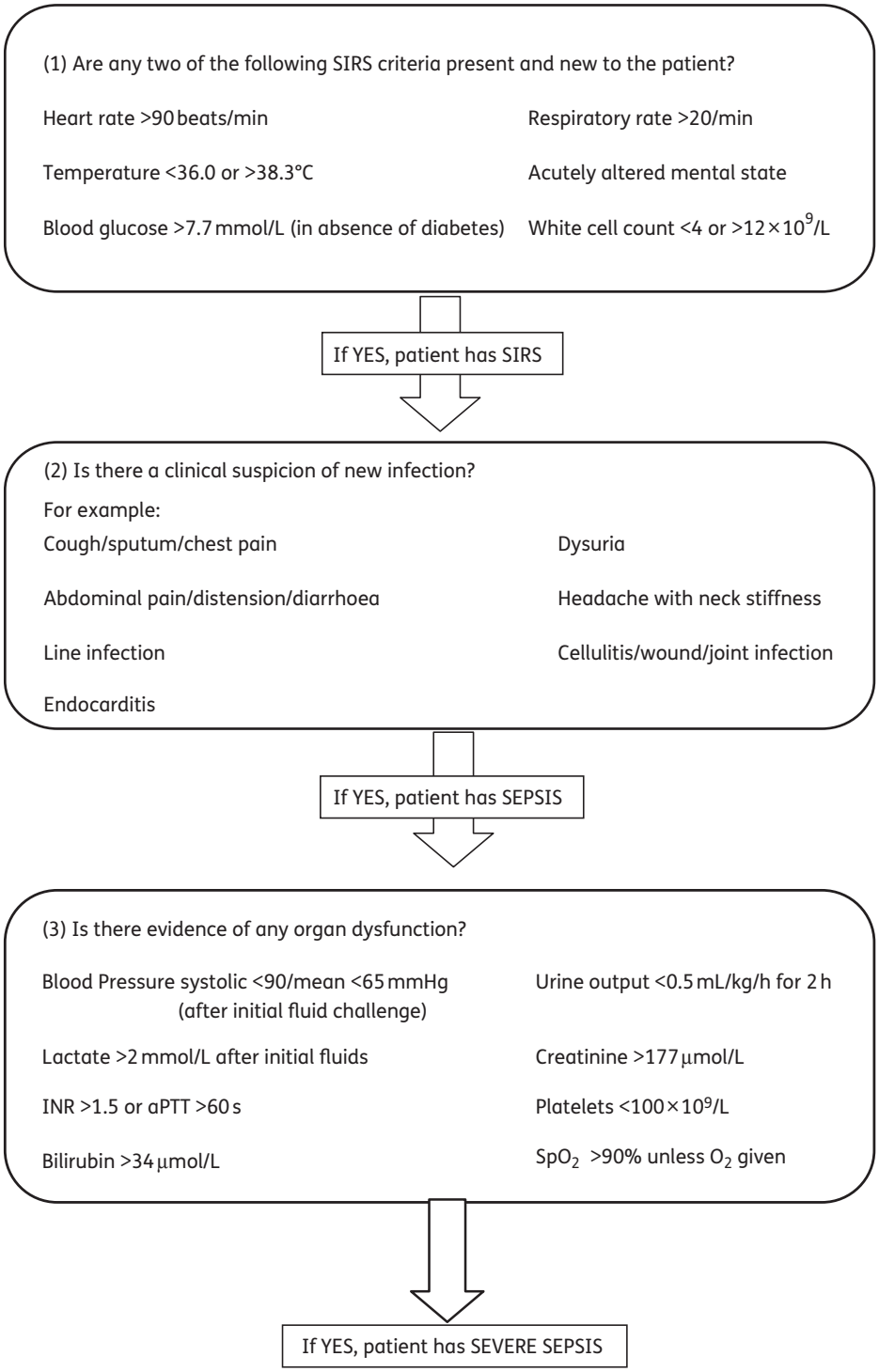

Figure 3. Diagnostic criteria for sepsis. SIRS, systemic inflammatory response syndrome; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

1980s, which showed a 99% sensitivity for the detection of bacteraemia when two samples were cultured using manual techniques.[29] More recent work with automated culture has demonstrated a much lower sensitivity of only 80% with two cultures, with three samples yielding only 96% sensitivity.[30] Current evidence suggests that four samples may be necessary to reliably detect all episodes.[31] However, patients requiring antimicrobial chemotherapy as a matter of the utmost urgency may present at all hours and in all clinical areas; hence, the sampling of four sets of blood cultures is rarely practicable.

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Pragmatism is required, as is close liaison between ward-based clinicians and the microbiology team to optimize capture rate (and therefore potential for de-escalation) while minimizing unwarranted delays in therapy. The administration of antibiotics is recommended within 1 h of onset of sepsis; hence, sampling is also recommended to occur within that time. While feasible for blood, sputum, stool and urine, cultures of more invasive samples (such as CSF) and high-quality samples (such as tracheal aspirates, protected brush samples and those from bronchoalveolar lavage) are likely to be acquired later and after antimicrobial administration.

Current recommendation in the UK demands that, unless sampling is likely to significantly delay antimicrobial administration, at least one set of blood cultures be drawn with consideration to other samples.[16,21] In the acute setting, this may be all that is reasonably achievable, certainly within the first hour. The SSC recommends a sample be drawn from each lumen of a vascular access device if the device has been in place for >48 h, again at Level 1, citing work on differential time to positivity.[32] This work, although in only 64 patients, showed that a cut-off lag time of 120 min between positivity of central venous and peripheral samples carried 100% specificity and 96.4% sensitivity for the diagnosis of catheter-related bloodstream infections.

Microbiological sampling is key to the identification of initially inadequate cover,[33] and to subsequent de-escalation of therapy and risk reduction for secondary infection. De-escalation of the antimicrobial spectrum of therapy has been demonstrated to benefit individual patients in addition to reducing selection pressure for resistance.[34] Despite this, de-escalation is unreliably practised. In one multicentre study (in which a carbapenem with or without an aminoglycoside and/or glycopeptide was administered in patients with nosocomial pneumonia), de-escalation based on cultures and susceptibilities at day 3–5 was practised in only 23% of eligible patients despite this being part of the study protocol.[35] In that multicentre study, a carbapenem with or without an aminoglycoside and/or glycopeptide was administered as empirical therapy to patients with nosocomial pneumonia. The regimen was de-escalated at day 3–5, based on the availability of microbiological data. For de-escalation to be reliable and successful, it relies not only on the availability of microbiological data, but also on the quality of interaction between the microbiology team and the critical care team (or the ward team for those not admitted to critical care) and on shared ownership of the antimicrobial prescription.

Antimicrobial therapy

Based upon Anand Kumar's work,[36] the SSC issued a recommendation at Level 1B to administer antimicrobials within 1 h in septic shock and, at 1D, to septic patients without shock. This landmark paper demonstrated an increase in mortality of 7.6% for every hour by which antimicrobials were delayed in septic shock. However, this was a retrospective study over 15 years and recruitment rates were relatively low, with 2154 patients included from 14 sites. Only 12% of patients had received antibiotics within the first hour.

A prospective controlled trial of time to antimicrobial administration is unlikely to recruit many centres. One recent observational study demonstrated an OR for death of 0.3 for patients receiving agents within 60 min of emergency department triage time, although median time from triage to administration was 119 min.[37] It is intuitively sensible, although not yet convincingly demonstrated, that early appropriate antibiotics will improve outcome in severe sepsis by reducing the microbial load. The majority of centres would strive to achieve this goal, yet the reality is that few do so, probably reflecting gaps in awareness and recognition. Few would argue with the initial use of broad-spectrum agents. The study by Ibrahim *et al.*[38] of patients with bacteraemia on critical care showed those treated inadequately with antimicrobials fared far worse than those treated adequately (mortality 61.9% versus 28.4%, $P<0.001$), with almost one-third receiving inadequate initial cover. Pathogens inadequately covered included *Candida* species in >8%, vancomycin-resistant enterococci, coagulase-negative staphylococci and *Pseudomonas aeruginosa*. The presence of fungal infection, prior administration of antibiotics and central venous catheters each independently increased risk of inadequate cover.[38] Recently, a large teaching critical care unit has shown that adherence to an antibiotic guideline resulted in appropriate cover in only 73.6% of cases, with 50% receiving monotherapy.[39]

Community-acquired pneumonia (CAP)

CAP treatment has been extensively studied. The publication of source-specific guidelines, intended to be applicable across entire healthcare systems, can give rise to variability in adequacy of cover for such patients due to local differences in resistance patterns. Rates of adherence to published guidelines are also highly variable, with one study across 22 centres quoting adherence rates of 0%–53%.[40] National guidelines for antimicrobial therapy in CAP have been produced by organizations including the American, British and Canadian Thoracic Societies, Spanish Society of Pulmonology and Infectious Diseases Society of America. Such guidelines have been shown to improve adherence rates, but reliability remains incomplete.[41,42] Such widespread implementation of guidelines does not take into account variations in resistance patterns and may be inappropriate. Associations between adherence and outcome are variably reported, with studies from Canada, England and Chicago finding no association,[43–45] in contrast with studies from Texas[46–48] that noted significant outcome improvements in patients whose treatment was compliant with guidelines.

These are all observational studies with attendant limitations from risk of confounding variables. A criticism valid to all studies evaluating guidelines is that compliance with the guideline may simply be a surrogate marker for globally improved care. Antibiotic protocols, professional body guidelines and the rationale for early antibiotic therapy are so embedded that large-scale randomized trials are highly unlikely.

Recently, increasing numbers of cases of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia have been reported, particularly in association with influenza virus infection.[49,50] Mortality rates appear somewhat higher than for non-MRSA severe CAP (as opposed to severe sepsis) at 26%–33%, the clinical course is more rapid and the recovery period is prolonged, with some patients requiring months of critical care support despite single-organ failure.[51] Community-acquired MRSA has greater susceptibility to antibiotics (with the exception of β-lactams), and is characterized by the presence of a type IV staphylococcal

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Table 1. Summary of studies comparing monotherapy with combination therapy in healthcare-associated pneumonia

Reference	Year	Comparison	Outcome	Outcome difference		Comment
				monotherapy	combination	
57	1988	cefoperazone versus cefalotin + gentamicin	cure rate	87%	72%	no difference in superinfection; monotherapy cheaper
58	1993	cefoperazone/ceftazidime ± gentamicin	cure rate	56%	31%	superinfection higher in combination
59	1994	imipenem versus imipenem + netilmicin	success	80%	86%	nephrotoxicity in combination
60	1994	ceftazidime versus ceftriaxone + tobramycin	clinical response	73%	65%	nephrotoxicity in combination
61	1997	meropenem versus ceftazidime + tobramycin	success	89%	72%	
62	2001	meropenem versus ceftazidime + amikacin	success	82%	66%	
63	2006	cefepime versus cefepime + amikacin or levofloxacin	mortality	10%	21%	ICU LOS no different; no difference in serial inflammatory markers
64	2008	meropenem versus meropenem + ciprofloxacin	success	80%	82%	combination higher eradication rate

LOS, length of stay.

cassette chromosome *mec* element (SCC*mec*IV) and the expression of genes governing production of Panton–Valentine leucocidin (implicated as a causative agent in cavitation).[52,53] Case reports have described a disease process characterized by high fever, severe necrotizing pneumonia with haemoptysis, leucopenia, respiratory failure and shock. In patients presenting with particularly severe CAP, especially in the presence of haemoptysis, shock and an influenza-like prodromal illness, MRSA should be considered. The recent Infectious Diseases Society of America/American Thoracic Society guidelines recommend either vancomycin or linezolid for CAP due to community-acquired MRSA.[54] Linezolid may be preferred due to its superior lung penetration.

Healthcare-associated pneumonia (HCAP)

Although the SSC made no specific recommendation in HCAP, a key debate in the treatment of HCAP is the use of combination antimicrobial therapy versus monotherapy. Recommendations had previously suggested the use of aminoglycosides in combination with β-lactams in Gram-negative ventilator-associated pneumonia.[55] However, it may be that HCAP encompasses too heterogeneous a group of patients to permit a single recommendation.[56] Those with recent acute hospital stay, severe illness, recent antibiotic exposure and poor functional status are at increased risk of infection with resistant organisms, and may warrant a broader spectrum of cover than, for example, nursing home residents. A number of studies (mostly unblinded randomized trials) have been conducted to evaluate monotherapy against combination therapy. A number are summarized in Table 1.[57–64] The literature is largely focused on critical care patients, although this is arguably the group most likely to benefit from combination therapy. Nonetheless, no study is convincingly in favour of combination therapy.

Pseudomonas infection

The SSC recommended at Level 2, supported by Grade D evidence, the use of combination therapy in patients with known or suspected *Pseudomonas* infections and in those with neutropenic sepsis. A number of studies pertain to this recommendation, but evidence in direct support is scant. The group led by Garnacho-Montero[65] found the use of initial combination therapy in ventilator-associated pneumonia to reduce the risk of inadequate cover, but not to impact on outcome. The 2004 meta-analysis by Paul *et al.*[66] of 64 trials comparing β-lactam monotherapy with combination therapy with an aminoglycoside showed no all-cause fatality difference in patients with sepsis, although a retrospective subgroup analysis did appear to show benefit in patients with *Pseudomonas*. The adverse event rate (nephrotoxicity) was higher with combination therapy. A later meta-analysis of six randomized controlled trials in patients with Gram-negative bacteraemia again found no advantage in all patients, but showed a reduction by half of mortality in patients with *Pseudomonas* infection.[67]

Neutropenic sepsis

No study has convincingly demonstrated benefit of combination therapy in this group, leading most groups to recommend monotherapy with a carbapenem over duotherapy. A large meta-analysis of 29 randomized controlled trials showed no benefit with the use of combination therapy, with an OR for failure of treatment (early modification or death during treatment) of 0.87 in monotherapy.[68]

Should we use antifungal agents empirically?

The fact that *Candida* infections are under-recognized and the lack of sensitivity of culture methods would suggest a possible role for empirical antifungals, particularly in patients with

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recent exposure to broad-spectrum antibiotics or immunosuppression. However, the SSC recommends against the routine use of empirical antifungals, based on the relatively low frequency of fungal causation of sepsis (~5% of cases), although this is likely to rise.[69] In a European point prevalence study, fungi were isolated from 17% of intensive care patients with nosocomial infection, although it is unclear whether these were the organisms responsible for the sepsis.[70]

A large retrospective study identified delay in administration of antifungal agents as a predictor of hospital mortality in patients subsequently found to have positive cultures for *Candida* spp.[71] With the relatively high morbidity associated with the use of antifungals, it would seem reasonable not to recommend their routine use. However, it is very likely that the timing of antifungal therapy in severe infection is just as critical as that of antibiotic therapy. In high-risk patients, a high index of suspicion for primary or secondary fungal infection and a low threshold for the use of antifungal agents are required.

Fungi are more prevalent as isolates in patients with secondary or tertiary peritonitis, with *Candida* spp. identified in up to 20% of patients with gastrointestinal tract perforation.[72] Risk factors include faecal soiling of the peritoneum, recurrent gastrointestinal perforation, immunosuppressive therapy for neoplasm or in post-transplant patients and the presence of inflammatory diseases. These high-risk patients have a high risk of mortality[73] and some case series suggest benefit from the empirical addition of agents with activity against *Candida* spp.[74,75]

The Infectious Diseases Society of America has produced guidelines recommending (at level B) the use of amphotericin B or fluconazole in patients with *Candida* peritonitis for a period of 2–3 weeks as a supplement to surgical drainage. However, these guidelines did not offer guidance on the use of prophylactic antifungal agents in patients with peritonitis with risk factors.[76] The increase in frequency of *Candida glabrata* may prompt some units to use echinocandins in preference to azole agents in these high-risk patients.[77,78]

Fluid resuscitation

The early phases of sepsis combine absolute hypovolaemia [due to fluid loss into interstitial spaces and reduced intake, and to increased insensible (not readily measurable) loss through perspiration and respiration] with relative hypovolaemia due to venodilatation and arteriolar dilatation. Compounded by ventricular dysfunction, microcirculatory disorders and hypercoagulability, organ perfusion may reduce and, in some, shock may result.[79] Treating hypovolaemia is thus a central tenet of sepsis.[14,80] Despite evidence in support of early fluid resuscitation being scant, few would argue with the practice and still fewer would claim equipoise in order to conduct a randomized trial.

It is important to distinguish between initial fluid resuscitation and aggressive, goal-directed fluid resuscitation. The SSC recommends initial boluses to a volume of 20–60 mL/kg body weight prior to the consideration of invasive monitoring and goal-directed therapy.[14] Initial fluid resuscitation should be delivered, according to the Level 1D recommendation, in fluid challenge aliquots of 1000 mL of crystalloid or 300–500 mL of colloid over ≤30 min, with clinical assessment of response to guide the need for further aliquots until the target volume is reached.

Initial resuscitation: which fluid?

With crystalloid solutions, greater volume will be needed to achieve the same degree of volume expansion and more oedema will result. However, it is not likely that peripheral oedema carries significant clinical risk. Colloid solutions are more expensive, but will give a greater and more prolonged volume expansion with less volume infused. At the time of the publication of the 2008 guidelines, evidence failed to categorically support the use of one intravenous fluid over another, with conflicting results from several large reports. The saline versus albumin fluid evaluation (SAFE) study failed to demonstrate benefit or harm with the use of albumin compared with crystalloid, although there did appear to be an insignificant tendency to favour colloid.[81] A systematic review of small studies dating from 1977 to 1994 and recruiting from a range of 18–141 patients showed no benefit of colloid over crystalloid, with a relative risk of 0.86 (95% CI 0.63–1.17) appearing to slightly favour crystalloids.[82] A further review of 26 randomized controlled trials showed potential harm with colloids, with an absolute risk reduction for mortality of 4% (0%–8%) associated with colloid use.[83] None of these three studies was specific to severe sepsis.

Concern regarding the potential for exacerbation of acute kidney dysfunction with the use of starch-based colloid solutions was acknowledged; one randomized, single-blinded multicentre trial had demonstrated an OR for renal dysfunction of 2.32 with hydroxyethyl starch (HES) use.[84] Conversely, and within the limitations of an observational cohort study, results from the SOAP study group showed no association between HES use and renal dysfunction.[85] More recently, a major multicentre trial has provided further information on the role of HES solutions in septic patients. The Volume Substitution and Insulin Therapy in Severe Sepsis study, a prospective randomized controlled trial, showed close to a significant mortality increase with 10% HES, and significant deleterious effects on renal function and the need for renal replacement therapy.[86] However, nearly 40% of patients received a dose of this hyperoncotic, hyperchloraemic HES that was higher than the manufacturer's recommendations. Newer starches are formulated with more physiologically balanced electrolyte solutions and lower molecular weights, and their impact has yet to be evaluated. *In vitro* work has suggested that a lower molecular weight solution more reflective of 'modern' starch solutions may not carry risk of renal dysfunction.[87] The Scandinavian Critical Care Trials group are actively recruiting to a randomized controlled trial comparing a 6% HES solution with Ringer's lactate.[88]

If not colloid, then which crystalloid? It is widely known that infusion of large volumes of normal saline can precipitate hyperchloraemic metabolic acidosis.[89,90] However, it has not been convincingly demonstrated *in vivo* that hyperchloraemic acidosis is harmful. A recent observational study of 548 patients has shown hyperchloraemic acidosis in critical care patients to be associated with a mortality of 29%, compared with 56% for lactic acidosis. There was a trend toward the hyperchloraemic group having increased mortality compared with patients with no acidosis, but this did not reach statistical significance.[91] Balanced solutions, such as Hartmann's solution or Ringer's lactate, do not risk hyperchloraemia, however, and may be safer.

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Early Goal-Directed Therapy—Standard Operating Procedure

Apply with critical care/sepsis team if patient remains hypotensive or lactate remains high following fluid challenges

(1) Site central venous catheter using ultrasound guidance where practicable, according to Trust procedure for infection control

(2) If central venous pressure (CVP) <8 mmHg, give further fluid challenges to achieve a target CVP of >8 mmHg (>12 if ventilated) unless the patient shows signs of fluid overload

(3) If patient remains hypotensive, start a norepinephrine infusion to target SBP >90 mmHg or MBP >65 mmHg. Ensure continuous presence of appropriately trained personnel. Start infusion during fluid resuscitation if patient is profoundly hypotensive or there is evidence of organ compromise due to hypoperfusion

(4) Measure central venous oxygen saturation ($ScvO_2$): draw 1 mL of blood in a heparinized syringe and send for blood gas analysis

(5) If $ScvO_2$ <70%, first check haemoglobin level. If [Hb] is <7 g/dL, arrange for blood transfusion

(6) If $ScvO_2$ <70% with [Hb] >7 g/dL, commence dobutamine infusion initially at 5 μg/kg/min and titrate to $ScvO_2$ unless patient develops severe tachycardia or signs of myocardial ischaemia ensue. Ensure continuous presence of appropriately trained personnel

Figure 4. Sample standard operating procedure for the delivery of early goal-directed therapy. Adapted from Rivers *et al.*[92] SBP, systolic blood pressure; MBP, mean blood pressure.

EGDT

In patients with persistent hypoperfusion, further challenges targeted to central venous pressures are recommended (at Level 1C) according to the work of Rivers *et al.*[92] in a Detroit emergency department as part of a strategy known as EGDT (Figure 4). A full discussion of EGDT is beyond the remit of this article. Within the protocol, patients in the intervention group were aggressively managed within an urban emergency department for 6 h with fluids, blood transfusion, vasopressors and inotropes, according to specified targets for central venous pressure, central venous oxygen saturation ($ScvO_2$) and mean arterial pressure. Patients in the intervention group did receive significantly greater volumes of fluid than those in the control group (4.98 L versus 3.49 L). An absolute risk reduction for mortality of 16% was claimed. Other centres have examined EGDT and noted improved outcomes,[93–95] although each of these studies was an observational 'before and after' trial. Opponents to EGDT cite an unreliability of central venous pressure and $ScvO_2$ in the assessment of ventricular filling pressures and oxygen delivery, and, in particular, high control group mortality (46.5%) in Rivers' patients, who were drawn from a public hospital in deprived inner-city Detroit. Groups from the USA and the Netherlands have found a low incidence of low $ScvO_2$ in their own populations, and found their mortality in the absence of EGDT to be lower than that of Rivers' intervention group.[96,97]

These arguments may not be entirely valid in the UK, where the mortality of patients admitted to critical care with severe sepsis in 2006 was 39.8%[6] and two studies evaluating patients across UK acute hospitals showed mortality at 1 year to be 35%.[7,17] Three multicentre prospective randomized controlled trials will evaluate EGDT over coming years. The Protocolized Care for Early Septic Shock (ProCESS) trial[98] from North America will randomize to one of three arms: treatment according to Rivers' protocol; standard care; and a simpler, modified resuscitation protocol. The Australasian Resuscitation of Sepsis Evaluation[99] study in Australia/New Zealand is recruiting to an open-label randomized trial examining Rivers' protocol against standard care. The ICNARC-sponsored Protocolized Management in Sepsis (ProMISe)[100] study from the UK aims to commence recruitment during 2010. Within a few years, we should have some robust answers as to the effectiveness of EGDT. What is clear is that although EGDT may be of benefit, it is unlikely to be the most effective of all potential protocols. In addition to the ProCESS trial, other groups are already attempting to evaluate alternative protocols, albeit as yet without demonstrating additional benefit.[101]

Bringing basic care together: the 'Sepsis Six'

Each of the early therapeutic and diagnostic interventions mentioned above is deliverable in the general ward setting, but the tasks are rarely delivered within appropriate time frames.[17] None have been conclusively demonstrated to be effective in prospective randomized controlled trials, yet the principles behind each are sound and their likely value intuitive. A number of organizations within the UK have attempted to operationalize the 'basic' tasks within the Resuscitation Bundle to improve immediate care. One example is the 'Sepsis Six' developed by the Survive Sepsis organization and is in use within ~30 organizations across the country.[102,103] The Sepsis Six adds the need for oxygen therapy and accurate urine output

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The Sepsis Six— to be delivered within 1 h

(1) Deliver high-flow oxygen

(2) Take blood cultures and other cultures, consider source control

(3) Administer empirical intravenous (IV) antibiotics

(4) Measure serum lactate or alternative

(5) Start IV fluid resuscitation using Hartmann's or equivalent

(6) Commence accurate urine output measurement

Figure 5. The Sepsis Six.

Table 2. Potential target sites for the development of novel therapeutic agents in sepsis

Pathway/target	Treatment
Pathogen recognition	
lipopolysaccharide	anti-endotoxin
TLRs	TLR antagonists—TAK-242
neutrophil depletion	granulocyte colony-stimulating factor
cell adhesion	leucocyte–endothelial interactions
Inflammatory cascade	
TNF-α	anti-TNF
IL-1β	IL-1-receptor antagonist
IL-6	IL-6 antagonist
prostaglandins, leukotrienes	NSAIDs, steroids (high dose)
PAF	PAF acetyl hydrolase
isoprenoid intermediates	statins
high-mobility group box protein	ethyl pyruvate
oxidants	*N*-acetylcysteine
Coagulation	
protein S	protein S
tissue factor	tissue factor antagonist
antithrombin III	antithrombin III
Microcirculation	
microcirculatory dysfunction	prostacyclin, nitrates, dobutamine
Apoptosis	
epithelial and white cell apoptosis	anticaspases

TLR, toll-like receptor; TNF, tumour necrosis factor; IL, interleukin; PAF, platelet-activating factor; NSAIDs, non-steroidal anti-inflammatory drugs.

monitoring to the four steps detailed above, thus comprising three diagnostic/monitoring steps and three therapeutic interventions (Figure 5), and has been adopted by a number of professional and public bodies.[16,104] Prospective observational work from the developing institution of these measures has shown an association with improved delivery of the Resuscitation Bundle and improved outcomes.[105]

Future developments

In addition to further evaluation of the diagnostic and therapeutic interventions described above, including refinements to EGDT, it is likely that advances in three areas—our recognition of severe sepsis and causative organisms, our understanding of the condition's pathophysiology, and the development with industry of new targeted therapies—hold the key to improving outcomes.

The use of biomarkers to diagnose, stage and assess risk is a major current field of study. Pro-calcitonin, adrenomedullin, C-reactive protein, interleukin-6, cellular adhesion molecules and other mediators may be used in combination to develop a 'blueprint' of sepsis that may ultimately help with early diagnosis, risk stratification and in determining appropriate treatment strategies.[106] PCR amplification and detection of pathogen DNA has the potential to revolutionize the identification of causative organisms, including fungi, and guide the appropriate use of antimicrobials,[107] with microarrays permitting the screening of multiple organisms simultaneously.[108] Although capture rates for organisms may not be greater than for blood cultures, identification and selection of relatively narrow spectrum antimicrobials may occur much earlier.[109]

Newer molecular assay techniques, including multiplex real-time PCR, ribosomal RNA typing and pyrosequencing, are likely to transform the early detection of pathogens and de-escalation of antibiotics, and may offer greater sensitivity than blood cultures in bacterial detection.[110] Commercial array kits, such as the LightCycler® Septi*Fast* Test MGRADE (Roche Molecular Diagnostics)[111] and the BlackLight® Sepsis Kit (BlackBio, Madrid, Spain),[112] can identify up to 25 organisms in 6 h and 70 organisms in 4 h, respectively. Fungi (*Candida* spp. and *Aspergillus fumigatus*) are also rapidly detectable using molecular methods.[113,114] Such techniques are likely to pave the way to simplifications of initial antimicrobial regimens in sepsis, with early detection permitting a rapid second-dose de-escalation of antimicrobial agents in some cases. However, at present these techniques are qualitative rather than quantitative which limits their clinical utility to an extent.

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Our knowledge of the pathophysiology of sepsis is rapidly expanding. The integral role of Toll-like receptors (TLRs) with intermediary binding molecules such as CD14 in the recognition of bacteria and initiation of the immune response was first mooted little more than 10 years ago.[115] Genetic polymorphisms of TLR-4 predispose to septic shock in response to Gram-negative invasion. The vascular endothelium, in general, and the microcirculation in particular, are now known to be responsible for immunomodulation and disordered oxygen delivery to tissues; this is compounded by disruption of mitochondrial function.[116,117] Over the last decade, it has become clear that sepsis is a bimodal syndrome, with an initial hyperimmune response characterized by an abundance of pro-inflammatory cytokines gradually giving way to a state of relative immune paralysis known as the compensatory anti-inflammatory response syndrome. Lymphocyte apoptosis appears to play a pivotal role.[118]

A vast array of potential sites in the inflammatory cascade for the development of immunomodulatory therapies are under investigation, some of which are listed in Table 2. At present, a single specific agent, activated protein C (Xigris®, Eli Lilly and Co.), is available to intensivists. Even this agent, the most promising new drug for the treatment of sepsis in decades, is currently being re-evaluated in a randomized controlled trial following the acknowledgement of methodological flaws in the original study.[119] Of particular interest for development are agents targeting TLRs (TLR-4), the receptor for advanced glycation endproducts and high mobility group box 1, a cytokine-like molecule that promotes tumour necrosis factor release from mononuclear cells.

Conclusions

The spectrum of disease that includes sepsis, severe sepsis and septic shock remains a major cause of morbidity and mortality globally, with mortality for severe sepsis ≥5-fold higher than that for acute coronary syndrome or for stroke. The SSC has been the first major international initiative to drive improvements in outcome and has demonstrated improvements in process across many countries. Large-scale studies are underway to evaluate complex therapies, such as EGDT. Of equal importance are the basic therapies, such as antimicrobial administration, sampling and fluid resuscitation. Observational evidence suggests that the earlier these are delivered, the better the outcomes. Evidence for optimal timing from controlled trials is unlikely to be forthcoming, but the therapies and rationale for their urgency are based on sound principles. The challenge to practitioners and to healthcare organizations is in achieving early recognition, and in improving the reliability of the delivery of basic care pathways, such as the Sepsis Six.

As our understanding of pathophysiology develops, strategies for recognition and intervention are likely to improve. In the wake of the SSC, new initiatives to drive this change, and to begin to translate research into permanent changes to clinical practice, are needed. The Global Sepsis Alliance (a collaboration of the Sepsis Alliance, the International Sepsis Forum, the World Federation of Paediatric Intensive and Critical Care Societies, and the World Federation of Societies of Intensive and Critical Care Medicine) is emerging as the champion of improvements in sepsis outcomes for the future.

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