

What is sepsis and how to manage it?

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Overview

- What is sepsis
- Pathophysiology of sepsis
- Scoring systems
- Epidemiology
- Management protocol
- Antibiotic principles
- Primarily bacterial focus - not going to talk much on fungal/parasitic/viral causes

What is sepsis?

“Sepsis should be defined as life-threatening **organ dysfunction** caused by a dysregulated host response to infection”

Previous definitions focused on SIRS (systemic inflammatory response criteria + infection) - that is no longer recommended.

Issues

SIRS criteria do not necessarily indicate a dysregulated, life-threatening response.

SIRS criteria are present in many hospitalized patients, including those without infection

Some patients with infection and new organ failure did not meet SIRS criteria for sepsis

Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$

Heart rate $>90/\text{min}$

Respiratory rate $>20/\text{min}$ or $\text{Paco}_2 <32 \text{ mm Hg}$ (4.3 kPa)

White blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ immature bands

Sepsis definitions continued

“Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone”

“Patients with septic shock can be clinically identified by a combination of
require
and se
of hypotension
greater
presence

Lay definition of sepsis: the Merinoff definition

‘Sepsis is a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs.’

Defining organ dysfunction in sepsis

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ /FIO ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Pathophysiology of sepsis



Mediator molecules	Function
Nitric oxide	Nitric oxide causes and maintains vasodilation. This helps to make capillaries more permeable ('leaky')
Bradykinin	Bradykinin is responsible for the pain at the site of inflammation (preventing us from damaging ourselves further), and is also involved in vasodilatation and making capillaries more permeable
Complement proteins	Complement proteins act directly to neutralise pathogens, mobilise white blood cells and amplify the immune response
Thrombin	Thrombin helps clot formation by turning fibrinogen into fibrin, and is involved in nitric oxide production
Interleukins	Interleukins are a complex group of proteins which help white blood cells to function, attract them to the area and modulate inflammation – some cause inflammation, some damp it down
Tumour Necrosis Factor	Tumour Necrosis Factor (TNF) is a pro-inflammatory cytokine

The Global Burden of Sepsis and Septic Shock

Luigi La Via ^{1,*}, Giuseppe Sangiorgio ², Stefania Stefani ², Andrea Marino ³, Giuseppe Nunnari ³,
Salvatore Cocuzza ⁴, Ignazio La Mantia ⁴, Bruno Cacopardo ³, Stefano Stracquadanio ², Serena Spampinato ³,
Salvatore Lavallo ⁵ and Antonino Maniaci ⁵

11.0 million sepsis-related fatalities and 48.9 million instances of sepsis globally in 2017

Higher rates in Low/middle income countries (LMICs) in comparison to high income countries (HICs). US: ~500 cases/100,000. LMICs ~1500/100,000 people

Sepsis mortality ~15% to 25% in HICs, septic shock mortality 30% to 40%

Sepsis priorities

HICs:

Lowering healthcare associated infections, improving sepsis management, tackling ageing population

LMICs:

Cost-effective sepsis management, improving IPC, increased access to healthcare

UK management of sepsis

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THE SEPSIS MANUAL

UK sepsis mortality

~20% mortality in the UK, ~50,000 deaths a year

**SEPSIS CLAIMS MORE LIVES THAN LUNG
CANCER, AND MORE THAN BOWEL, BREAST
AND PROSTATE CANCER COMBINED**

RISK FACTORS FOR SEPSIS

(adapted from NICE guideline [NG51], Sepsis: recognition, diagnosis and early management, 2016)

— **The very young (under one year) and older people (over 75 years) or people who are very frail**

— **People who have impaired immune systems because of illness or drugs, including:**

- people being treated for cancer with chemotherapy
- people who have impaired immune function (for example, people with diabetes, people who have had a splenectomy, or people with sickle cell disease)
- people taking long-term steroids
- people taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis
- people who have had surgery, or other invasive procedures, in the past 6 weeks
- people with any breach of skin integrity (for example, cuts, burns, blisters or skin infections)
- people who misuse drugs intravenously
- people with indwelling lines or catheters

— **Women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the past 6 weeks are in a high-risk group for sepsis. In particular, women in this group who:**

- have impaired immune systems because of illness or drugs
- have gestational diabetes or diabetes or other comorbidities
- have needed invasive procedures (for example, Caesarean section, forceps delivery, removal of retained products of conception)
- had a prolonged rupture of membranes
- have or have been in close contact with people with group A streptococcal infection, for example, scarlet fever
- have continued vaginal bleeding or an offensive vaginal discharge

— **For neonates, risk factors include:**

- invasive group B streptococcal infection in a previous baby
- maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy
- premature rupture of membranes
- preterm birth following spontaneous labour (before 37 weeks' gestation)
- suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth
- intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
- parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection at any time during labour, or in the 24-hour periods before and after the birth (this does not refer to intrapartum antibiotic prophylaxis)
- suspected or confirmed infection in another baby in the case of a multiple pregnancy

Thinking about/identifying sepsis

Predominantly use National Early Warning Score 2 (NEWS2)

Symptoms of infection helpful: e.g. fever, cough, confusion, urinary tract symptoms

We recommend that a patient be screened for sepsis when in the context of presumed or confirmed infection:

- **HAS A NEWS2 SCORE OF 5 OR ABOVE**
- **LOOKS UNWELL TO A CLINICIAN OR CARER**
- **HAS HAD RECENT CHEMOTHERAPY OR IMMUNOTHERAPY**
- **HAS A LACTATE 2mmol/L OR ABOVE**

NEWS key		FULL NAME		DATE OF BIRTH		DATE OF ADMISSION	
0	1	2	3				
		DATE				DATE	
		TIME				TIME	
A+B Respirations Breaths/min	≥25				3		≥25
	21-24				2		21-24
	16-20						16-20
	15-17						15-17
	12-14						12-14
	≤8				1		≤8
A+B SpO ₂ Scale 1 Respirations (%)	94-95				1		94-95
	92-93				2		92-93
	89				3		89
	98% on O ₂				3		98% on O ₂
	95-96% on O ₂				2		95-96% on O ₂
	93-94% on O ₂				1		93-94% on O ₂
SpO₂ Scale 2 Oxygen saturation (%) Use Scale 2 if target range is 95-100%, eg in hypotensive, respiratory failure	98% on O ₂				3		98% on O ₂
	95-96% on O ₂				2		95-96% on O ₂
	93-94% on O ₂				1		93-94% on O ₂
	88-92						88-92
	86-87				1		86-87
	84-85				2		84-85
Air or oxygen?	At/Air						At/Air
	O ₂ L/min Device				2		O ₂ L/min Device
C Blood pressure mmHg Score uses systolic BP only	≥220				3		≥220
	201-210						201-210
	181-200						181-200
	161-180						161-180
	141-160						141-160
	121-140						121-140
	111-120						111-120
	101-110				1		101-110
	91-100				2		91-100
	81-90						81-90
	71-80						71-80
	61-70						61-70
	51-60				3		51-60
	≤50						≤50
C Pulse Beats/min	≥131				3		≥131
	121-130				2		121-130
	111-120						111-120
	101-110						101-110
	91-100				1		91-100
	81-90						81-90
	71-80						71-80
	61-70						61-70
	51-60						51-60
	41-50				1		41-50
D Consciousness Score for NEWS (no score if comatose)	Alert						Alert
	Confusion						Confusion
	V				3		V
	P						P
E Temperature °C	≥38.1°				2		≥38.1°
	38.1-38.0°				1		38.1-38.0°
	37.1-38.0°						37.1-38.0°
	36.1-37.0°						36.1-37.0°
	35.1-36.0°				1		35.1-36.0°
	≤35.0°				3		≤35.0°
NEWS TOTAL						TOTAL	
Monitoring frequency						Monitoring frequency	
Escalation of care: Y/N						Escalation of care: Y/N	
Initials						Initials	

'RED FLAG' criteria indicating a high risk of deterioration

02 **IS NEWS2 7 OR ABOVE?**
OR NEWS2 IS 5 OR 6 AND ONE OF:

- ☐ Any one NEWS2 parameter with score of 3
- ☐ Mottled or ashen skin
- ☐ Non-blanching rash
- ☐ Cyanosis of skin, lips or tongue
- ☐ Deterioration since last assessment
- ☐ Deterioration since recent intervention
- ☐ Lactate > 2mmol/L OR known AKI

HIGH RISK
OF
SEPSIS

YES

START
SEPSIS SIX

Screening Tool below:

Sepsis 6

Key intervention for saving lives

Should be conducted within first hour

Action (complete ALL within 1 hour)	Time	Initials	Why we do this
1. Ensure senior clinician attends ST3+, or equivalent senior nurse			Sepsis is a complex condition. Experience is essential to deliver the right care and confirm diagnosis
2. Give oxygen if required Start if saturations less than 92%. Aim for saturations of 94-98%. If at risk of hypercarbia use target range of 88-92%			There's a critical imbalance between oxygen supply & demand in sepsis. Correcting low saturations helps to reduce tissue hypoxia
3. Obtain IV access, take bloods Include blood cultures, glucose, lactate, FBC, U&Es, CRP, LFTs, Clotting. Consider lumbar puncture/ other samples as indicated			Laboratory and POC tests help stratify risk & identify causative pathogen allowing more targeted antibiotic therapy
4. Give IV antibiotics and consider source control Maximum dose broad spectrum therapy. Consider local policy, allergies, antivirals			To control the source of infection, reducing the stimulus to the immune system
5. Give IV fluids Give up to 20 ml/kg fluid in divided boluses. Give more if indicated - seek senior advice. Use lactate to help guide further fluid therapy			Hypovolaemia (absolute & relative) contributes to shock in sepsis restoring volume can help correct
6. Monitor Use NEWS2. Measure urine output- may require catheter. Repeat lactate at least hourly if initial lactate elevated or clinical condition changes			Sepsis is a dynamic state. Urine output and lactate can help guide fluid therapy and determine need for ITU referral

Sepsis 6

Lactate is useful for three reasons.

1. Identifies cryptic shock

2. Predicts outcome and need for ICU

3. Guides therapy

The Sepsis 6, and the rationale behind each element, is described in the annotated version of our Screening Tool below:

Action (complete ALL within 1 hour)	Time	Initials	Why we do this
1. Ensure senior clinician attends ST3+, or equivalent senior nurse			Sepsis is a complex condition. Experience is essential to deliver the right care and confirm diagnosis
2. Give oxygen if required Start if saturations less than 92%. Aim for saturations of 94-98%. If at risk of hypercarbia use target range of 88-92%			There's a critical imbalance between oxygen supply & demand in sepsis. Correcting low saturations helps to reduce tissue hypoxia
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5. Give IV fluids Give up to 20 ml/kg fluid in divided boluses. Give more if indicated - seek senior advice. Use lactate to help guide further fluid therapy			Hypovolaemia (absolute & relative) contributes to shock in sepsis restoring volume can help correct
6. Monitor Use NEWS2. Measure urine output- may require catheter. Repeat lactate at least hourly if initial lactate elevated or clinical condition changes			Sepsis is a dynamic state. Urine output and lactate can help guide fluid therapy and determine need for ITU referral

Step 4: Give antibiotics and consider source control

A 2006 study by showed an increase in mortality of 7.6% for every hour's delay in administration of appropriate antibiotic therapy.

Antibiotics should be tailored to suspected source e.g. urine, chest, meningitis

Initially broad-spectrum if in doubt! E.g. Gram positive and Gram-negative cover

Refer to guidelines



THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

Uganda Clinical Guidelines 2023

National Guidelines for Management
of Common Health Conditions

7.2.2 Acute Pyelonephritis ICD10 CODE: N10

Upper urinary tract infection involving one or both kidneys (but not usually involving the glomeruli)

Management

TREATMENT	LOC
☐ Ensure adequate intake of fluid (oral or IV) to irrigate bladder and dilute bacterial concentrations	HC3
☐ Give paracetamol 1 g every 6-8 hours for pain and fever If outpatient (only adults):	HC3
☐ Ciprofloxacin 500 mg every 12 hours for 10-14 days (only adults)	HC3
In severe cases, all children or if no response to above in 48 hours:	HC3
☐ Ceftriaxone 1 g IV once a day Child: 50-80 mg/kg IV once a day Following initial response to parenteral therapy	
☐ Consider changing to: - Ciprofloxacin 750 mg every 12 hours to complete 10 days (adults only) - Or cefixime 200 mg every 12 hours to complete 10 days of treatment Child: 16 mg/kg the first day then 8 mg/kg to complete 10 days	
Alternative regimen	
☐ Gentamicin 5-7 mg/kg IV in one or divided doses with or without ampicillin 2 g IV every 6 hours Child : gentamicin 2.5 mg/kg every 8 hours (or 7.5 mg/kg once daily on outpatient basis) with or without ampicillin 25 mg/kg every 6 hours	HC2
☐ Consider referral if there is no response in 72 hours and for children with recurrent infections (to exclude urinary tract malformations)	

Source control!!!

If source of infection is amenable to drainage or removal, then need to do this once patient stabilised and assuming safe.

Examples

Urosepsis with hydronephrosis 2 to stone -> needs urgent nephrostomy

Perforated appendicitis -> removal of appendix and abdominal washout

Cholangitis 2 to obstructing CBD stone -> ERCP to remove stone

Step 5: consider IV fluids

Crystalloids are preferred resuscitation fluid for sepsis e.g. Hartmann's solution, Plasmalyte, normal saline.

KEY POINT

The aims of fluid therapy are:

1. To correct absolute and relative hypovolaemia
2. To bring the patient's pulse, blood pressure, mental state, lactate and urine output within target
3. To do this judiciously, and to avoid pushing the patient into overload.

FLUID	ADVANTAGES	DISADVANTAGES
Hartmann's	30% of fluid remains in intravascular space Not associated with hyperchloraemic metabolic acidosis	Contains potassium, so make sure the patient is not potassium overloaded Caution in liver disease - Hartmann's contains small amounts of lactate which can accumulate
0.9% Sodium chloride	30% of fluid remains in intravascular space Does not contain potassium, so may be safer in established renal failure without urine output	Risk of hyperchloraemic acidosis if high volumes given
5% dextrose	None (in the acutely hypovolemic patient)	Only 10% of fluid remains in the intravascular space: poor at replenishing circulating volume Can cause hyponatremia
Colloids (except albumin)	As for 0.9% sodium chloride	Starch solutions carry a risk of acute kidney injury compared to crystalloids and are NOT RECOMMENDED in patients with sepsis
Albumin	Stays predominantly in the vasculature. Consider when large volumes of resuscitation fluid needed. SAFE study suggestive of benefit in sepsis, currently being evaluated in the ABC Sepsis Trial	Very expensive
Packed red cells	Corrects anaemia and stays in vasculature	Risks of blood transfusion Crossmatched blood not immediately available Contains a lot more potassium than Hartmann's!

Fluid replacement guidelines

NICE recommends that the initial total volume in patients with evidence of poor perfusion should be at least 500ml, delivered as quickly as possible and certainly within 15 minutes.

NICE in NG51 suggest an initial bolus of up to **20 ml per kg**. This is our current recommendation. This can be delivered in divided fluid challenges of 500ml of crystalloid, provided that there is a favourable response after each challenge.

Fluid challenges should always be commenced within the first hour (with the first 500ml delivered within 15 minutes)

PRACTICAL TIP

First fluids fast, second set slower

When you see your patient with sepsis, you can deliver three of the Sepsis 6 as soon as you have IV access:

1. Send bloods, including cultures
2. Give a stat IV dose of antibiotics (remember to also consider source control)
3. Give your first fluids, if indicated, fast.

Your usual challenge if indicated will be an initial 500 ml within five minutes, followed by further challenges up to a total of 20ml/kg of Hartmann's or Plasmalyte (or equivalent) (or 'normal' Saline 0.9% if these are unavailable)

given in divided boluses as quickly as possible but always within the first hour, although lower volumes (but not lower rates) should be used in those at risk of overload.

Monitor the response to each fluid challenge, and repeat if the systolic blood pressure remains <90 mmHg, the patient's mental state has not returned to normal, or their lactate is still >2 mmol/l. Capillary refill time, pulse rate and urine output are good additional signs of adequate restoration of circulating volume.

Stop if there are signs of overload. If you have reached 20ml/kg in total within an hour and the patient remains poorly perfused, or their blood pressure, mental state or lactate have not returned to acceptable levels, then refer immediately to Critical Care and tell your senior.

Once the patient has a systolic blood pressure >90 mmHg, their mental state has returned to normal, and their lactate is <2 mmol/l, ensure the patient has regular observations (at least every 30 minutes initially) and that further fluids will be prescribed if needed. It is a good idea to write up maintenance fluids e.g. eight hourly bags of Hartmann's if the patient will not have sufficient oral intake.

These are only guides, and some patients will still need senior review even if you have attained these goals. If the patient 'doesn't look right', trust your instinct!



01 SENIOR
HELP



02 GIVE O₂ IF
REQUIRED



03 IV ACCESS
AND BLOODS



04 GIVE IV
ANTIBIOTICS
AND CONSIDER
SOURCE CONTROL



05 CONSIDER
IV FLUIDS



06 MONITOR

SEPSIS

Spot it. Treat it. Beat it.

Summary

- Sepsis has a high mortality
- Need to identify patients who may have it
- Urgently need to instigate sepsis 6
- Patients need enhanced monitoring
- If not improving, get HDU/ICU support
- Source control where possible