Challenging Concepts in Emergency Medicine:
Cases with Expert Commentary

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CASE

The sepsis resuscitation bundle

Adham Khalek

Expert Commentary Jeff Keep and Emmanuel Rivers

Case history

A 48-year-old man is brought to the emergency department (ED) by his wife complaining of a 5-day history of worsening dyspnoea, chest pain, and fever. He has a history of hypertension for which he is on an ACE inhibitor, and diet-controlled diabetes. He has no allergies. He works in the financial industry and is normally well. He smokes 3–4 cigars a day.

On initial assessment, he is noted to be clammy and appears pale. He is short of breath at rest. Observations taken during triage are as follows: heart rate 118 regular, BP 96/49 mmHg, temperature 38.8 °C, respiratory rate 28 breaths per minute, oxygen saturation 87 % on room air.

The potential diagnosis of sepsis is recognized and he is moved to the resuscitation room for further assessment and interventions.

See Box 1.1 for a clinical summary of sepsis.

Box 1.1 Clinical summary of sepsis

- Sepsis describes a spectrum of illness, the severe end of which represents some of the sickest patients seen in the ED.
- It represents a growing problem; in the UK, cases of severe sepsis requiring admission to the intensive treatment care unit (ITU) have risen from 50 to 70 per 100 000 population per year over the last decade.
- 21 % of these patients are admitted from the ED and in-hospital mortality for these patients is over 35 %.[1]
- It is estimated that the UK spends £700 million per year treating severe infections in ITU patients.

Learning point Definitions

The definition of sepsis was produced by consensus in 1991.[2] The diagnosis requires the presence of the systemic inflammatory response syndrome and a suspected or confirmed source of microbiological infection. Additional definitions were produced at the time to further categorize sepsis into severe sepsis and septic shock (see Table 1.1).

Table 1.1 Consensus definition of SIRS and sepsis (2)

Systemic inflammatory response syndrome (SIRS)	At least 2 of the following: Temperature <36 °C or > 38.8 °C Heart rate > 90 Respiratory rate > 20 breaths/minute or PaCO2 < 4.2 kPa White cell count < 4000 or > 12 000 or > 10 % immature forms 7.7mmol/L (unless patient is diabetic) Acute confusion / reduced conscious level

(continued)

Sepsis	SIRS + confirmed or suspected infection
Severe sepsis	Sepsis + organ hypoperfusion or dysfunction
Septic shock	Sepsis with refractory hypotension or vasopressor-dependent after adequate volume resuscitation

Data from Bone RC, Balk RA, Cerra FB *et al.*, 'Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis', The ACCP/SCCM Consensus Conference Committee, American College of Chest Physicians/Society of Critical Care Medicine, *Chest*, 1992, 101, pp. 1644–1655.

Assessment of organ dysfunction should take place early when managing any patient with suspected sepsis in order to risk stratify their condition. Measurement of blood lactate provides objective evidence of hypoperfusion and can help to identify patients with severe sepsis or septic shock rapidly. Venous and arterial lactate have been shown to be closely correlated[3] and the relative ease with which the former can be tested can help reduce the delay in identifying this group of patients. Early measurement of blood lactate has been shown to be independently linked with mortality[4,5] and can help identify those who would benefit from more urgent intervention. A raised lactate in the presence of a normal blood pressure is known as 'cryptic shock' and suggests organ hypoperfusion in spite of haemodynamic compensation maintaining arterial pressure. Lactate levels over 4.0 mmol/L are associated with a significantly increased in-hospital mortality (LR+2.6, 95 % CI 1.9–3.7).[6]

Clinical tip Signs associated with organ dysfunction

Organ system	Examples of dysfunction
Cardiovascular system	Systolic BP < 90 mmHg
	Decrease in systolic BP > 40 mmHg
	Mean arterial pressure < 65 mmHg
	Increased capillary refill time or mottling
Respiratory system	Increasing FiO_2 to maintain SaO_2
Renal system	Cr > 176.8micomol/L
	Creatinine increase > 60 micromol/L from baseline
	Creatinine increase > 60 micromol/L in 24 hours
	Urine output < 0.5 ml/kg/hour for 2 hours despite fluid resuscitation
Coagulation	Activated partial thromboplastin time > 60 seconds
	International normalized ratio > 1.5
	Platelets < 100×10^9/L
Hepatic	Bilirubin > 34.2micomol/L
Acid-base	Lactate > 2 mmol/L
Central nervous system	Confusion or decreased level of consciousness

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Identification of septic patients in the ED remains a challenge. A recent audit of three EDs in the UK[8] found that only 17 % of patients were recognized as having severe sepsis or septic shock while they were in the ED.

Clinical question: Does the timing of antibiotics in sepsis have a significant effect on outcome?

The surviving sepsis campaign (SSC), launched in 2004 in response to the high mortality of sepsis, published international guidelines for the resuscitation and management of septic patients: they were revised in 2008 and 2013. The campaign recommends that patients should receive intravenous antibiotics within an hour of recognition of severe sepsis or septic shock.[9] Originally based largely on expert consensus, there are now compelling data to support this recommendation.

Evidence base Early administration of antibiotics in sepsis

Kumar *et al.* (2006):[10] performed a multi-centre retrospective cohort study on 2731 adult patients with septic shock in the ITU. 44.4% of patients had been admitted from the ED. Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay was associated with an average decrease in survival of 7.6% (range 3.6–9.9%).

Puskarich *et al.* (2011):[11] performed an analysis of a multi-centre randomized controlled trial of early sepsis resuscitation. 291 patients presenting to the ED with septic shock were included. Mortality was significantly increased in patients who received initial antibiotics after shock recognition compared with before shock recognition (OR 2.4; 1.1–4.5).[2]

Answer

Antibiotics should be given without delay upon recognition of severe sepsis or septic shock.

Expert comment

Early administration of antibiotics to the patient with severe sepsis/septic shock reduces mortality. This means that it is a time-critical illness similar to acute myocardial infarction, acute stroke, and trauma.

As such, it is imperative to develop emergency systems to triage these patients. Like all time-critical illnesses there must be an acceptable level of false positives within the system making it highly sensitive in the early stages. Systems for a pre-hospital alert from the local ambulance service would be ideal, and indeed these are in various stages of development in the UK. Complementary to this, early recognition through education, triage, and/or a modified early warning score system using initial patient history and observations should be used. Pre-hospital development of early risk stratification and identification has been shown to improve outcomes.[3-5]

A dedicated area within the ED with a more favourable staff to patient ratio, such as a resuscitation room, must be used. Point-of-care testing for serum lactate should be available. There should be clear local antibiotic guidelines available and all antibiotics mentioned therein should be available in the ED.

Delays may occur when hypoperfusion and organ dysfunction are diagnosed on blood tests alone. Point-of-care testing for serum lactate analysis and blood culture bottles should be available. Local antibiotic guidelines must include guidance for sepsis of unknown aetiology (and variants for neutropaenia and nosocomial infections), and should be clearly available to all staff. These antibiotics must be adequately stocked in the ED and staff should be appropriately trained in their administration. Blood sampling and laboratory turnaround times are the major issues here. Above all else, staff education, clinical audit, and regular review of a 'whole systems' approach are the key to success.

Case progression

A focused history reveals no recent travel, a cough producing purulent green sputum and right-sided pleuritic chest pain. Sputum is obtained and sent for culture. Intravenous access is sited and blood is taken and sent for blood cultures, haematology and biochemistry. A 12-lead ECG shows a sinus tachycardia. An arterial blood gas (ABG) sample is taken on 40 % oxygen which shows the following (see Table 1.2):

Table 1.2 ABG on 40 % O_2

pH	7.32
pO_2	9.1 kPa
pCO_2	2.8 kPa
HCO_3	15 mmol/l
BE	–7 mmol/l
Lactate	5.1 mmol/l

Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. *Crit Care Med* 2006; 34:857–863.

A chest X-ray is taken which demonstrates right lower lobe consolidation with effusion.

A diagnosis of severe sepsis secondary to a community-acquired pneumonia is made. A 20 ml/kg fluid bolus is given at the same time as the first dose of antibiotics in accordance with the hospital antibiotic policy.

His initial blood tests demonstrate the following (see Table 1.3).

Table 1.3 Initial blood test results

Hb	14.1 g/dL	Sodium	148 mmol/L
WCC	18.2×10^9/L	Potassium	3.8 mmol/L
Neutrophils	17.8×10^9/L	Urea	16.5 mmol/L
Platelets	420×10^9/L	Creatinine	198 micromol/L
CRP	370 mg/L	Glucose	11.4 mmol/l

Clinical tip Risk factors associated with invasive fungal infections

Risk factors associated with candidaemia

- Immunosuppression
- Renal failure
- Severe liver failure
- Antibiotic use
- Intravenous catheters
- Candida colonization
- Oropharyngeal candidosis
- Parenteral nutrition

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Learning point Antibiotics in sepsis

Once severe sepsis has been identified, further investigations and treatment should be carried out concurrently as delays in initial therapy have been shown to worsen outcome.[10] The core elements of resuscitation of the septic patient are microbiological testing, appropriate antibiotics, and restoration of adequate tissue perfusion.

Broad-spectrum antibiotics should be given as soon as possible, within an hour of recognition of severe sepsis or septic shock. Blood cultures and other microbiological specimens taken before antibiotic administration are important and may later prove crucial to the care of the patient, but should never significantly delay (> 45 minutes) antibiotic administration.[9]

Antibiotic choice should be influenced by the suspected source of infection, hospital guidelines, and patterns of infection and resistance. Inappropriate initial antibiotics are associated with increased mortality,[10,12] and if the source is unclear, broad-spectrum agents should be used and rationalized when further microbiology results are available.

Certain patient groups are at increased risk of invasive fungal infections (see Table 1.3) and in these cases consideration should be given to co-treatment with an anti-fungal agent. If a fungal infection is suspected, commercially available antigen assays such as 1,3 β-D-glucan, mannan, and anti-mannan assays[13] can assist the early diagnosis and treatment of invasive candidiasis.

Surgically drainable sources of infection are unlikely to respond to antibiotics alone: examples of these include pelvic collections, infections surrounding foreign bodies and empyemas. In such cases, or with sepsis of unknown origin, further diagnostic imaging may be required to locate collections which could then be considered for surgical or percutaenous drainage.

Fluid resuscitation with the aim of restoring tissue perfusion should be given as soon as signs of hypoperfusion are recognized (see Table 1.2). Large volumes of crystalloid (20–40 ml/kg) may be required initially. Albumin can be added to the fluid regimen if it is anticipated or known that the serum albumin is low.[15] Central venous catheters and arterial lines are usually required in patients with severe sepsis and are unavoidable in those with septic shock to assist administration and monitoring of resuscitative efforts.

The use of a quantitative resuscitation (QR) strategy can also help guide fluid and vasoactive agent administration. QR, a 'structured cardiovascular intervention with intravascular volume expansion and vasoactive agent support to achieve explicit, predefined end points'[16] was originally reported in surgical patients in 1988.[17] In 2001, a QR strategy for septic patients known as early goal-directed therapy (EGDT) was described by Rivers *et al*. The protocol structured the use of fluids and vasoactive agents in the initial resuscitation of septic patients. The three principal endpoints targeted were:

- Central venous pressure (CVP) of between 8 and 12 mmHg.
- Mean arterial pressure (MAP) of between 65 and 90 mmHg.
- Central venous oxygen saturation ($ScvO_2$) of over 70 %.

Lactate clearance is an alternative to $ScvO_2$ as a measure of tissue oxygen delivery,[18] and the aim of resuscitation should be to normalize lactate as rapidly as possible in those patients with a raised level.[9] One benefit of lactate clearance is that it does not require a central line to be inserted so it can be used on ward patients.

Expert comment

Regional rates of systemic fungal infections are variable and not insignificant—probably around 5 %. The patient's risk factors should be assessed and the likelihood, investigations, and treatment options discussed with a microbiologist. Although empirical administration is not recommended, delays increase mortality. The risk of a fungal infection must be frequently considered and actively sought in all patients beyond the ED.

Expert comment

Caution is advised when using lactate clearance as a sole resuscitation target because a normal lactate (< 2 mmol/L) can be present in up to 50 % of septic shock patients. These patients are prone to multisystem organ failure with a mortality of over 50 %.[6–14] These observations indicate that using lactate and $ScvO_2$ are complementary endpoints and not mutually exclusive.

Early involvement of critical care is essential to ensure adequate monitoring of the patient during resuscitation using central venous and arterial lines, and their placement (and by whom) is a resource-management issue that should be resolved in advance through protocol to ensure time-critical management. The ED must be adequately equipped in this respect and if it is not, as soon as possible the patient must be transferred to a facility that is.

Clinical question: Is the timing of goal directed therapy important at reducing mortality in septic patients?

In 2001, Rivers *et al*.[19] published the results of a landmark randomized controlled trial that described a significant reduction in mortality in ED patients with severe sepsis and septic shock treated with early (within 6 hours) goal-directed therapy

(EGDT). The results showed an absolute mortality reduction of 16 %. Critics of the trial stated that the presence of extra resources in the ED impacted on the external validity of the study.

Jones *et al.* (2008)[16] conducted a systematic review of randomized controlled trials comparing quantitative resuscitation with standard resuscitation in septic patients. All 9 studies were based in the ITU with the exception of the Rivers study. A clear mortality benefit was found when quantitative resuscitation was used at or near the time of recognition (OR 0.5; 95 % CI 0.37–0.69) that was completely lost if the intervention was initiated late (OR 1.16; 95 % CI 0.60–2.22).

Answer

Early goal-directed resuscitation reduces the mortality of patients with severe sepsis.

Case progression

Despite fluid resuscitation, his blood pressure is 87/44 mmHg. Intensive care is contacted and a review of the patient requested. Central venous, arterial, and urinary catheters are placed. Further fluid boluses are administered against his central venous pressure (CVP) up to a total of 40 ml/kg but he remains hypotensive. A noradrenaline infusion is started and titrated to maintain a mean arterial blood pressure (MAP) of greater than 65 mmHg. Over the next hour, he appears drowsier and a repeat ABG on 60 % oxygen at this point shows the following (see Table 1.4):

Table 1.4 Results at repeat ABG

pH	7.21
pO_2	10.1 kPa
pCO_2	6.1 kPa
HCO_3	15 mmol/L
BE	–6 mmol/L
Lactate	3.8 mmol/L

The patient undergoes a rapid sequence intubation and lung-protective mechanical ventilation is commenced. While waiting for transfer to the ITU, a sliding scale is commenced to maintain tight glycaemic control. Thromboprophylaxis and gastric protection are prescribed.

Expert comment

The 2013 SSC guidelines recommend (grade 1, the strongest) the protocolized resuscitation of a patient with sepsis-induced shock. It further recommends that it should start as soon as hypoperfusion is recognized and should not be delayed pending ITU admission. CVP, MAP, urine output, and $ScvO_2$ measurement are all listed as inclusions within the QR.[1]

Clinical tip Noradrenaline in the ED

Patients with sepsis require noradrenaline if the MAP is < 65 mmHg despite adequate CVP post fluid resuscitation.[19]

The College of Emergency Medicine provides a noradrenaline infusion reference guide (available at <http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Standards/Sepsis/>).

4 mg = 4 ml of 1:1000 noradrenaline

4 mls of 1:1000 noradrenaline should be added to 46 ml of 5 % dextrose making 50 mls and placed in a syringe driver.

The starting dose is 0.025 mcg/kg/minute (infusion table available on the CEM website).

Learning point Care bundles in sepsis

Sepsis is a complex systemic pathophysiological process and as such, it requires a complex multifaceted approach to treat it.

The optimal endpoints for resuscitation will evolve as the evidence base grows. The Surviving Sepsis campaign[9] recommends the following bundle of measures as seen in Box 1.2:

Taking blood cultures before administering antibiotics, commencing broad-spectrum antibiotics, and achieving tight blood glucose control are individual aspects of sepsis management that have a significant effect on mortality (OR 0.76, 0.86, 0.67 respectively, all $p < 0.0001$).[20] Optimal care therefore involves paying attention to all aspects of managing the critically ill septic patient once resuscitation has commenced. Liaison with intensive care, medicine, surgery, radiology, and microbiology may all be required prior to the patient leaving the ED.

(continued)

Box 1.2 To be completed within 3 hours:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate

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Clinical question: Are care bundles effective in reducing mortality in septic patients?

The theory behind care bundles is that several evidence-based interventions, grouped or 'bundled' together, will improve overall outcome. The sepsis bundle was an idea first introduced by the Surviving Sepsis campaign in 2004.[10,17,18,20] Individual bundle components will have different levels of evidence behind them necessitating subjective application in certain circumstances.

Evidence base Care bundles in sepsis

Nguyen *et al.* (2007)[21] published a prospective observational cohort study looking at the effects of implementing a bundle of measures in septic patients presenting to the ED. The study described the achievement of a bundle of 5 targets in 330 patients. In those patients in whom no aspect of the bundle were completed, in-hospital mortality was 39.5% which dropped to 20.8% ($p<0.01$) in those patients in whom all aspects of the bundle were competed.

Levy M *et al.* (2010)[22] published an analysis of the data on 15 022 subjects (over half from the ED) at 165 sites comparing surviving sepsis bundle compliance and hospital mortality over 3 years. Resuscitation bundle compliance increased from 10.9% initially to 31.3% ($p<0.0001$). Unadjusted in-hospital mortality over the same period decreased from 37% to 30.8% ($p=0.001$), the adjusted mortality reduction was 5.4% over 2 years (95% CI = 2.5 – 8.4%).

Answer

Sepsis care bundles provide significant reductions in the mortality of septic patients attending the ED.

See Box 1.3 for future advances in sepsis care.

Box 1.3 Future advances

There are 3 separate randomized multi-centre trials on goal-directed resuscitation and protocolized sepsis care that are ongoing at the moment. PRoCESS in the US, ProMISE in the UK, and ARISE in Australasia[2] will all add significantly to the evidence base regarding EGDT and sepsis resuscitation in the ED and ITU settings.

Other areas of development include the use biomarkers of bacterial infection (such as procalcitonin) to rationalize the use of antibiotics in non-bacterial infections and help combat antibiotic resistance.

The VANISH trial aims to identify the best first-line vasopressor to use in septic shock by comparing vasopressin with noradrenaline in a randomized controlled trial.

A Final Word from the Expert

As sepsis becomes better understood, and as our management of it improves through further research, its place as a time-critical illness is likely only to become more firmly established. The role of the ED is crucial to decreasing mortality.

All aspects of the initial few hours of care are simple and effective and success depends upon early recognition and the activation of collaborative multidisciplinary processes. The results of the College of Emergency Medicine's national clinical audit in severe sepsis and septic shock showed that success is possible for all of these patients who present to the ED.

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