SEPSIS AND SEPTIC SHOCK

Sepsis is the leading cause of death from infection and its reported incidence is on the rise. Mortality rates from sepsis are higher than heart attacks, strokes or trauma. Sepsis needs to be viewed with the same urgency as these other life-threatening conditions and early, effective treatment can significantly decrease mortality. For each hour antibiotics are delayed, survival in patients with septic shock is decreased by ~7.6%.

DEFINITIONS

Sepsis has recently been redefined after 25 years by the Society of Critical Care Medicine and European Society of Intensive Care Medicine. There is no reference standard for the diagnosis of sepsis, so the definition of sepsis and septic shock will remain work in progress and may change in the future. Clinical criteria for diagnosing sepsis were first proposed in 1991 and previously updated in 2001. Due to advances in our understanding of the pathobiology, management and epidemiology, new consensus definitions for sepsis and septic shock were published in the February 2016 issue of the *Journal of the American Medical Association**.

The old definition had the view that sepsis resulted from the host's inflammatory response to infection, where it is now thought to be a consequence of a dysregulated host response to infection rather than just an accompanying inflammatory response. The systemic inflammatory response syndrome (SIRS) criteria are now considered unhelpful as it may be present in many hospitalised patients including those who do not develop infection.

OLD DEFINITIONS	NEW DEFINITIONS
Sepsis: two or more of the SIRS criteria plus a documented or suspected infection SIRS criteria: • Heart rate ≥ 90 beats/minute • Respiratory rate ≥ 20 breaths/minute or $PaCO_2 < 32$ mm Hg (4.3 kPa) • White blood cell count < 4000 cells/mm^3 or >12 000 cells/mm^3 or > 10% immature bands • Temperature < 36°C or > 38°C	**Sepsis:** Life-threatening organ dysfunction caused by a dysregulated host response to infection
Severe sepsis: sepsis and evidence of end organ dysfunction (e.g. decreased urine output, increased serum creatinine)	**Severe sepsis:** This term is now superfluous under the new definitions

Septic shock: sepsis and hypotension after adequate fluid resuscitation; described as a 'state of acute circulatory failure'	**Septic shock:** Sepsis with circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality. Septic shock is a more severe illness with a high likelihood of death compared to sepsis and as such includes cellular metabolic abnormalities in addition to circulatory abnormalities.

* Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J.D, Coopersmith CM. and Hotchkiss RS, 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*, Vol. 315(8): 801–810.

HOW DO WE IDENTIFY PATIENTS WITH SEPSIS?

Various clinical criteria have been evaluated to identify which bedside clinical and laboratory findings are most predictive of sepsis. Various scoring systems have been developed for critically ill patients, including the Sepsis Organ Failure Assessment (SOFA) score, which include both clinical and laboratory findings to complete the score. A total SOFA score of two points or more has been shown to represent organ dysfunction and a two to 25-fold increased risk of dying compared to patients with a SOFA score of less than two.

As the SOFA score requires multiple laboratory tests which may not be available in a timely manner, a simple bedside tool known as the 'qSOFA' for quick sepsis-related organ dysfunction assessment score was developed as a fast bedside tool to identify adult patients with suspected sepsis. The simple qSOFA model was demonstrated to perform similarly to more complex models like SOFA outside the ICU, however was less robust than a SOFA score of two or greater in ICU patients. The qSOFA score does not require laboratory test results and can be performed quickly and repeatedly. The score ranges from zero to three points. The presence of two or more qSOFA points should prompt clinicians to investigate and manage a patient as having possible sepsis and consider referral to a critical care facility.

HOW DO WE IDENTIFY PATIENTS WITH SEPTIC SHOCK?

Septic shock is defined as a subset of sepsis where there are both circulatory and cellular metabolism abnormalities that substantially increase patient mortality. The following three variables have been identified and tested and can be used to identify patients with septic shock and high in-hospital mortality ($> 40\%$):

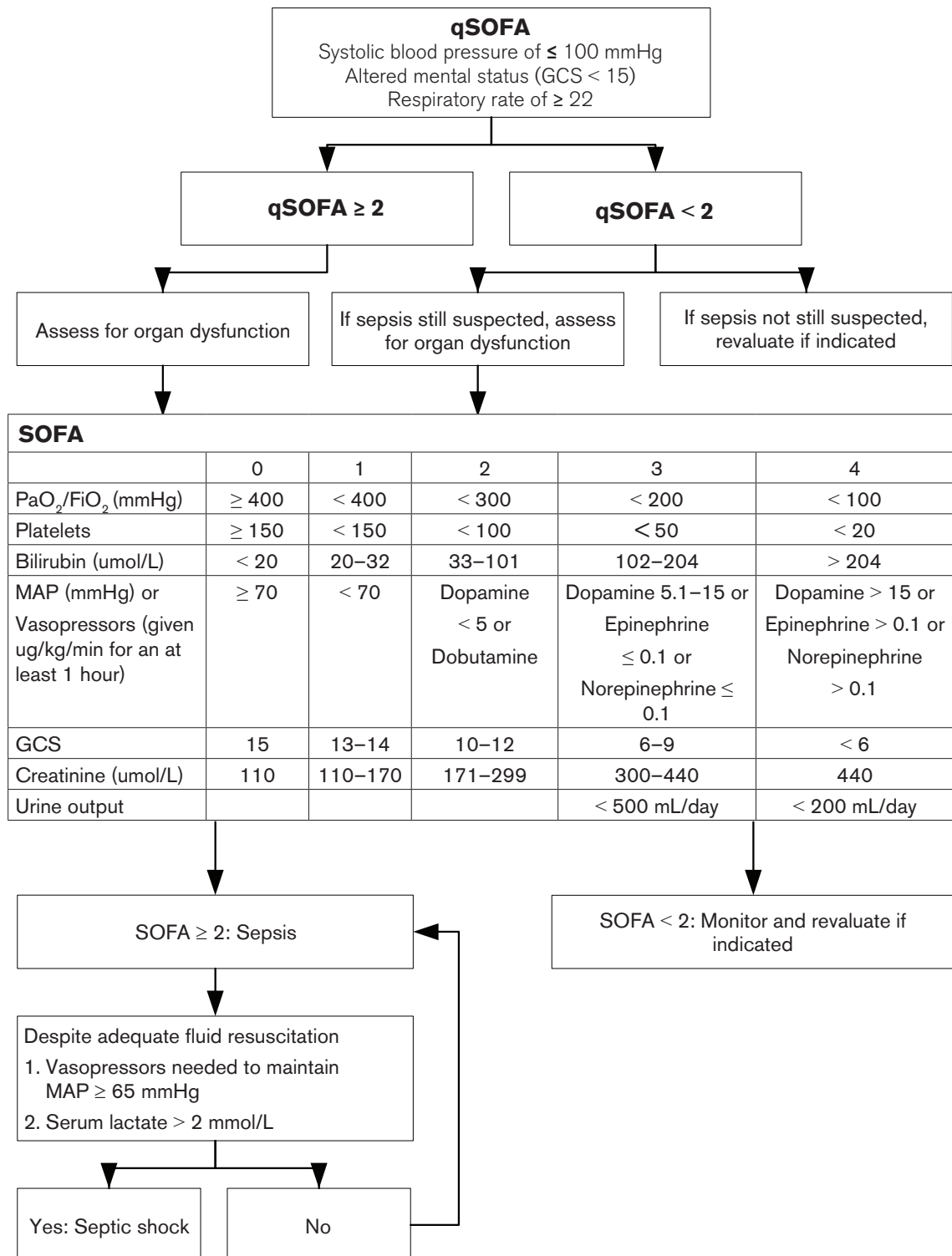Sepsis (i.e. evidence if organ dysfunction in a patient with suspected infection),

AND

Persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mm Hg

AND

Serum lactate > 2 mmol/L (18 mg/dL) after adequate fluid resuscitation.

USING THE NEW DEFINITIONS AND CLINICAL CRITERIA AT THE BEDSIDE TO IDENTIFY PATIENTS WITH SEPSIS AND SEPTIC SHOCK

qSOFA
Systolic blood pressure of ≤ 100 mmHg
Altered mental status (GCS < 15)
Respiratory rate of ≥ 22

qSOFA ≥ 2

qSOFA < 2

Assess for organ dysfunction

If sepsis still suspected, assess for organ dysfunction

If sepsis not still suspected, revaluate if indicated

SOFA

	0	1	2	3	4
PaO_2/FiO_2 (mmHg)	≥ 400	< 400	< 300	< 200	< 100
Platelets	≥ 150	< 150	< 100	< 50	< 20
Bilirubin (umol/L)	< 20	20–32	33–101	102–204	> 204
MAP (mmHg) or Vasopressors (given ug/kg/min for an at least 1 hour)	≥ 70	< 70	Dopamine < 5 or Dobutamine	Dopamine 5.1–15 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine > 15 or Epinephrine > 0.1 or Norepinephrine > 0.1
GCS	15	13–14	10–12	6–9	< 6
Creatinine (umol/L)	110	110–170	171–299	300–440	440
Urine output				< 500 mL/day	< 200 mL/day

SOFA ≥ 2: Sepsis

SOFA < 2: Monitor and revaluate if indicated

Despite adequate fluid resuscitation
1. Vasopressors needed to maintain MAP ≥ 65 mmHg
2. Serum lactate > 2 mmol/L

Yes: Septic shock

No

Adapted from: Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM and Hotchkiss RS, 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*, Vol. 315(8): 801-810.

THE 2016 SURVIVING SEPSIS CAMPAIGN BUNDLES

The Surviving Sepsis Campaign is a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide. For detailed information please refer to the comprehensive guidelines for the management of sepsis and septic shock which are published by the Surviving Sepsis Campaign and can be accessed on their website at www. survivingsepsis.org

The Surviving Sepsis Campaign care 'bundles' are the core of the sepsis improvement efforts which simplifies the complex processes of caring for patients with severe sepsis. A bundle is an evidenced-based, selected set of elements of care, that when implemented as a group has an effect on outcomes beyond implementing the individual elements alone.

BUNDLE IMPLEMENTATION

Each hospital's sepsis protocol may be customised, however it must meet the standards created by the bundle with the overall aim to significantly reduce sepsis mortality. The 2016 bundles have been updated and changes made to the six hour bundle; the three hour bundle is not affected.

Rx **INITIAL RESUSCITATION OF PATIENTS WITH SEPSIS**

TO BE COMPLETED WITHIN THREE HOURS OF THE TIME OF PRESENTATION:

- Measure blood lactate
- Collect two sets of blood cultures within 45 minutes and prior to antibiotic administration
- Take appropriate specimens based on focus of infection (refer to recommended diagnostic procedures below)
- Commence broad spectrum antibiotics within one hour of recognising sepsis in a patient
- Administer at least a 30 mL/kg crystalloid fluid challenge for sepsis-induced hypotension or lactate $\geq$ 4 mmol/L. More rapid administration or greater amounts of fluid may be needed for some patients.

TO BE COMPLETED WITHIN SIX HOURS OF THE TIME OF PRESENTATION:

- Give vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) $\geq$ 65 mm Hg. Norepinephrine is the preferred initial agent
- In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was $\geq$ 4 mmol/L, re-assess volume status and tissue perfusion with either:
  - Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse and skin findings OR
  - Two of the following:
    - Measure CVP
    - Measure $ScvO_2$
    - Bedside cardiovascular ultrasound
    - Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
- Re-measure lactate if initial lactate elevated

DIAGNOSTIC PROCEDURES RECOMMENDED FOR DETECTING INFECTION

Gram-stain of material from sites of possible infection may give early clues to the aetiology of infection whilst cultures are incubating. Appropriate sites and tests include

SUSPECTED SITE	MICROBIOLOGICAL EVALUATION
All patients with suspected sepsis	Blood cultures • Cultures are taken before antimicrobial therapy if they cause no significant delay in starting antimicrobials ($>$ 45 mins) • Collect at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently ($<$ 48 hours) inserted. • Collect 10 mL blood per bottle
Lower respiratory tract	Sputum or bronchoalveolar lavage MC&S
Urinary tract	Urine MC&S
Wound or burn	Pus MC&S
CNS	CSF MC&S
Gastrointestinal	Stool MC&S
Intra-abdominal	Intra-abdominal fluid MC&S

* Request a ß-D-glucan assay (serum Fungitell®) and serum galactomannan assay if invasive fungal infection is in the differential diagnosis.
* Use imaging studies performed promptly to confirm a potential source of infection.

ANTIMICROBIAL THERAPY

* Administration of effective intravenous antimicrobials within the first hour of recognition of sepsis and septic shock is the goal of therapy.
* For initial empiric antimicrobial therapy use one or more drugs that have activity against all likely pathogens (bacterial, fungal and/or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis.
* Empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock is recommended.
* The antimicrobial regimen should be reassessed daily for potential de-escalation. The empiric antimicrobial therapy must be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
* Dosing strategies of antimicrobials must be optimised based on accepted pharmacokinetic/ pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock.
* Antimicrobial treatment duration of seven to 10 days is adequate for most serious infections associated with sepsis and septic shock.

- Longer courses of antimicrobial treatment are appropriate in patients who have a slow clinical response, foci of infection that cannot be drained, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia.

- Shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis.

- Measurement of procalcitonin (PCT) levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).

- A low procalcitonin level or similar biomarker can assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection.

- Antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin.

- Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of a non-infectious cause.

SOURCE CONTROL

- A specific site of infection requiring source control should be sought and diagnosed or excluded as rapidly as possible, and a specific intervention(s) for source control performed within the first 12 hours after the diagnosis of sepsis is made, if feasible.

- When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.

- When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g. percutaneous rather than surgical drainage of an abscess).

- If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.

Sepsis is the primary cause of death from infection. The key steps to optimise outcomes when managing sepsis include:

- Early triage and identification of patients.
- Rapid and appropriate fluid resuscitation.
- Laboratory testing (always including blood cultures), prompt antibiotic administration, and source control of infection.
- Close clinical and biomarker monitoring.

Definitions and guidelines will evolve as new evidence becomes available that improves our understanding of how best to detect and care for patients with sepsis and septic shock.