THE NORTHERN HOSPITAL

SEPTIC SHOCK

"The Winged Victory of Samothrace", or "Nike", in marble, c. 190 B.C,
Musee du Louvre, Paris.

This is "The Winged Victory of Samothrace", otherwise known as Nike, the ancient Greek Goddess of Victory. It stands imposingly, an 8-foot tall marble monument at the head of the grand Daru Staircase in the Louvre museum, Paris. It appears as though it has just put down from flight upon the brow of the ship on which it stands. The draped garments cling to the body as though wet from the spray of the sea. With wings outstretched and cloak slipping from the shoulders to fall around the legs, it is as though the body is being thrust forward against the force of the wind. It is without doubt one of the finest artistic achievements of the Hellenistic Age and has become in turn one of the greatest cultural icons of Western civilization.

In 190 BC, the small independent Island State of Rhodes was being severely threatened by Antiochus III of the Seleucid Empire. This Empire was the biggest and most aggressive of the Alexandrian successor states and had embarked on a policy of conquest that would eventually lead to a direct collision with the smaller but equally aggressive and rapidly expanding Empire of Rome. Rhodes stood between these two powers. In a desperate attempt to ward off Antiochus the Rhodians managed to negotiate an alliance with the Roman Senate. Together they defeated the Seleucids in a major naval engagement. The Rhodians commissioned the Winged Victory to give thanks to Nike for granting them deliverance from Antiochus. Although the Rhodians could not have procured a more powerful ally, they soon leant that they had a very dangerous one as well. They watched with some unease as in the following few years the legions went on to crush the Seleucid Empire and incorporate its territories into their own. This unease grew to outright fear over the next century as the Roman Empire continued to expand relentlessly until it had assimilated the entire Eastern Mediterranean world into its own Empire. Finally in 42 BC, Rome dropped any further pretense of alliance and invaded the island and made it part of its Empire. Over the ensuing millennia the Roman Empire came and went to be replaced by numerous others in the region. The "Winged Victory" once the symbol of Rhodes' finest hour was lost to the world. It became a faint memory, then only a legend. The Rhodians never regained their former independence.

Then over 2,100 years later in one of the most stunning archeological finds of the Nineteenth century it was rediscovered on the island of Samothrace. In 1863 Charles Champoiseau, an archeologist serving at Adrianople as consul for France, found over 100 pieces of marble of apparently great antiquity embedded in a hillside on the island of Samothrace, overlooking the Aegean sea. Not quite sure of what he had found he arranged to have these pieces transported to Paris, where they were reassembled at the Louvre the next year and although tragically not complete, was displayed to an awestruck public as one of its greatest treasures. It stands today in memory of a long lost civilization and in tribute to an unknown ancient craftsman the equal of any Renaissance master.

The human body, like the ancient Rhodians faced with the severe threat of Antiochus, may be faced with a severe threat of its own in the form of sepsis. If it is to overcome this threat it must, like the Rhodians, employ powerful allies to assist. It does this in the form of an alliance with "legions" of inflammatory mediators. These mediators however, like the Romans, often prove to be dangerous allies and the body may soon become consumed by them in turn in the form of Septic Shock. If we are to achieve final victory over sepsis, future treatments may need to be directed not only against the invading organism but also against these allies should they get out of hand. Newer treatments are continually being sought. It is hoped that like the partial recovery of the Winged Victory, that they may one day also provide at least a partial part of the recovery of our septic patients.

SEPTIC SHOCK

Introduction

Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly.

Its recognition mandates urgent attention.

The definitions of **sepsis** and **septic shock** have been recently reviewed by the **SEPSIS - 3** taskforce. The term "severe" sepsis is now not used.

Organ dysfunction can be objectively defined according to a number of scoring systems. One such system is the **SOFA Score** (**S**equential - sepsis related - **O**rgan **F**ailure **A**ssessment score).

Patients with **suspected infection** who are likely to have a prolonged ICU stay or to die in the hospital can be identified *early at the bedside* via the "**quick SOFA**" Score, (**qSOFA**).

The predominant hallmarks of the *treatment* of sepsis/ septic shock remain:

- **Rapid recognition of a state of sepsis.**
- **Early administration (within 1 hour) of empirical board spectrum antibiotics**
- **Aggressive search for the cause/ source of sepsis enabling more directed antibiotic therapy and/ or surgical drainage.**

Other factors include:

- **Aggressive and early hemodynamic resuscitation with fluids and vasopressors/ inotropes.**
- **Early lung protective ventilation.**

These factors appear to be more important than strategies of so called "early goal directed therapy", i.e therapy aimed primarily at achieving certain "ideal" physiological parameters. [8,9, 10]

Strategies aimed at improving outcomes by attenuating the SIRS response have thus far not proved successful, but research continues in this area

Steroids (unless there is a specific indication for these) and APC, despite early claims of efficacy, have not subsequently shown to be of benefit.

Useful parameters to monitor appear to be:

- **Systemic blood pressure**
- **Biochemistry**
    - ♥ **Serum lactate levels (and clearance)**

- ♥ **Serum creatinine**

- **Urine output.**

Terminology

The following definitions were formulated at the consensus conference of the American College of Chest Physicians and Society of Critical Care Medicine in 1992:

Infection:

- Inflammatory response due to the presence of microorganisms.

Bacteremia:

- The presence of viable bacteria in the blood (usually confirmed by positive culture)

The following definitions were formulated at the consensus conference of SEPSIS 3:

Sepsis:

- **Sepsis** is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

  In other words, what differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

  In *lay terms*, therefore, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

Septic Shock:

- **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 with a clinical construct of sepsis with:

  - ♥ Persisting hypotension requiring vasopressors to maintain **MAP > 65 mmHg.**

  And

  - ♥ Having a serum **lactate level > 2 mmol/L** (18mg/dL) despite adequate volume resuscitation.

  With these criteria, hospital mortality is in excess of 40%.

Pathophysiology

Current concepts of severe sepsis and septic shock recognize that these clinical syndromes are the result not only of the infecting organism but also the body's inflammatory, immune and procoagulant responses to the organism.

This process is thought to involve:

1. Introduction of microorganism toxins:

    - As synthesized exotoxins, (e.g. diphtheria, clostridia)

    - As structural components of the microorganism itself, (including the peptidoglycan of gram positive organisms and the lipopolysaccharide endotoxin of gram negative organisms)

2. Toxins act on host's cells, (including macrophages, monocytes, neutrophils and endothelial cells) which results in the release of inflammatory mediators:

    - Cytokines (tumor necrosis factors and interleukins)

    - Cell membrane derived mediators, which are primarily arachidonic acid metabolites produced via the action of cyclo-oxygenase and lipo-oxygenase.

3. The physiological actions of these mediators fall into two main groups (as summarized in the diagram above):

    - Stimulators of the inflammatory response

    - Suppressors of the inflammatory response.

4. When there is an overly predominant effect of the pro-inflammatory response, the effects will be detrimental and result in:

    - Myocardial depression

    - Greatly increased vascular permeability and vasodilatation.

    - Microvascular pathology leading to dysfunctional tissue utilization of oxygen:

      Oxygen flux (i.e the total oxygen delivery to the tissues) is a product of cardiac output, Hb levels and the PaO_2.

      In septic shock the oxygen flux may be above normal due to an increased cardiac output and whilst the Hb and PaO_2 levels may be normal, nonetheless a profound tissue hypoxia and lactic acidosis develops.

      This is thought to be due to abnormalities in the microvascular tissue beds that result in abnormal tissue utilization of the oxygen. Microvascular thrombosis with shunting of blood is thought to be one cause of this abnormal tissue utilization.

5. These effects lead to the clinical syndromes of **SIRS** (systemic inflammatory response syndrome) and **MODS** (multiorgan dysfunction syndrome).

Clinical Assessment

Important Points of History

1. A thorough history is often the most useful guide to the likely source of sepsis.

2. It is important to establish if there are any risk factors for depressed immunity, including:

    - Does the patient have HIV?

    - Is the patient an oncology patient, in particular are they receiving **radiotherapy** or **chemotherapy**, (suspect **febrile neutropenia)** or on any other immuno-depressant drugs.

    - Does the patient have Addison's disease?

    - Other significant co-morbidities:

        - ♥ Diabetics, chronic renal failure, chronic liver failure, heart failure, chronic respiratory disease, malignant disease.

3. Are there any important epidemiological risk factors?

    - Has the patient been overseas recently: **falciparum, malaria** needs to be considered, (see separate document on malaria).

    - Has there been any recent contact with infectious disease, such as meningococcus or recent legionella outbreaks?

4. Devices / Implants:

    - Does the patient have any IV access ports or surgical devices, (these may be the source of infection) or implants (e.g. VP shunts).

5. Structural cardiac disease:

    - if the patient has any structural cardiac disease, (in particular valvular) suspect bacterial endocarditis as the source of infection.

6. Has the patient had any recent surgery?

7. Has the patient been on recent antibiotics?

Important Points of Examination

1. Assess ABCs/ conscious state/ orientation.

2. Vital signs:

- Fever:
    - ♥ But note that the patient may be febrile, normothermic or hypothermic, (sometimes severely so)
- Hypotension
- Tachypnea
- SaO_2
- Tachycardia
- Peripheral perfusion:
    - ♥ Reduced capillary return
    - ♥ In particular look for signs of **skin mottling**, (see separate document on the assessment of skin perfusion in Clinical Presentations Folder).
    - ♥ The patient may present in a state of vasodilation with relatively warm periphery and widened pulse pressures. It is important to recognize however that this classical description of "warm shock" is rarely how the patient presents in practice.

      In more advanced sepsis, there patient may he hypothermic and peripherally shut down, due to CVS collapse and failure of thermoregulation.
- The Systemic Inflammatory Response Syndrome, (SIRS):

  Previously, this concept was integral to the concept of sepsis. SIRS however is really a *generic* response of the body to illness, sepsis, being only one among many causes, (others for example include, burns, trauma, severe pancreatitis).

  Additionally some patients with severe infection, may not even fulfill SIRS criteria, (1 in 8 patients admitted to critical care units in Australia and New Zealand with infection and new organ failure did not have the requisite minimum of 2 SIRS criteria to fulfill the definition of sepsis (poor concurrent validity) yet had protracted courses with significant morbidity and mortality). [11]

  Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

  Despite these limitations the SEPSIS – 3 task force stresses that SIRS criteria may still remain useful for the identification of infection.

  Evidence of a "*systemic inflammatory response*" is defined as 2 or more of the following:

  - Tachypnoea:

- ♥ RR > 20 / min, or a $PaCO_2$ < 32 mmHg, or a minute ventilation value of > 10 L / min, where the patient is intubated and spontaneously breathing.

- Tachycardia:
  - ♥ > 90 beats per minute.
- A core body temperature:
  - ♥ > 38 ^{0} C or < 36 ^{0} C.
- A WCC of:
  - ♥ > 12,000 cells / microL or < 4000 cells / microL.

3. Check carefully for any obvious **source** of sepsis including:

- Respiratory
- Urinary
- Skin/ deep soft tissue - limbs - necrotizing infections/ joints
- Occult surgical conditions
- CNS
- Head/neck/oropharynx

Screening Assessment - The Quick SOFA Score:

Patients with **suspected infection** who are *likely* to have a **prolonged ICU stay** or to **die in the hospital** can be identified early at the bedside via the "**quick SOFA**" Score, (**qSOFA).**

This can be assessed on 3 simple bedside parameters:

1. Respiratory rate ≥ 22 / minute.
2. Altered mentation (i.e. GCS < 15)
3. Systolic blood pressure ≤ 100mmHg

≥ 2 of these clinical variables identifies the patient at higher risk of sepsis/ septic shock.

qSOFA criteria can be used to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken.

Furthermore:

- **Sepsis induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection.**

- **Conversely, unrecognized infection may be the cause of new onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.**

The Assessment of Organ Dysfunction - the SOFA Score:

Organ dysfunction can be identified as an **acute change** in the total **SOFA score ≥ 2 points** consequent 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 ≥ 2 reflects an overall mortality risk of approximately10% in a general hospital population with suspected infection.

  Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

The SOFA Score is based on 6 parameters: (**see Appendix 1 below**).

1. Respiratory:
   - PaO_2 / FiO_2 ratio
2. Coagulation:
   - Platelet level.
3. Liver:
   - Bilirubin level.
4. CVS:
   - MAP
   - Requirement for inotropes.
5. CNS:
   - GCS
6. Renal:
   - Creatinine level
   - Urine output.

Approach to the Septic Patient:

The qSOFA and SOFA systems can be used to assist management of the septic patient, (**see Appendix 2 below**).

Investigations

Investigations will be guided by the severity of illness and the degree of clinical suspicion for a particular causative pathology.

The following will need to be considered:

Blood tests:

1. FBE

    - Note that the WCC may be elevated or depressed, the latter being associated with a poor prognosis.

    - If the neutrophil count is low and the patient is febrile, this is "**febrile neutropenia"** and is a true emergency, (**see separate document for this condition**)

2. CRP

3. U&Es / glucose

4. Coagulation profile, including DIC screen.

5. ABGs,/ VBGs including **lactate levels**:

    - **All patients at risk of sepsis should have a lactate level.**

      Elevated lactate levels reflect tissue hypoxia and correlate with the severity of illness and likely outcome.

      Lactate level is a sensitive, though nonspecific, stand-alone indicator of cellular (or metabolic) stress rather than "shock" per se.

      However, the *combination* of hyperlactatemia with fluid-resistant hypotension identifies a group with particularly high mortality and thus offers a more robust identifier of the physiologic and epidemiologic concept of septic shock than either criterion alone.

6. Cardiac enzymes

7. LFTs

8. Lipase

9. Blood for PCR studies.

10. Blood cultures:

- Ideally two sets of blood cultures (at different sites) should be taken prior to antibiotic therapy, (however this should not be allowed to significantly delay the administration of antibiotics)

- A set should also be taken from any indwelling lines.

Urine analysis:

1. Urinalysis by "diptix" FWT.

2. Microscopy and culture.

3. Bacterial antigen studies:

- Legionella antigen, this a useful initial investigation if legionella is being considered.

- Pneumococcal antigen

Plain radiography:

CXR

- All patients with severe sepsis should have a CXR, regardless of the presumed source of infection.

  Secondary complications such as ARDS is possible in addition to significant unrecognized co-morbidity

AXR

- May be done if an abdominal problem is suspected, but has limited utility.

ECG:

As for any unwell patient an ECG should be done.

Look for associated changes of myocardial ischemia, electrolyte disorders or arrhythmias.

Ultrasound:

Especially if an abdominal source of sepsis is suspected.

Biliary disease is a common cause of sepsis in the elderly. Both calculus and acalculus cholecystitis can be a cause of severe sepsis.

Look for renal tract obstruction.

Ultrasound can be done urgently in the resus cube for patients who are very unwell.

MRCP/ ERCP:

MRCP may be required to establish a diagnosis of choledocholithiasis

ERCP can be both therapeutic as well as diagnostic.

CT Scan:

Abdomen CT for occult surgical conditions, renal tract obstruction or ischemic gut

Chest, this may fully define the nature of obscure CXR findings.

Brain, must be considered in all cases where there is an altered conscious state or confusion.

Imaging for occult infection when indicated, must be done early

Lumbar Puncture:

This should be considered when a diagnosis of meningitis or encephalitis is being considered, however it is **not** recommended when there are concerns about raised intracranial pressure.

It is best to treat these conditions empirically early.

The LP may be done later, when the patient is more stable and *after* a CT brain has been done to help exclude edema or mass lesions leading to raised intracranial pressure.

Echocardiography:

This will be urgent if the patient is thought to have bacterial endocarditis.

It provides invaluable information as to the degree of myocardial dysfunction.

It is useful in ruling out other pathologies resulting in hypotension, when the cause of this hypotension is unclear.

Management

Issues in the management of septic shock include:

1. Initial resuscitation and stabilization
2. Urgent empirical broad spectrum antibiotics
3. Establishing monitoring.
4. Systems supportive measures:
    - Cardiovascular support
    - Respiratory support
    - Renal support

- Hematological support
- GIT support

5. Adjunctive measures.
6. Surgical measures
7. Early referral pathways.

Initial resuscitation and stabilization

As for any severely ill patient the priority will be:

1. Immediate assessment and management of any ABC issues.
2. Fluid resuscitation:

   IV access and initial fluid bolus resuscitation:

   - Crystalloids are given (as opposed to colloids)

     Traditionally normal saline was favoured, however recently it has been shown that in critically ill patients "**balanced salt solutions**" - such as **Hartmann's solution** or **Plasma-lyte** are now preferred (**see also separate document on Crystalloid Fluid Therapy in Critical Care & Anaesthetics folder**). [14]

   - Traditional recommendations have been for aggressive fluid resuscitation to achieve a central venous pressure (CVP) greater than **8 mm Hg** by giving **20-30 mls /kg** (2-3 litres) of fluid.

     However recent clinical trials have demonstrated that this approach does not improve the outcome of patients with sepsis and septic shock. [12]

     Septic shock is not primarily a volume depletion state - but rather a "vasoplegic" state, with arterial and venous dilatation, as a result of failure of the vascular smooth muscle to constrict.

     Some patients may have a limited response to fluid therapy (in part because they may have concomitant dehydration), however most septic patients are actually poorly responsive to fluids, and excessive fluid therapy may in fact be detrimental.

     Ideally, fluid resuscitation should be guided by the determination of *fluid responsiveness* (i.e. improvement in blood pressure), and if not responsive then inotropes should be commenced rather than additional fluid loading.

     Marik and Bellomo have recommended *initial* fluid resuscitation of patients with 250 - 500 ml boluses of crystalloid (Ringer's lactate), to a *maximum* of about 20 ml / kg. [12] It should be stressed however that the authors also maintain that clinical judgement on a case by case basis also remains a **crucial factor.**

Empirical antibiotic treatment

1. Broad-spectrum antibiotics should be commenced **within one hour of diagnosis.**

   In cases of **febrile neutropenia**, they should be commenced within **30 minutes** (see febrile neutropenia document)

2. The antibiotic regimen should be reviewed according to the microbiological results when available.

3. Empiric antibiotic treatment:

   This will depend on a number of factors including:

   - How unwell the patient is
   - Local bacterial sensitivities
   - The index of suspicion for any particular given pathology/ organism
   - The immune status of the patient (i.e is the patient immunosuppressed?)
   - Life-threatening allergies/ potential side effects in individual patients.

   In **general terms** choices may include:

   - For febrile neutropenia:
     - ♥ See separate document on **Febrile Neutropenia (in ID folder)**
   - For severe pneumonia:
     - ♥ Ceftriaxone and azithromycin.
     - ♥ Oseltamivir (can be given via NG tube) if viral etiology suspected.
   - For urosepsis:
     - ♥ Ceftriaxone and ampicillin.
   - For intraabdominal sepsis:
     - ♥ Ceftriaxone, ampicillin, metronidazole.
   - Skin/ soft tissue and indwelling lines:
     - ♥ Flucloxacillin or vancomycin
   - CNS:
     - ♥ Ceftriaxone, benzylpenicillin, vancomycin

- **Unknown source:**
  - ♥ Ceftriaxone, flucloxacillin (or vancomycin)
  - ♥ **In severe cases tazocin/ meropenem may also be used**

For full prescribing details and other choices of antibiotics or for alternatives in cases of contraindications, see latest edition of Antibiotic Therapeutic Guidelines.

Establishing monitoring

1. Urinary catheter:
   - Aim for a minimum urine output of **> 0.5 mls / kg / hr**
2. Central venous pressure monitoring
   - Current recommendations suggest **8 mmg Hg** is optimal
3. Arterial line:
   - Aim for a mean arterial pressure of **at least 65 mmHg.**
4. Cardiac output monitors are generally placed once the patient is in ICU:

   Pulmonary artery catheters are now rarely used and have largely been replaced by specialized cardiac output measuring devices, such as:
   - Peripherally inserted continuous cardiac output (PiCCO) monitor.
   - Pulse contour monitor (Vigileo)

   Summary of hemodynamic parameters seen in Septic Shock compared to cardiogenic and hypovolemic shock:

Type of Shock	Cardiac Index	CVP	Systemic Vascular Resistance	Oxygen Delivery
Septic Shock	↑	N or ↓	↓↓	↑
Cardiogenic Shock	↓	N or ↑	↑	↓
Hypovolemic Shock	↓	↓	↑	↓

Systems supportive measures:

Cardiovascular support

1. Fluid therapy:

   - IV fluids to initially aim for a systolic BP of 90 mmHg, (or MAP of > 65 mmHg)

     Crystalloid solutions are used in the form of "balanced salt solutions", such as **Hartmanns** or **Plasma-lyte.**

2. Inotropes:

   Noradrenaline

   - If systolic pressure is not maintained with fluid bolus, (SP < 90 mmHg, MAP > 65 mmHg) then **Noradrenaline** should be commenced.

     Norepinephrine increases preload, systemic vascular resistance and cardiac output and its use in patients with persistent hypotension is recommended *early* in the course of sepsis unresponsive to fluid therapy.

   - Noradrenaline is generally considered the **first line** inotrope for **septic shock.**

   - Digital and limb ischaemia and ischaemic skin lesions are *extremely rare* with the use of norepinephrine usually only occurring with high dosages and usually when used together with vasopressin.[12].

     Noradrenaline can thus be initiated, through a well-functioning peripheral line and its administration should not be excessively delayed by attempts at central line placement.

   Adrenaline:

   - **Adrenaline** is another option, although in experimental sepsis models, noradrenaline appears preferable to adrenaline. [12]

   - **Adrenaline** is the inotrope of choice in cases of **anaphylactic shock**.

   - Significant tachycardia and lactic acidosis generated by adrenaline can be problematic however in practice in higher doses both these agents (i.e. noradrenaline and adrenaline) have virtually the same effects.

   Vasopressin:

   - If hypotension persists, then **Vasopressin** may be considered as an adjunct to noradrenaline or adrenaline.

   - **The dose is 0.01 - 0.04 units / minute.**

   Dopamine:

- **Dopamine** is **not** favored as an inotrope for septic shock in Australia or New Zealand, (due to inferior potency as a primary vasopressor as well as a number of adverse effects such as increased risk of arrhythmias and death in patients with sepsis). [2, 12]

  Low "renal" dose dopamine has **not** been shown to improve outcomes in septic patients. [8]

3. **Augmented** cardiac output treatments have **not** been shown to improve outcomes. More important considerations are restoration of blood volume and organ perfusion pressure (e.g. MAP) with fluids and vasopressors.

Respiratory support

Maintain oxygenation

Initially this may be by high flow oxygen delivered by Hudson mask, or even by a High Flow Nasal oxygen delivery device.

If patients in septic shock require more respiratory support than this then intubation is preferred over NIV as the next step.

Patients in septic shock who require respiratory support should be intubated and ventilated early.

For intubated patients:

1. Use an ARDS type ventilation pattern:

   - Lower tidal volumes, (**6 mls/kg**, lean body mass), to reduce the risk of lung injury.
   - PEEP 5 cm or greater.
   - RR of 20
   - Plateau pressures < 30 mmHg, (this is the equilibrated pressure achieved at the end of inspiration and correlates with alveolar pressure. It is not the same as "peak inspiratory flow pressure")
   - FiO_2 = 1.0, (aim for an SaO_2 > 90% or a mixed venous SvO_2 > 70 %)
   - Some hypercapnia, is not harmful and will allow for low tidal volumes and to minimise plateau pressures.

   If ventilation is difficult (e.g. persistent hypoxia or high peak pressures), check ETT has not inadvertently slipped down the right main bronchus and consider further intravenous sedation (e.g. morphine).

2. Neuromuscular blockade:

- This may be used initially whilst the patient is in the ED, undergoing stabilization and being moved for CT scans and the like.

- In the ICU setting, sedation is preferred, rather than repeated doses of neuromuscular blocking agents, because they increase the risk of prolonged myopathy.

3. Sedation and analgesia:

   - In the ED this will generally be with **morphine** and/or **propofol** infusions.

   - In ICU, daily interruption will prevent drug accumulation and the need for prolonged ventilation.

4. There should be early tracheotomy (after 5-7 days) for patients who will require prolonged ventilation periods. (An ICU consideration)

5. Daily T-piece (or CPAP) trials will reduce the period of mandatory ventilation. (An ICU consideration)

6. Nursing ventilated patients in a semirecumbent (30- 45 degree) position in ICU will help reduce the risk of hospital-acquired aspiration pneumonias.

Renal support

1. Optimizing fluid loading is the best initial step for maintaining urine output.

2. For patients who are in acute renal failure there should be **early** referral to ICU for dialysis.

   Like early ventilation, **early** renal support is also recommended in patients with septic shock and renal failure.

3. The following measures are **not** recommended:

   - Renal dose dopamine, (this has not been shown to improve outcomes)

   - Diuretics have no outcome benefit in oliguric acute renal failure, and may in fact increase mortality risk.

Hematological support

1. Hemoglobin is best maintained at a level of **7-9 gm/dl.**

   There is no outcome benefit for transfusion for anemia for Hb levels above 7 gm/dl, unless the patient has a concomitant acute coronary syndrome.

2. FFP is not routinely recommended for coagulopathy, unless bleeding is present.

3. Platelets:

   - If < 5000 /mm^3 (5 x 10^9 / L) give platelets regardless of bleeding.

- If 5000 - 30,000 /mm^3 and there is a significant bleeding risk
- Counts of > 50,000 / mm^3 are generally required for surgery or invasive procedures.

GIT support

1. Nutritional support should be commenced within the first 48 hours.
2. The **enteral route** may reduce nosocomial sepsis risk.
3. TPN has **not** been shown to be more beneficial than the enteral route. It will be necessary when the enteral rout is contraindicated.

Adjunctive measures:

2. *DVT prophylaxis*

- TED stockings
- Low dose heparin is recommended for patients with severe sepsis, unless:
  - ♥ There is a coagulopathy, (INR > 2.0 or APTT > 40 seconds)
  - ♥ There is bleeding, or a high risk of bleeding.

3. *Steroids*

- Stress dose IV hydrocortisone (100mg b.d) should be given if the patient is already on or has recently been on steroids or if the patient is known to have Addison's disease or has bacterial meningitis.
- It has been proposed that steroids may also be beneficial for patients within 48 hours and who are requiring increasing levels of inotrope / vasopressor support.

  There is however, no proven benefit for the *routine* use of steroids in septic shock.

  Despite this however, steroids **are** often given when noradrenaline requirements reach 15-20mcg/min. Steroids are not detrimental in septic shock, and there are theoretical reasons why it may be of benefit, including enhanced efficacy of catecholamines.
- There is no outcome benefit for *"High Dose"* steroids, unless the patient requires these for cerebral abscess, where there may be significant mass effect from edema.

4. *Bicarbonate*

- The treatment of increased anion gap metabolic acidosis is treatment of the cause. There is no outcome benefit for metabolic / lactic acidosis by the administration of bicarbonate.

5. *Hypoalbuminemia*

- There has been no outcome benefit shown for treating hypoalbuminaemia with albumin infusions in the setting of severe sepsis.

6. *Stress ulcer prophylaxis*

- This is recommended for all patients who are on mandatory ventilation and are not receiving full enteral nutrition.

- Give a proton pump inhibitor such as omeprazole IV

7. *Normoglycemia*

- It is desirable to avoid *excessive* hyperglycemia and any hypoglycemia.

  Attempts at **rigid** control within narrow parameters by continuous insulin infusions however, have not proven of benefit and in fact have proved detrimental due to the propensity for episodes of severe hypoglycemia.

Source control / Surgical Intervention:

When the source of sepsis is not readily apparent, an occult surgical condition should always be considered, especially in the elderly or in any case where the patient is difficult to assess for reasons of communication.

If there is a surgical source of infection, these will need to be treated early and aggressively:

1. Abscesses will need drainage

2. Necrotic tissue will need debriding, e.g. clostridial myonecrosis.

3. Any potentially infected devices will need to be removed.

Disposition:

1. ICU

- **Early referral is essential, especially if patients will be requiring ventilation or dialysis.**

2. Surgical:

- Refer early if a surgical condition is suspected.

3. Infectious Diseases:

   Seek urgent Infectious Diseases advice for:

- Suspected unusual infections
- The severely immunocompromised.
- The “returned traveller”.

Appendix 1

The Sequential Organ Failure Assessment Score (SOFA):

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, $\times 10^3/\mu L$	≥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: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

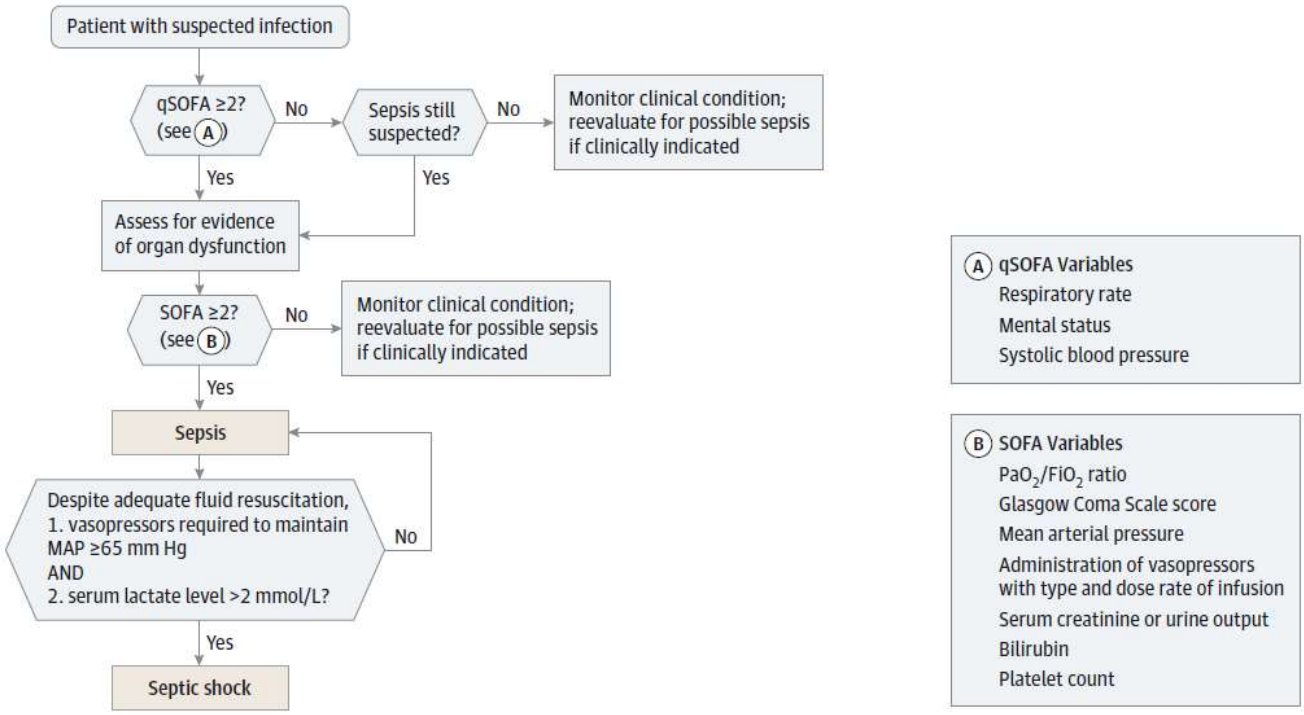
[a] Adapted from Vincent et al.[27]

[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.

Appendix 1

Approach to the patient suspected sepsis:



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

The Daru staircase, with "The Winged Victory of Samothrace", or "Nike", in marble, c.190 B.C, Musee du Louvre, Paris.

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