CONTENTS

CASE

Sepsis

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Expert Commentary Ron Daniels

Case history

A 68-year-old man was brought into the emergency department (ED) at 19:00 by his son, having been found at home generally unwell. The patient was not able to answer any questions himself, but the son reported that he tried to call his father in the day with no answer, and on visiting found him confused. He last spoke to him 4 days previously, when his father had seemed well. His only past medical history was recently diagnosed hypertension for which he had just started lisinopril 10 mg once daily prescribed by his general practitioner.

On initial assessment in the ED, his lungs were clear on auscultation, heart sounds normal, central capillary refill time was 4 seconds, and his peripheries were cool with no oedema. He had a soft abdomen with no palpable masses or organomegaly but grimaced on palpation of the left side. Bowel sounds were absent. He answered only direct questions and was confused, although no focal neurology was found and his pupils were equal and responsive to light.

His observations were as follows:

A. Oxygen saturation by pulse oximetry (SpO_2) 99% on room air.
B. Respiratory rate 18 breaths/min.
C. Heart rate 99 beats/min (bpm).
D. Blood pressure (BP) 96/40 mmHg.
E. Glasgow Coma Scale (GCS) score 13 (E3, V4, M6).
F. Temperature 35.8°C.

He had not passed any urine since being found. His National Early Warning Score (NEWS) was 7 (Table 1.1).

Table 1.1 National Early Warning Score (NEWS), developed by the Royal College of Physicians. Each variable is allocated a score and each of these is added to give a total NEWS score

Physiological parameters	3	2	1	0	1	2	3
Respiratory rate (breaths/min)	≤8		9–11	12–20		21–24	≥25
Oxygen saturations (%)	≤91	92–93	94–95	≥96			
Any extra oxygen		Yes		No			
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Heart rate (bpm)	≤40		41–50	51–90	91–110	111–130	≥131
Level of consciousness				A			V, P, or U

A, alert; P, pain; U, unresponsive; V, voice.

Initial management involved placement of an 18-gauge peripheral venous cannula with venous blood samples sent for full blood count, urea and electrolytes, liver function tests, clotting studies, and gas analysis, and starting an intravenous (IV) infusion of 1 L of 0.9% sodium chloride.

His results returned at 20:00 and were as follows:

Venous blood gas		
pH	**7.28**	(7.35–7.45)
$PaCO_2$ (kPa)	**6.6**	(4.7–6)
PaO_2 (kPa)	**3.9**	(>10)
HCO^{3-} (mmol/L)	**18.8**	(22–28)
BE (mmol/L)	**–6.7**	(±2)
Lactate (mmol/L)	**5.5**	(0.5–2)

Full blood count		
Hb (g/L)	**98**	(130–180)
Plat ($\times 10^9$/L)	**118**	(150–400)
WCC ($\times 10^9$/L)	**18.2**	(4–11)

Liver function and clotting		
Bili (μmol/L)	**8**	(3–20)
Alk Phos (U/L)	**131**	(30–130)
ALT (U/L)	**27**	(10–40)
INR	**1.6**	

Urea and electrolytes		
Na (mmol/L)	**148**	(135–145)
K (mmol/L)	**4.7**	(3.5–5)
Urea (mmol/L)	**22**	(2.5–6.7)
Cr (μmol/L)	**380**	(60–110)
Alb (g/L)	**22**	(35–50)
CRP (mg/L)	**183**	(<10)
Glucose (mmol/L)	**15.0**	(6–10)

Alb, albumin; Alk Phos, alkaline phosphatase, ALT, alanine aminotransferase; BE, base excess; Bili, bilirubin; Cr, creatinine; CRP, C-reactive protein; Hb, haemoglobin; INR, international normalized ratio; K, potassium; Na, sodium; Plat, platelets; U, units; WCC, white cell count.

After being reviewed by the ED doctor, his acute kidney injury (AKI) was identified and attributed to dehydration, and his mild hypothermia was noted.

Learning point **Defining and identifying sepsis**

The first consensus definitions were determined by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992, which formally defined the systemic inflammatory response syndrome (SIRS), sepsis, and other clinical classifications. This was updated in 2001 in conjunction with the European Society of Intensive Care Medicine [1], a collaboration which resulted in a widening of the original list of four SIRS criteria to over 20 signs and symptoms of infection to improve specificity. This was later condensed into a more pragmatic set of six criteria by the Surviving Sepsis Campaign (SSC) [2]. However, it was widely recognized that the consensus definitions continued to be imperfect, as the SIRS criteria as a tool for detecting sepsis tended to be oversensitive and poorly specific to either critical illness in general or sepsis in particular.

A third revision was published in 2016 by the European Society of Intensive Care Medicine and Society of Critical Care Medicine, coined Sepsis-3, which abandoned the term severe sepsis and attempted to simplify recognition [3]. Sepsis is now described as organ dysfunction secondary to infection. Organ dysfunction can be tracked with the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score, a clinical scoring system already used for identifying organ dysfunction in intensive care units (ICUs). SIRS was still described as a useful tool to identify possible infection, but no longer formed part of the formal diagnosis of sepsis. The authors instead recommended the use of bedside clinical scoring systems to improve reliability of recognition, and proposed 'quick SOFA' (qSOFA) as a bedside test.

The qSOFA comprises:

- alteration in mental status
- systolic blood pressure less than or equal to 100 mmHg, or
- respiratory rate at least 22/min.

(*continued*)

with any two indicating a high risk of sepsis.

qSOFA was derived by a retrospective analysis of large (primarily US derived) datasets as a method of clinically identifying patients who were likely to have a poor outcome, defined as an ICU stay of 3 days or more, or death.

Sepsis-3: terms and definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score of 2 points or more due to the infection.
- The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction.
- A SOFA score of 2 or greater reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Patients with septic shock can be identified by the presence of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) at 65 mmHg or higher and a serum lactate level greater than 2 mmol/L despite adequate volume resuscitation. With these criteria, hospital mortality is greater than 40%.

This patient presented with an elevated white blood cell count which leads to a suspicion of infection, along with a qSOFA score of 2 which identifies him as more likely to have a poor outcome.

qSOFA has not been universally embraced. Organizations such as the Latin American Sepsis Institute and the UK National Institute for Health and Care Excellence (NICE) have gone as far as to intentionally avoid recommending its use. In 2016, a large prospective validation exercise in over 30,000 patients found qSOFA to be inferior to existing early warning scores (EWS) in identifying patients with sepsis at risk of adverse outcome [4].

Other groups have also developed diagnostic approaches to increase the reliability of suspecting sepsis and initiating treatment pathways. NICE offers guidance with age-specific risk stratification tools for anyone presenting with possible sepsis. These stratify elements of history and examination into categories indicating low, moderate–high, and high risk of severe illness/death (Table 1.2) [5].

These remain included in operational tools such as the UK Sepsis Trust's Red Flag Sepsis system (Figure 1.1) [6].

Expert comment

A reliance on laboratory investigations to identify many of the organ dysfunction criteria means, in a resource-challenged busy clinical environment, that patients without obvious shock or hypoxia are missed. Patients get one opportunity to present their illness to a health professional—it is not always possible to review the patient in a timely manner with laboratory results as soon as they become available. qSOFA, and proposed alternatives such as the NEWS, move away from reliance on laboratory criteria.

Table 1.2 Risk stratification tool for adults, children, and young people aged 12 years and older with suspected sepsis

Category	High-risk criteria	Moderate- to high-risk criteria
History	Evidence of new altered mental state	History of new alteration in behaviour or mental state History of acute deterioration of functional ability Immune impairment (including oral steroids) Recent (within 6 weeks) history of trauma, surgery, or invasive procedure
Respiratory	Elevated respiratory rate: ≥25 breaths/min Acquired oxygen requirement >FiO_2 0.4, to maintain SpO_2 >92% (or >88% in known COPD)	Elevated respiratory rate: 21–24 breaths/min

(*continued*)

Table 1.2 Continued

Category	High-risk criteria	Moderate- to high-risk criteria
Blood pressure	SBP ≤90 mmHg or at least 40 mmHg below normal	SBP 91–100 mmHg
Circulation and hydration	HR >130 bpm Not passed urine for at least 18 hours If catheterized, urine output <0.5 mL/kg/hour	HR 91–130 bpm or new arrhythmia Not passed urine for 12–18 hours For catheterized patients, urine output 0.5–1 mL/kg/hour
Temperature		Tympanic temperature <36°C
Skin	Mottled or ashen appearance Central or peripheral cyanosis Non-blanching rash	Any signs of potential infection e.g. discharge at surgical site

bpm, beats per minute, COPD, chronic obstructive pulmonary disease; HR, heart rate; SBP, systolic blood pressure.
Source: data from The National Institute for Health and Care Excellence (NICE). (2016) *Sepsis: recognition, diagnosis and early management* [NG51]. Copyright © 2016 NICE. Available at https://www.nice.org.uk

Expert comment

There are concerns that, while valid in hospital, the new definitions used in Sepsis-3 may not be sensitive enough for use outside hospital, for example, when considering hospital referral. As serum lactate has been validated as a predictor of mortality, including identifying 'cryptic shock' (hypoperfusion with normotension) [7], organizations not already using track-and-trigger EWS might usefully include qSOFA as a screening tool, adding lactate where necessary. Until there is further prospective validation of qSOFA, those already using NEWS/modified EWS can reasonably continue using a combination of a high index of suspicion of sepsis and the EWS to trigger consideration of sepsis. In the UK, NICE will be issuing a Quality Standard which is likely to reinforce the use of its risk stratification system described previously, which the UK Sepsis Trust has operationalized into Red Flag and Amber Flag Sepsis criteria (Figure 1.1).

The formal identification of sepsis using a change in SOFA score is more widely accepted, but in low- and middle-income countries needs careful interpretation, for example, to identify the criteria for septic shock.

Noting the high lactate, the ED junior doctor suspected high-risk ('Red Flag') sepsis (likely septic shock) according to NICE guidelines and initiated treatment. Supplemental oxygen was given and a further litre of 0.9% saline started. A urinary catheter was inserted, draining 280 mL of residual urine, which was clear but concentrated, with dipstick testing showing no evidence of leucocytes.

A venous blood culture sample was sent and antibiotics started according to hospital protocols (IV amoxicillin 1 g, metronidazole 500 mg, and gentamicin 320 mg for sepsis with a suspected intraabdominal cause). Although a 5-day course was anticipated, the antibiotics were prescribed for an initial 48-hour period with a plan to review the drug, indication, and duration at this point. The chest X-ray was unremarkable.

After discussion with the ED middle-grade doctor, the patient was referred to the surgical team and to the ICU team for review, due to his clinical deterioration as shown by his elevated NEWS score.

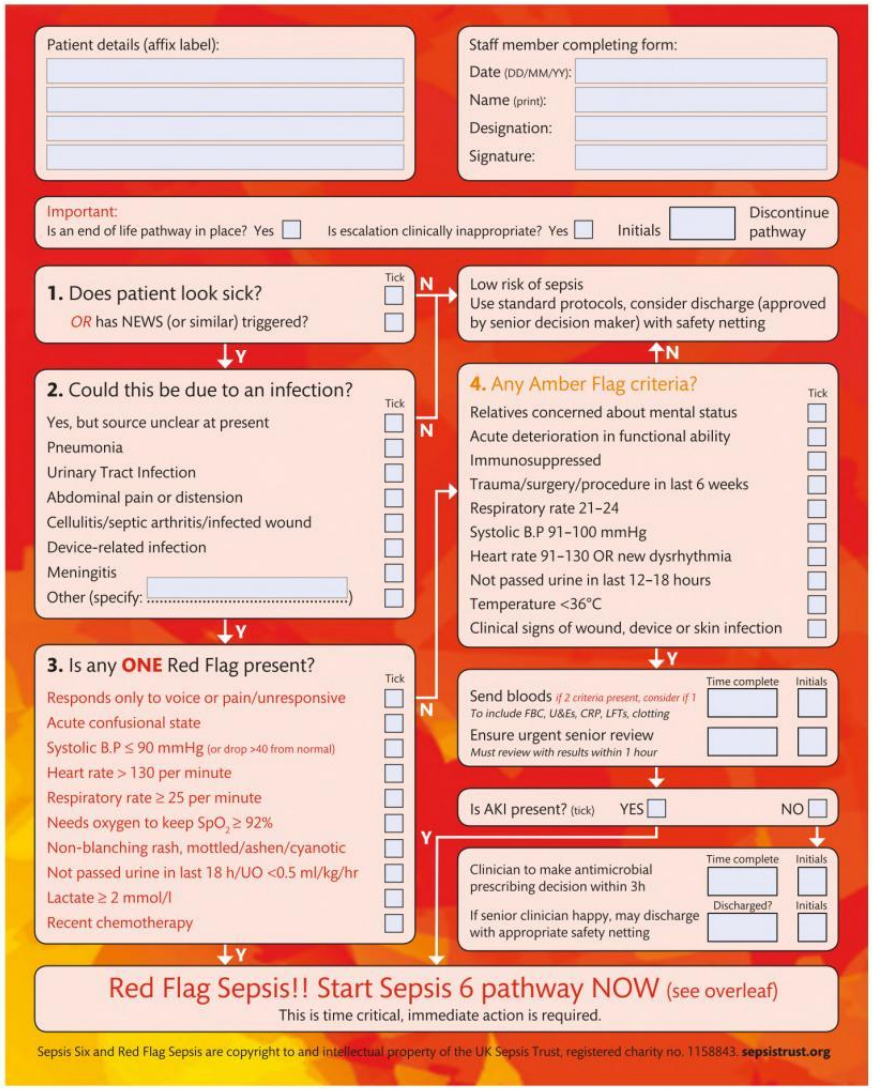

Figure 1.1 Extract from the UK Sepsis Trust clinical toolkit for emergency departments made with formal arrangement with NICE.
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Case 1 Sepsis

Your logo

Sepsis Six Pathway

To be applied to all adults and young people over 12 years of age with suspected or confirmed Red Flag Sepsis

THE UK SEPSIS TRUST

Make a treatment escalation plan and decide on CPR status
Inform consultant *(use SBAR)* patient has Red Flag Sepsis

Time zero | Consultant informed? (tick) | Initials

Action (complete ALL within 1 hour)	Time complete / Initials	Reason not done/variance
1. Administer oxygen Aim to keep saturations >94% (88–92% if at risk of CO_2 retention e.g. COPD)		
2. Take blood cultures At least a peripheral set. Consider e.g. CSF, urine, sputum *Think source control!* Call surgeon/radiologist if needed CXR and urinalysis for all adults		
3. Give IV antibiotics According to Trust protocol Consider allergies prior to administration		
4. Give IV fluids If hypotensive/lactate >2mmol/l, 500 ml stat. May be repeated if clinically indicated- do not exceed 30ml/kg		
5. Check serial lactates Corroborate high VBG lactate with arterial sample *If lactate >4mmol/l, call Critical Care and recheck after each 10ml/kg challenge*		Not applicable- initial lactate ☐
6. Measure urine output May require urinary catheter Ensure fluid balance chart commenced & completed hourly		

If after delivering the Sepsis Six, patient still has:

- systolic B.P <90 mmHg
- reduced level of consciousness despite resuscitation
- respiratory rate over 25 breaths per minute
- lactate not reducing

Or if patient is clearly critically ill at any time
Then call Critical Care Outreach immediately!!

Space available for local short antimicrobial guideline/escalation policy

Figure 1.1 Continued

Learning point Initial management

Prompt early initiation of treatment has consistently been shown to reduce mortality from sepsis [8–10]. For this reason, there has been much effort to ensure that, once the diagnosis of sepsis is made, evidence-based care bundles are implemented.

The SSC divides the initial management into two care bundles, the first to be completed by 3 hours from the diagnosis being made:

1. Measure serum lactate level.
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Administer 30 mL/kg crystalloid in divided aliquots for management of hypotension or if lactate is 4 mmol/L or greater.

The ideal time of administration of antibiotics is immediately before sepsis develops from the underlying infection, but attempting to predict this risks overtreatment.

Once sepsis does develop, any delay is linked to increasing progression of the septic process to multiorgan failure. Empiric antibiotics should be administered within 1 hour of the identification of sepsis. When possible, blood cultures should be obtained before administering antibiotics, but this should not delay initiation of antibiotics.

As with the diagnostic criteria, keeping therapeutic protocols simple improves uptake and ultimately patient outcomes. The value of early treatment has been shown by several care bundles which reduce the time to completion of all tasks to 1 hour. For this reason, the UK Sepsis Trust's 'Sepsis Six' has become widely popular as an effective 1-hour bundle for when sepsis is suspected and has been shown to reduce sepsis-associated mortality rates by up to 50% [11, 12]. The Sepsis Six can be remembered as 'take three, give three'.

The Sepsis Six:

Take 3

1. Take blood cultures.
2. Measure serial serum lactates.
3. Measure accurate hourly urine output.

Give 3

4. Administer oxygen to maintain saturations at greater than 94% (88–92% in chronic obstructive pulmonary disease).
5. Give broad-spectrum antibiotics.
6. Give IV fluid challenges if the patient is hypotensive or their lactate is elevated.

Expert comment

The inclusion of high-flow oxygen was slightly contentious given that cautious oxygen therapy is recommended in other acute conditions. The harmful effects of hyperoxia have been demonstrated in healthy individuals, and growing evidence highlights the deleterious effects of high inspired oxygen concentrations in treating patients with acute myocardial infarction, ischaemic stroke, neonatal resuscitation, and adult resuscitation following cardiac arrest [13]. The recent Hyperoxia and Hypertonic Saline in Patients with Septic Shock (HYPERS2S) trial documented significantly more serious adverse events in patients with sepsis treated for 24 hours with 100% oxygen versus those treated to achieve normoxia (SpO_2 88–95%) [14]. While hyperoxia is potentially harmful, significant hypoxia is undeniably harmful and must be avoided or treated.

The patient was reviewed by the surgical team who did not consider the patient to have peritonitis but arranged an abdominal computed tomography scan.

On review by the intensive care senior trainee at 20:35, an arterial line was inserted, and on examination the patient was found to have cool peripheries. Based on clinical

judgement and the presence of suspected sepsis, a fluid bolus of 500 mL Hartmann's solution was infused IV.

The patient's NEWS score subsequently deteriorated to 9 with minimal urine output.

Expert comment

The value of fluid resuscitation has always been unclear, and recently the routine use of liberal fluid resuscitation has been called into question [15]. Until further evidence becomes available, even considering recent evidence, we recommend that fluid be given rapidly to correct hypovolaemia in the early stages following presentation, but relatively restricted compared with historical practice once the patient has stabilized.

Learning point Fluid resuscitation

Fluid resuscitation remains one of the mainstays of early treatment for patients with sepsis and septic shock, working by increasing intravascular volume, venous return, and hence cardiac output to improve blood pressure and organ/tissue perfusion. However, the type and quantity of fluid to use is contentious and studies have produced conflicting results. Problems arise from the complex and variable pathophysiological changes in sepsis, and interpretation of trials is complicated by the inclusion of heterogeneous patients at different stages in their clinical course.

Fluid type

The two main groups are crystalloid and colloid, with further division between balanced and non-balanced solutions.

Crystalloids

Crystalloid solutions can either be balanced solutions (e.g. Hartmann's solution and Plasma-Lyte 148), which are designed to mimic plasma and buffer against pH changes, or unbalanced 0.9% sodium chloride (commonly known as normal saline). Normal saline has been used historically because it is a cheap, stable, and easily manufactured isotonic solution; however, in studies comparing it with balanced solutions [16] it has been shown to:

- increase metabolic and dilution acidosis
- decrease renal blood flow
- increase risk of renal failure [17]
- create a coagulopathy
- increase inflammation
- be associated with an increased risk of death.

Although these perceived attributes have generated a move towards use of balanced solutions and away from 'abnormal' saline, in the 0.9% Saline versus Plasma-Lyte 148 for ICU fluid Therapy (SPLIT trial), use of a buffered crystalloid compared with saline did not reduce the risk of AKI in a heterogeneous group of critically ill patients [18].

Colloids

Colloidal solutions became popular because of the theoretical physiological advantage of being retained in the intravascular space for longer than crystalloids. The three main colloids are albumin, gelatin, and hydroxyethyl starch (HES).

Research has identified side effects and worsening outcomes (including higher mortality rates) associated with the use of some colloids, particularly in the setting of sepsis. The US Food and Drug Administration and the European Medicines Agency issued warnings after a proven increased risk of renal failure and death when HES was used in septic patients in the ICU [19]. The use of HES is contraindicated in critically ill patients.

These adverse effects of HES are thought to be from the colloid molecule accumulating in the interstitial tissues, exacerbated by the endothelial dysfunction brought about by the septic process. Within the kidney, this causes an osmotic nephrosis and a renal compartment syndrome within the capsule. There are observational data suggesting that use of gelatin is also associated with an increase in AKI.

Albumin, a natural colloid, has theoretical advantages over synthetic colloids: it maintains endothelial function as well as having antioxidant and anti-inflammatory properties. A subgroup analysis of septic patients in the Saline versus Albumin Fluid Evaluation (SAFE) trial, and a larger meta-analysis [20], suggested an association with reduced mortality. However, a more recent meta-analysis that included subsequent trials from the Early Albumin Resuscitation for Sepsis and Septic Shock (EARSS) study group and the Albumin Italian Outcomes Study (ALBIOS) trial found that albumin, when included in a fluid regimen for septic patients, showed no benefit in reducing mortality, though neither did it cause harm [21].

Given the additional expense of colloids over crystalloids, there should be evidence of benefit to justify their use. The SSC guidance currently recommends crystalloids as the initial fluid of choice and recommends albumin when patients require substantial amounts of crystalloids.

(*continued*)

How much fluid?

The complex pathophysiology of sepsis necessitates caution: give too little fluid and circulatory function will not be restored, give too much and excess fluid quickly leads to tissue oedema increasing organ dysfunction, morbidity, and mortality. Tissue oedema manifests clinically as peripheral oedema, increased extravascular lung water and, in some patients, acute respiratory distress syndrome. Multiple studies have shown an association between mortality and excessively positive fluid balance [22–25] and increased extravascular lung water [26].

The goal is to identify those patients whose cardiac output will improve with fluid—those who are *fluid responsive*. Patients can be divided into *fluid responders*, who may benefit from more fluid, or *fluid non-responders* in whom further fluid may be detrimental: these patients will require other support. Approximately 50% of all patients—with and without sepsis—in ICU are fluid responders [27].

Several variables have been used to predict fluid responsiveness with variable success, either as static measurements or dynamically in response to a fluid challenge or passive leg raise (PLR) (Table 1.3). From a basic science perspective, this is a clinical intervention to attempt to identify the patient's position on the Frank–Starling curve.

Table 1.3 Methods of monitoring fluid responsiveness

Static monitors	Dynamic monitors
Central venous pressure (CVP)	Stroke volume variation (SVV)
Pulmonary artery occlusion pressure (PAOP)	Pulse pressure variation (PPV)
Heart rate (HR)	Pleth variability index (PVI)
Mean arterial pressure (MAP)	Doppler and ultrasound measured changes (oesophageal Doppler monitor (ODM)/ echocardiography)
Flow time corrected (FTc)	Inferior vena cava distensibility/collapsibility index on ultrasonography

Static measurements have generally been found to be unhelpful in identifying fluid responders. The central venous pressure (CVP) or CVP responsiveness is now considered to be of little or no value. In conjunction with a PLR, the pulse pressure is useful [28]. The flow time corrected has mainly been used in perioperative patients, but is determined by systemic vascular resistance as well as intravascular volume [29].

Dynamic monitors rely on measurement of haemodynamic responses to variations in cardiac filling (e.g. caused by natural variation in heart rate during respiration). In patients undergoing positive pressure ventilation, the intermittent rise and fall of intrathoracic pressure leads to alterations in venous return and reflex responses in heart rate. These affect cardiac filling and the resulting haemodynamic changes can be used to assess the likelihood of fluid responsiveness. Dynamic monitors perform better in stable situations such as a patient who is undergoing pressure control ventilation and who has a normal heart rate and rhythm. Minimally invasive monitors are grouped into uncalibrated and calibrated devices, the latter being the more accurate. Other cardiac output monitors estimate cardiac output based on detection of a change in concentration of a dye (LiDCO), cold (PICCO), thoracic bioimpedance (CCO, Edwards Lifesciences), or analysis of the arterial line waveform (LiDCO rapid, FloTrac) and may rely on fluid administration or PLR to predict fluid responsiveness [30].

Bedside echocardiography is used routinely on many ICUs and is increasingly being undertaken by intensive care clinicians. Echocardiography enables assessment of right and left cardiac function, regional wall movement abnormalities (pre-existing or new ischaemic heart disease), valvular function, and, importantly, fluid status. While static measurements give some information, dynamic measures are more useful to determine fluid volume status. Variations in vena cava diameter (distensibility index) with the respiratory cycle provide good predictive information: visualization of the superior vena cava with transoesophageal echocardiography and the inferior vena cava with transthoracic echocardiography or transabdominal ultrasonography are possible, the latter requiring less extensive training. The main advantage of these methods is that the patient does not have to be in sinus rhythm—atrial fibrillation is common in the critically ill [31].

Expert comment

The SSC recommends initial fluid challenges in patients with hypoperfusion with suspicion of hypovolaemia up to a maximum of 30 mL/kg; further fluid challenges are based on haemodynamic improvement of static or dynamic variables. Little controversy surrounds the rationale behind initial restoration of circulating volume; however, too much fluid beyond the initial correction of hypovolaemia will worsen tissue oedema and oxygen delivery. Adequate initial fluid resuscitation should be followed by conservative late fluid management, defined as even or negative fluid balance measured on at least two consecutive days during the first 7 days after the onset of septic shock [32].

Clinical tip Passive leg raise

The PLR is a clinical tool to determine fluid responsiveness and is a simple, non-invasive, and accurate bedside test which can be performed by nursing staff in conjunction with monitoring of dynamic variables [33]. Leg elevation induces an autotransfusion roughly equivalent to a 500 mL fluid challenge but is in effect reversible so that the non-responder is not given fluid that could be harmful.

A PLR requires positioning of the patient head up at 45° and then tilting the bed back in a Trendelenburg position until the head of the bed is horizontal (Figure 1.2). This provides a greater autotransfusion volume than simply elevating the legs with the trunk in a supine position. Any response occurs in the first minute and therefore requires a dynamic flow measurement (or flow derivation) device with sufficiently fast response time. It has been studied with a variety of minimally invasive cardiac output monitors: an increase in cardiac output or stroke volume of 10% is taken to indicate a fluid-responsive patient. Intra-abdominal hypertension may impair venous drainage and invalidate the results.

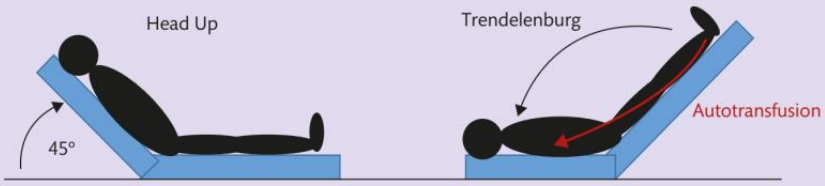

Figure 1.2 Performing a passive leg raise test.

Given the patient's lack of response to an initial 3 L of fluid resuscitation (the patient weighed approximately 80 kg), he was admitted to the ICU for invasive monitoring and early goal-directed therapy (EGDT). On arrival in the ICU at 21:30, a central venous catheter was inserted.

Vital signs at this time were:

Heart rate	92 bpm
Average BP (MAP)	99/43 (62) mmHg
SpO_2	99%
GCS score	14
Urine output	35 mL/hour
Central venous oxygen saturation	56%

Arterial blood gas values, breathing 80% oxygen were:

Arterial blood gas	FiO_2 0.8	
pH	**7.35**	(7.35–7.45)
$PaCO_2$ (kPa)	**7.35**	(4.7–6)
PaO_2 (kPa)	**25.6**	(>10)
HCO_3^- (mmol/L)	**28.1**	(22–28)
BE (mmol/L)	**–4.7**	(±2)
Lactate (mmol/L)	**5.1**	(0.5–2)
Na (mmol/L)	**144**	(135–145)
K (mmol/L)	**3.4**	(3.5–5)
Glucose (mmol/L)	**15.0**	(6–10)
Cl^- (mmol/L)	**106**	(97–107)

An insulin infusion was started to normalize the blood glucose values; a nasogastric feeding tube was inserted, its position confirmed, and enteral feeding started.

Learning point

The second SSC care bundle, to be completed within the first 6 hours, gives physiological end points to be met as an indication of adequate organ perfusion and oxygen delivery.

1. Infuse vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a MAP of at least 65 mmHg.
2. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or an initial lactate level greater than or equal to 4 mmol/L (36 mg/dL):
   - Measure central venous oxygen saturation ($ScvO_2$).
   - Measure cardiac output if available.
   - Consider inotropic support.
3. Remeasure lactate if initial lactate was elevated.

Earlier recommendations with rigid physiological end points had been taken from an initial study of EGDT [34] but this approach has been overturned by three more recent studies. The US ProCESS, the Australian ARISE, and the UK ProMISe studies have all failed to show a difference in outcome when EGDT was compared with usual care [35–37]. The SSC now advises that measurement of CVP and $ScvO_2$ are not routinely necessary for patients with septic shock. The SSC is revising the haemodynamic bundle in accordance with the latest evidence [38].

Expert comment

In addition to source control and antimicrobial therapy, fluid resuscitation to correct hypovolaemia remains the central tenet of resuscitation in septic shock. The failure of ProCESS, ARISE and ProMISe to show treatment benefit in the intervention groups may reflect that basic care has improved so much that protocolized care has less impact. This was demonstrated recently across a group of hospitals in North America in a study identifying that early compliance with basic care elements meant illness did not progress and meant patients were subsequently ineligible for EGDT as they did not meet entry criteria [39]. A pragmatic approach, using basic physiological principles, is to fluid resuscitate using a suitable end point, such as warm peripheries, improved GCS score, and good urine output; to support persistent hypotension using vasopressors; and to assess for and address signs of inadequate cardiac output or oxygen delivery.

Despite fluid resuscitation, haemodynamic goals were not being achieved and noradrenaline was started to maintain the patient's MAP at greater than 70 mmHg. This

goal was chosen because of the patient's previous poorly controlled hypertension. Once the blood pressure had been stabilized, an abdominal computed tomography scan was undertaken, which identified diverticulitis without evidence of perforation or abscess formation. On review, the surgical team decided on conservative management. The microbiology consultant recommended a change in antibiotic therapy to meropenem.

Learning point Microbiology

Appropriate antibiotic therapy is an essential component in the management of the septic patient. To initiate appropriate antibiotics, and to subsequently narrow the spectrum in response to culture results, it is essential to investigate the patient thoroughly to identify a source of sepsis, and to take several samples for microbiology testing. Ideally, microbiology samples should be collected prior to commencement of antibiotic therapy, so long as this does not delay administration of the treatment.

Liaison with a microbiologist ensures appropriate antibiotic choice taking into account likely pathogens and local antibiotic resistance patterns. It also enables narrowing of the antibiotic therapy when culture results become available. Good antibiotic stewardship involves the use of appropriate antibiotics, for an appropriate duration, to effectively treat the underlying infection while minimizing development of antimicrobial resistance.

The patient did not improve overnight, and so a PiCCO arterial line was inserted to enable dynamic cardiac output measurement. This guided his vasopressor requirement, and further crystalloid boluses were guided by PLRs.

The vital signs at this time were:

Heart rate	89 bpm
BP (MAP)	98/43 (61) mmHg despite 0.32 mcg/kg/min noradrenaline
SpO_2	98%
GCS score	14 (E4 V4 M6)
Urine output	35 mL/h

Arterial blood gas on 80% oxygen		
pH	**7.37**	(7.35–7.45)
$PaCO_2$ (kPa)	**7.34**	(4.7–6)
PaO_2 (kPa)	**10.7**	(>10)
HCO^{3-} (mmol/L)	**28.9**	(22–28)
BE (mmol/L)	**–5.8**	(±2)
Lactate (mmol/L)	**3.5**	(0.5–2)
Na (mmol/L)	**143**	(135–145)
K (mmol/L)	**3.8**	(3.5–5)
Glucose (mmol/L)	**8.9**	(6–10)
Cl^- (mmol/L)	**111**	(97–107)

A bedside focused cardiac ultrasound was undertaken, enabling specific conditions to be excluded from contributing to his increasing inotropic requirement. The focused echocardiogram showed good global cardiac function without any regional wall movement abnormalities or major valve dysfunction, no pericardial effusion, normal right-sided pressures, and a subjectively adequate volume status.