Sepsis: Time is Life

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SEPSIS: TIME IS LIFE

INTRODUCTION: BURDEN OF SEPSIS

Sepsis is a systemic injurious state that results in significant morbidity and mortality. In high income, developed countries, sepsis accounts for up to 30% of ICU admissions. In these countries, sepsis related mortality ranges between 30 and 46%. In the United States up to 750000 patients developed severe sepsis annually, mostly bacterial. Of these 29% may die. Costs for each patient are almost $23000.

In Africa statistics on sepsis related admissions are much less available. It is, however, expected to be much higher with the prevalence of immunocompromising states especially HIV/AIDS.

Many studies into the management of sepsis have been conducted in resource rich settings of high income countries. This includes the surviving sepsis guideline, first introduced in 2004. Many authors have questioned whether these strategies can be adapted to low income countries and indeed our South African setting.

Severe sepsis management requires ICU resources including staff and equipment. In low income countries these are usually very limited and sometime non-existent.

WHAT IS SEPSIS?

Sepsis can be defined as a spectrum of clinical conditions caused by the immune response of a patient to infection that is characterized by systemic inflammation. It includes the full range of response from systemic inflammatory response (SIRS) to organ dysfunction to multiple organ failure and ultimately death.

The varying degrees of sepsis each have their own criteria to aid in management of the patient.

Some definitions can be made to simplify things:

**Infection:** infection is a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

**Bacteraemia:** bacteraemia refers to the presence of viable bacteria in the blood.

**Systemic inflammatory response syndrome (SIRS):** is a widespread inflammatory response to a variety of severe clinical insults. It may also occur without infection.
This syndrome is clinically recognized by the presence of two or more of the following:
General variables:-
- Fever (38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate > 90/min
- Tachypnoea
- Leukocytosis (WBC count >12,000)
- Leukopenia (WBC count <4000)
- Normal WBC count with >10% immature forms

Sepsis: sepsis is the systemic response to infection. Thus, in sepsis, the clinical signs describing sirs are present together with definitive evidence of infection. Severe sepsis: sepsis is considered severe when it is associated with organ dysfunction distant from the site of infection, hypoperfusion or hypotension.

Organ dysfunction variables:-
- Arterial hypoxemia (PaO2/FIO2 <300)
- Acute oliguria (urine output <0.5 mL/Kg/hr) despite adequate fluid resuscitation
- Creatinine increase to >176 mcmol/L
- Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count, <100,000)
- Hyperbilirubinaemia (plasma total bilirubin >2mg/dl)
- Lactate greater than the upper limits of normal laboratory results
- ALI with PaO2/FIO2 >250 in the absence of pneumonia as infection source
- ALI with PaO2/FIO2 >200 in the presence of pneumonia as infection source

The manifestations of hypoperfusion may include, but are not limited to:-
- serum lactate >2mmol/l
- oliguria <0.5ml/kg/hr
- acute alteration in mental status

Septic shock: Septic shock is sepsis with hypotension despite adequate fluid resuscitation (at least 1l crystalloid or 300-500ml colloid) and requiring inotropic support
- Arterial hypotension (SBP <90 mmhg; MAP <70 mmhg; or an SBP decrease >40mmhg in adults), in the absence of other causes for the fall in blood pressure. It includes perfusion abnormalities.

Refractory sepsis: Septic shock for >1 hour, not responding to vasopressor therapy.
CAUSES OF SEPSIS

Severe sepsis may have infective and non-infective causes. Infections are common and can be treated, therefore, in patients presenting with clinical signs of SIRS, an infective cause must be actively sought.

Community-acquired infections in previously well patients are easier to recognize than nosocomial infections in debilitated hospitalized patients. Infections leading to sepsis include CNS infections (e.g. meningitis or encephalitis), cardiovascular infections (e.g. infective endocarditis), respiratory infections (e.g. pneumonia), gastrointestinal infections (e.g. peritonitis) or urinary tract infections (e.g. pyelonephritis).

Although bacterial infections are the most common infective cause, viruses and fungi can also cause septic shock.

Non-infective causes include severe trauma or haemorrhage and acute systemic disease, including myocardial infarction, pulmonary embolus, acute pancreatitis, burns, dissecting aortic aneurism, cardiac tamponade, adrenal insufficiency, anaphylaxis and drug overdose.

<table>
<thead>
<tr>
<th>System affected</th>
<th>Signs and symptoms</th>
<th>Mechanism</th>
<th>Common systemic pathogens</th>
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</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Confusion, drowsiness, irritability, coma, headache, neck stiffness, photophobia</td>
<td>Alteration in blood-brain barrier neurotransmitter levels; receptor function energy availability</td>
<td>Community-acquired pathogens: Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Hypotension, impaired myocardial contractility, tachycardia, increased cardiac output, decreased systemic vascular resistance (SVR), impaired responsiveness to vasoconstrictor agents, short of breath, orthopnoea, raised venous pressure</td>
<td>(a) Poor intake, inadequate replacement; excessive insulin sensitive losses (b) Increase in microvascular permeability and hypoalbuminaemia (c) Myocardial depression (d) Down-regulation of adrenergic receptors heart valve dysfunction</td>
<td>Major community-acquired pathogens: Enterococcus, Streptococcus bovis, Streptococcus spp., coagulase-negative staphylococci, Escherichia coli, Staphylococcus aureus, Campylobacter, E. coli, fungi</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Hypoxia, cyanosis, tachycardia, use of accessory muscles, change in sputum: volume, purulence</td>
<td>(a) Increase in capillary permeability; alveolar flooding (b) Neutrophils recruited to the lung (c) Pulmonary microemboli, platelet aggregates</td>
<td>Major nosocomial pathogens: Pseudomonas aeruginosa, Methicillin-resistant S. aureus, Methicillin-resistant Staphylococcus epidermidis, methicillin-resistant coagulase negative Staphylococcus</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>Vomiting, diarrhoea, abdominal pain, tenderness, liver failure, cholestasis</td>
<td>Major community-acquired pathogens: E. coli, Bacteroides fragilis</td>
<td>Major nosocomial pathogens: aerobic Gram-negative bacilli, anaerobes</td>
</tr>
<tr>
<td>GU system</td>
<td>(a) Frequency, dysuria, haematuria, flank pain, renal failure</td>
<td>Major community-acquired pathogens: any of the above-mentioned organisms as a result of bacteremia</td>
<td>Major nosocomial pathogens: any of the above-mentioned organisms as a result of bacteremia</td>
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Anaesthetic management of patients with severe sepsis
D. Eissa, E. G. Carton and D. J. Buggy
HIGHER RISK PATIENTS

Although sepsis can develop in anyone the risk for developing severe sepsis and complications depends mainly on the presence of co-morbid conditions associated with immune defects and/or the use of immunosuppressive therapies. The site of primary infection and the specific infecting microbe plays an additional role while genetic factors may also be important.

Extremes of age, lack of splenic function, alcoholism with significant liver disease, chronic renal disease, intravenous drug use, malnutrition, HIV infection, diabetes mellitus and malignancy all predispose to specific infections, frequently with increased severity. Cancer chemotherapy, immunosuppressive therapies after organ transplantations and chronic steroid therapy also increase the risk for sepsis.

Certain sites of primary infection may provide a nidus for bacterial invasion: recent upper or lower respiratory tract infections, prior major trauma, disruption of cutaneous barriers due to lacerations, burns, surgery or decubitus ulcers and the presence of foreign material such as nasal packing, barrier contraceptives, tampons, arteriovenous fistulas, indwelling catheters, prosthetic joints and mechanical ventilation are all associated with an increased risk for sepsis.

Specific organisms that may predispose to more severe infection are often associated with the above risk factors and include *pseudomonas aeruginosa*, *escherichia coli*, *klebsiella pneumoniae*, *staphylococcus aureus* and *streptococcus pneumoniae*.

Circulating bacteria and their products may also directly stimulate inflammatory responses within the vasculature, e.g. meningococcal endotoxin, or inflammatory mediators from the local site of infection, e.g. pneumonia caused by *p. Aeruginosa*. 
PATHOPHYSIOLOGY OF SEPSIS

It is a very complex sequence of events that results in a patient going from SIRS to septic shock. Patients with septic shock have a biphasic immunological response. Initially they manifest an overwhelming inflammatory response to the infection. This is most likely due to the pro-inflammatory cytokines Tumour Necrosis Factor (TNF), IL-1, IL-12, Interferon gamma (IFNgamma), and IL-6. The body then regulates this response by producing anti-inflammatory cytokines (IL-10), soluble inhibitors [TNF receptors, IL-1 receptor type II, and IL-1RA (an inactive form of IL-1)]. This can manifest in the patient as a period of immunodepression. Persistence of this hyporesponsiveness is associated with increased risk of nosocomial infection and death.

This systemic inflammatory cascade is initiated by various bacterial products. These bacterial products (gram-negative bacteria = endotoxin, formyl peptides, exotoxins, and proteases; gram-positive bacteria = exotoxins, super antigens [toxic shock syndrome toxin (TSST); streptococcal pyrogenic exotoxin A (SpeA)], enterotoxins, hemolysins, peptidoglycans and lipotechoic acid; fungal cell wall material) bind to cell receptors on the host’s macrophages and activate regulatory proteins [Nuclear Factor Kappa B (NFkB)]. Endotoxin activates the regulatory proteins by interacting with several receptors.

The CD receptors are responsible for the protein aggregation on the surface of the cell and then the TLR receptors translate the signal into the cells.
The pro-inflammatory cytokines produced are tumour necrosis factor (TNF), Interleukins 1, 6 and 12 and Interferon gamma (IFN gamma). These cytokines can act directly to affect organ function or they may act indirectly through secondary mediators. The secondary mediators include nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins and complement.

TNF and IL-1 (as well as endotoxin) can also cause the release of tissue-factor by endothelial cells leading to fibrin deposition and disseminated intravascular coagulopathy (DIC).

Then these primary and secondary mediators cause the activation of the coagulation cascade, the complement cascade and the production of prostaglandins and leukotrienes. Clots lodge in the blood vessels which lowers perfusion of the organs and can lead to multiple organ system failure. In time this activation of the coagulation cascade depletes the patient's ability to make clots resulting in DIC and ARDS.

The cumulative effect of this cascade is an unbalanced state, with inflammation dominant over anti-inflammation and coagulation dominant over fibrinolysis. Microvascular thrombosis, hypoperfusion, ischemia, and tissue injury result. Severe sepsis, shock, and multiple organ dysfunction may occur, leading to death.

MANAGEMENT OF SEPSIS

Sepsis and its complications are major burden on health systems, costing a lot in both financial and human resources. There are multiple causes involving all medical disciplines from cardiology to surgery. Each patient with their own disease profiles and genetic make up, respond differently to infection. This makes management a complex, multidisciplinary task which has been studied and debated over the years.

In 2002, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock. This was the beginning of the Surviving Sepsis Campaign (SSC), an international effort to increase awareness and improve outcome in severe sepsis. Simply by increasing awareness of the complexity of sepsis, the SSC and their guidelines have improved sepsis management and outcomes.

In Our Setting

The surviving sepsis guidelines were developed in Europe by European doctors and it has shown to be most effective in high income countries. The feasibility for the implementation of the guidelines has not been tested in low income countries. South Africa has a unique situation of having both high and low income country resources. Our ICUs are able to implement most of the recommendations of the SSC. The biggest obstacle in our population is access to ICU beds.
Firstly there are usually a limited number of beds available to service the entire population and secondly, there is usually a delay in getting a patient from the diagnosing centre to the ICU.

In this setting alternative management approaches have to be found. These strategies aim to stabilise the patient, improve outcomes and reduce hospital stay.

**Recognition of Sepsis**

To ensure patients are started on the correct management path, early recognition of sepsis needs to be made.

Education of health care providers from primary health care to tertiary institutes will be the first line in sepsis management. Definitions of sepsis and its complications, made in 2001 by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), make diagnosis easier.

In 2002 diagnostic criteria created for SIRS also improved diagnosis.

With the 2008 SSG, the Surviving Sepsis Campaign, created 6 goals in an attempt to reduce sepsis mortality
- Build awareness of sepsis.
- Improve early and accurate diagnosis.
- Increase the use of appropriate treatments and interventions.
- Educate HCPs about sepsis diagnosis, treatment, and management.
- Improve access to post-ICU care for sepsis patients.
- Develop global standards of care.

**Early Goal-Directed Therapy**

Survival in sepsis is very time dependent. Delays in recognition and treatment, even as short as 6 hours, affect outcomes negatively. Delayed patients had a longer median hospital LOS (7.0 days vs. 6.0 days), a higher ICU mortality (10.7% vs. 8.4%), and a higher total in-hospital mortality (17.4% vs. 12.9%). Among delayed subjects, significantly higher rates of utilization of mechanical ventilation and central venous catheterization in the ICU were observed (Donald B. Chalfin et al, 2007).

In 2001, Rivers’ early goal-directed therapy (EGDT) used CVP, serum lactate and central venous oxygen saturation (ScvO₂) targeting in the initial management of septic patients. The first surviving sepsis guidelines in 2004 advised caution on the use of rivers data because of the study design.

In the 2008 revision, EGDT had been re-introduced. Initial resuscitation targets were CVP, blood pressure, urine output and ScvO₂. Optimising haemoglobin concentration is also suggested.
For patients awaiting definitive management or transfer to a better equipped setting, these measures could be life saving. In these settings invasive devices may be limited by the resources of the facility and the skill of the practitioner.

Below is the original EGDT algorithm created by Rivers and colleagues in 2001. Mortality was lower in the EGDT protocol group compared with the standard therapy group. In addition multiple organ dysfunction scores (MODS), and some coagulation indicators (prothrombin time, concentration of fibrin-split products, d-dimer concentration) were significantly better in the EGDT group 7 to 72 hours after protocol entry.
The 2008 SSG included the EGDT goals as part of the initial resuscitation bundle

Fluid therapy
- Fluid-resuscitate using crystalloids or colloids (1B)
- Target a CVP of >8 mm Hg (>12 mm Hg if mechanically ventilated) (1C)
- Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- Give fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

Vasopressors
- Maintain MAP >65 mm Hg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

Inotropic therapy
- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)

Antibiotics

Once sepsis has been identified, definitive treatment can be initiated even at the base hospital/clinic. The early identification of septic source and pathogen can be done just from history. Identifying the most likely source of infection can point to the likely pathogen. Knowledge of local pathogens and their resistance patterns also helps in early antibiotic choice.

Obviously blood cultures and appropriate swabs must be taken prior to this. Broad spectrum antibiotics can be started first and narrowed once cultures and sensitivities are available.

Several factors must be considered when selecting empiric antimicrobial therapy:
- Patient-specific factors
  - Presumed source of infection (i.e., blood, sputum, urine, intra-abdominal)
  - Presence of co-morbid conditions (i.e., recent surgery or trauma, chronic illness)
  - Previous antibiotic administration history
• Microbiological factors
  - Identification of the most likely pathogens and their unit-specific susceptibility patterns

• Pharmacologic factors
  - Potential drug toxicity (i.e. aminoglycosides)
  - Bioavailability
  - Distribution to the site of infection

Delays in effective antimicrobial coverage are associated with a detrimental impact on patient morbidity and mortality, with an increased risk of sepsis, higher costs and increased ventilator days. Tailoring of antibiotics once cultures are available may not compensate for initial inadequate therapy.

Combination therapy does increase the likelihood of appropriate therapy for multi-drug resistant (MDR) pathogens. Therefore, initial coverage should include agents from different classes. Gram-negative coverage typically involves a β-lactam, fluoroquinolone or aminoglycoside. Quinolones demonstrate better lung penetration and less renal toxicity as compared to aminoglycosides. However, there is evidence supporting a trend towards increased survival with aminoglycoside-containing regimens.

When selecting empiric antimicrobial therapy, an assessment for risk of infection with MDR organisms must be made. Risk factors include admission following recent hospitalization or residency in a healthcare-associated facility. Additionally, patients who develop symptoms after five days of hospitalization and/or mechanical ventilation are also at risk for MDR pathogens.

Algorithm recommended by Department of Surgical Education, Orlando Regional Medical Center for Empiric Antibiotic Choice.

The Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial, which enrolled patients with suspected sepsis, sought to determine whether adequate antibiotic therapy was associated with a decreased mortality rate. The study enrolled 2634 patients, 91% of whom received adequate antibiotic therapy. The mortality rate among patients given adequate antibiotic treatment was 33%, versus 43% among patients given inadequate treatment. Adequate antibiotic was defined as the isolated organism being susceptible to the given antibiotic.
This algorithm is intended to apply to nosocomial-acquired infections. See accompanying text for discussion of community-acquired infections commonly encountered in surgical patients.

Suspect infection? No → END

Suspect pneumonia OR bacteremia? Yes

Is patient hemodynamically unstable? Yes

Piperacillin / Tazobactam AND Tobramycin AND Vancomycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin AND Vancomycin
Vancomycin AND Ciprofloxacin AND Tobramycin AND Flagyl
→ See "Candida Guidelines"

Tobramycin

Gram stain available?

Yes

2 blood cultures positive OR sputum culture positive?

Yes

Mixed Gram (+) and (-)

Piperacillin / Tazobactam AND Tobramycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Ciprofloxacin AND Tobramycin

Piperacillin / Tazobactam AND Tobramycin +/- Vancomycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin +/- Vancomycin
Ciprofloxacin AND Tobramycin +/- Vancomycin

Gram (+):

Cefazolin OR Vancomycin

Gram (-):

Piperacillin / Tazobactam AND Tobramycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Ciprofloxacin AND Tobramycin

Piperacillin / Tazobactam AND Tobramycin +/- Vancomycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Ciprofloxacin AND Tobramycin

Piperacillin / Tazobactam +/- Vancomycin
Alternative Regimens:
Clindamycin AND Ciprofloxacin +/- Vancomycin

Suspect severe intra-abdominal infection? Yes

Suspect UTI? Yes

Look for alternative etiology
2008 Surviving sepsis guidelines

**Diagnosis**
- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)
- Obtain two or more BCs
- One or more BCs should be percutaneous
- One BC from each vascular access device in place >48 hrs
- Culture other sites as clinically indicated
- Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)

**Antibiotic therapy**
- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C)
  - Consider combination therapy in *Pseudomonas* infections (2D)
  - Consider combination empiric therapy in neutropenic patients (2D)
  - Combination therapy >/= 3–5 days and de-escalation following susceptibilities (2D)
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies (1D)
- Stop antimicrobial therapy if cause is found to be non-infectious (1D)

**Source identification and control**
- A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 hrs of presentation (1D)
- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C)
- Implement source control measures as soon as possible following successful initial resuscitation (1C) (exception: infected pancreatic necrosis, where surgical intervention is best delayed) (2B)
- Choose source control measure with maximum efficacy and minimal physiologic upset (1D)
- Remove intravascular access devices if potentially infected (1C)
In 2005 A. Kumar and his team showed the timing of antibiotic treatment relative to hypotension is closely associated with survival in septic shock. Delay in antibiotic treatment results in the persistence of inflammatory/stress markers even after antibiotic treatment is initiated. The same team showed that inappropriate initial antimicrobial therapy for septic shock occurs in about 20% of patients and is associated with a five-fold reduction in survival.

Source control

At peripheral hospitals specialised surgery may not be possible. Clinical assessment and basic investigations can identify the source of sepsis. Simple source control measures can be performed at most facilities, e.g. removal of invasive lines, intercostals drains for empyemmas, cleaning of wounds and drainage of abscesses.

The selection of optimal source control methods must weigh benefits and risks of the specific intervention. Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. Specific clinical situations require consideration of available choices, patient’s preferences, and clinician's expertise.

At more specialised centres, definitive care can be carried out. The term source control is used to describe clinical interventions that endeavor to remove or neutralize (i.e., control) the source that is responsible for the development of sepsis. This intervention can be :-

* Surgical in nature, such as
  - meticulous surgical debridement of necrosed infected tissues or
  - diversion, repair, or excision of ongoing contamination from a perforated hollow viscus;

* A less invasive procedure, such as
  - removal of an infected intravascular catheter or
  - introduction of a chest tube to drain a thoracic empyema; or

* Some other minimally invasive procedure to drain infected fluid collections, such as
  - ultrasound-directed percutaneous cholecystostomy in severe acute cholecystitis,
  - CT-guided drainage of intra-abdominal abscesses, or
  - endoscopic sphincterotomy for acute suppurative cholangitis
Source control is particularly important in managing patients who have sepsis. A persistent, septic source that continuously stimulates the inflammatory reaction cascade usually will result in development of multiple organ failure syndrome. This syndrome is associated with a significantly increased morbidity and mortality. Inefficient control of the septic source is associated with a poor prognosis.

Clinical judgment is required to determine the optimal timing for the intervention to control the infection source. Benefits of the intervention should be measured against possible associated risks.

Usually, the therapeutic intervention should be performed as soon as the diagnosis has been made. A short delay may be required to correct electrolytic disturbances, serious anemia, or severe cardiovascular instability.

Many of these patients are at high surgical risk because of their severely failing general condition. Nevertheless, the surgeon should keep in mind that the patient's severe general condition is caused by the sepsis, and early and effective source control is an extremely important step in the management of these patients.

Consequently, delaying intervention with the hope that conservative management will improve the general condition of a patient who has sepsis is an error that may result in an even greater deterioration of the patient's general condition.

The most usual cause of bacteremia from S aureus among hospitalized patients is central venous catheter-related infections. Gram-negative bacteria, such as Enterobacter, Pseudomonas, Acinetobacter, and Candida species frequently are isolated in catheter-related infections.

Patients demonstrating clinical manifestations of sepsis without an obvious source of sepsis should have the central venous catheter removed, and the tip of the catheter (ie, the intravascular portion) should be sent to the laboratory to be cultured.

The diagnosis of catheter-related bacteremia should be based on isolating the same microorganism in the patient's blood and on the catheter-tip. Moreover, clinical, microbiological, and radiological examinations should exclude the presence of another septic focus.
Evaluating Intervention Results

After each attempt to control a septic source, the physician should evaluate the results of his or her therapeutic intervention. The intervention is considered successful when

* The patient’s general situation improves;
* The clinical signs and symptoms of sepsis recede;
* The wound shows signs of physiological healing with the formation of healthy granulation tissue (e.g., after surgical debridement for necrotizing fasciitis);
* The function of various organic systems that were dysfunctional or failing improves; and
* Radiological and microbiological signs indicating the control of the septic source are evident.

If there is any concern about the effectiveness and adequacy of the effort to control the septic source, the patient should undergo re-operation.

Surviving Sepsis Guidelines

Once patient is at a facility with better resources, the SSG can be better implemented. The “bundles” for patient care created by the Sepsis Campaign, aim at highlighting all their recommendations and an approach to sepsis management. A committee of specialists looked at many studies and used their own clinical experience and judgement to come up with the guidelines.

Quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria. The GRADE system is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between benefits vs.

Risks, burden, cost and, based on the preceding, development and grading of management recommendations. Keeping the rating of quality of evidence and strength of recommendation explicitly separate constitutes a crucial and defining feature of the GRADE approach.

This system classifies quality of evidence as
- high (grade A),
- moderate (grade B),
- low (grade C), or
- very low (grade D).
The GRADE system classifies recommendations as strong (grade 1) or weak (grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. A strong recommendation in favour of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients, and cost savings) will clearly outweigh the undesirable effects (harms, more burden, and greater costs).

A weak recommendation in favour of an intervention indicates that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these tradeoffs.

Randomized trials begin as high quality evidence but may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias.

Adoption of the guidelines at many institutions resulted in significant reduction in mortality of septic patients.

Some authors suggest that the biggest benefit of the SSG was to bring more awareness to sepsis management rather than its actual implementation.

After recognition of sepsis, resuscitation, antibiotics and source control, the next step is the so called “sepsis management bundle”. This is aims at reversing organ dysfunction, preventing or identifying further complications and supporting the patient until recovery.
Steroids
- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B)
- Hydrocortisone is preferred to dexamethasone (2B)
- Fludrocortisone (50 mcg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used (2C)
- Steroid therapy may be weaned once vasopressors are no longer required (2D)
  - Hydrocortisone dose should be $<=$300 mg/day (1A)
  - Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it (1D)
Recombinant human activated protein C
- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II $>=25$ or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients).
- Adult patients with severe sepsis and low risk of death (typically, APACHE II $<20$ or one organ failure) should not receive rhAPC (1A)
Other supportive therapy of severe sepsis
Blood product administration
- Give red blood cells when haemoglobin decreases to $<7.0$ g/dL ($<70$ g/L) to target a haemoglobin of 7.0–9.0 g/dL in adults (1B). A higher haemoglobin level may be required in special circumstances (e.g., myocardial ischaemia, severe hypoxemia, acute haemorrhage, cyanotic heart disease, or lactic acidosis)
- Do not use erythropoietin to treat sepsis-related anaemia. Erythropoietin may be used for other accepted reasons (1B)
- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (2D)
- Do not use antithrombin therapy (1B)
- Administer platelets when (2D)
  - Counts are $<=$5000/mm$^3$ (5 $\times 10^9$/L) regardless of bleeding
  - Counts are 5000–30,000/mm$^3$ (5–30 $\times 10^9$/L) and there is significant bleeding risk
  - Higher platelet counts (>50,000/mm$^3$ [50 $\times 10^9$/L]) are required for surgery or invasive procedures
Mechanical ventilation of sepsis-induced ALI/ARDS
- Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B)
- Target an initial upper limit plateau pressure $<30$ cm H2O. Consider chest wall compliance when assessing plateau pressure (1C)
- Allow PaCO$_2$ to increase above normal, if needed, to minimize plateau pressures and tidal volumes (1C)
- Set PEEP to avoid extensive lung collapse at end-expiration (1C)
- Consider using the prone position for ARDS patients requiring potentially injurious levels of FIO$_2$ or plateau pressure, provided they are not put at risk from positional changes (2C)
- Maintain mechanically ventilated patients in a semi recumbent position (head of the bed raised to 45°) unless contraindicated (1B), between 30°and 45° (2C)
- Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild to moderate hypoxemic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly (2B)
- SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H2O or a T piece
- Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing
- Before the SBT, patients should
  - be arousable
  - be hemodynamically stable without vasopressors
  - have no new potentially serious conditions
  - have low ventilatory and end-expiratory pressure requirement
  - require FIO$_2$ levels that can be safely delivered with a face mask or nasal cannula
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (1A)
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion (1C)
Sedation, analgesia, and neuromuscular blockade in sepsis
- Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients (1B)
- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-titrate if necessary (1B)
- Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions (1B)
Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions (1B)

**Glucose control**
- Use intravenous insulin to control hyperglycaemia in patients with severe sepsis following stabilization in the ICU (1B)
  - Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment (2C)
- Provide a glucose calorie source and monitor blood glucose values every 1–2 hrs (4 hrs when stable) in patients receiving intravenous insulin (1C)
- Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values (1B)

**Renal replacement**
- Intermittent haemodialysis and CVVH are considered equivalent (2B)
- CVVH offers easier management in hemodynamically unstable patients (2D)

**Bicarbonate therapy**
- Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion induced lactic acidemia with pH <7.15 (1B)

**Deep vein thrombosis prophylaxis**
- Use either low-dose UFH or LMWH, unless contraindicated (1A)
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A)
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C)
- In patients at very high risk, LMWH should be used rather than UFH (2C)

**Stress ulcer prophylaxis**
- Provide stress ulcer prophylaxis using H2 blocker (1A) or proton pump inhibitor (1B). Benefits of prevention of upper gastrointestinal bleed must be weighed against the potential for development of ventilator-acquired pneumonia

**Consideration for limitation of support**
- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations (1D)
Problems with Surviving Sepsis Guidelines

As noted earlier, the Surviving Sepsis Campaign is based on recommendations from European and North American sources. There has been little written or studied about its application in African and other poor nations. Even in some high income countries (HIC), implementation had been difficult. By 2007 only 18.8% of English hospitals had successfully initiated SSG (N. Sivayoham, NEJ 2007).

In low income countries, resources are extremely limited. These restrictions occur with respect to the drugs, equipment, and disposable material required to implement SSC guidelines and correspond with an alarmingly low percentage of African hospitals (1.4%) equipped to implement the entirety of SSC guidelines when compared with hospitals in high income countries (81%). Lack of trained staff is also a major obstacle. Many severe sepsis patients are likely to be treated by non-critical care specialists.

In early 2009, the World Health Organization convened a working group of external experts focused on tailoring sepsis management to address the challenges relevant to low income countries.

The group has drawn on participant expertise in low income countries and available evidence from the HIC literature to create algorithms that focus primarily on hypotension (as an indicator of septic shock) and acute respiratory distress (as an indicator of acute lung injury). Although these algorithms represent the best effort to date, they lack data from research studies conducted in low income countries. (Jacob et al. Critical Care 2011)

In 2008, A. Cheng and colleagues devised an alternative Sepsis Guideline based on the SSC guidelines. He developed these from personal experience in resource limited environments. These suggestions can very easily suit the varying conditions in our own environment.
<table>
<thead>
<tr>
<th>Issue</th>
<th>Management Where Few Resources Are Available</th>
<th>Management Where Some Resources Are Available</th>
<th>Considerable Resources Available, But Less Than in Developed Countries</th>
<th>Standard of Care in Developed Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example of setting</td>
<td>Community health station</td>
<td>Community hospital</td>
<td>Provincial hospital, middle-income countries</td>
<td>Referral centre, developed countries</td>
</tr>
<tr>
<td>Strategy</td>
<td>Early recognition and treatment of sepsis</td>
<td>Early recognition and treatment of sepsis</td>
<td>Early recognition and management of sepsis and treatment of disease</td>
<td>Early recognition and management of sepsis and treatment of disease</td>
</tr>
<tr>
<td></td>
<td>Refer to city centre with basic supportive care where possible</td>
<td>Refer to city with basic supportive care where possible</td>
<td>Refer to city with more advanced supportive care where required</td>
<td>Rapid diagnostics with advanced supportive care</td>
</tr>
<tr>
<td>Initial assessment</td>
<td>Recognition of sepsis syndrome</td>
<td>Recognition of sepsis syndrome</td>
<td>Recognition of sepsis and severe sepsis syndrome, comprehensive assessment of organ dysfunction</td>
<td>Recognition of sepsis and severe sepsis syndrome, comprehensive assessment of organ dysfunction</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td>Prompt oral (+/- parenteral) antibiotic management to cover common causes of sepsis</td>
<td>Prompt empirical antibiotic treatment to cover common causes of sepsis</td>
<td>Prompt empirical antibiotic treatment to cover common causes of sepsis</td>
<td>Prompt (within 1 hour) empirical antibiotic treatment to cover common causes of sepsis</td>
</tr>
<tr>
<td></td>
<td>Gram stain to guide antibiotic management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source control</td>
<td>Clinical assessment and referral is appropriate</td>
<td>Clinical assessment of deep focus of infection +/- drainage</td>
<td>Clinical assessment and imaging with surgical or radiologically guided drainage</td>
<td>Clinical assessment and imaging for deep focus of infection with drainage</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>Oral fluid administration</td>
<td>Fluid challenge (60-200 ml/kg) if hypotensive</td>
<td>Fluid challenge if hypotensive</td>
<td>Fluid challenge if hypotensive</td>
</tr>
<tr>
<td></td>
<td>Fluid management guided by clinical assessment of volume status</td>
<td>Fluid management guided by central venous monitoring</td>
<td>Fluid management guided by central venous monitoring and replacement</td>
<td>Fluid management guided by central venous monitoring and replacement</td>
</tr>
<tr>
<td></td>
<td>Electrolyte monitoring and replacement when possible</td>
<td></td>
<td></td>
<td>Late conservative fluid strategy if ARDS present</td>
</tr>
<tr>
<td>Vasopressors and inotropes</td>
<td>Refer if required, where possible</td>
<td>Continuous arterial pressure monitoring</td>
<td>No norepinephrine or dopamine (+/- inotropes) if central venous infusions can be administered</td>
<td>Continuous arterial pressure monitoring</td>
</tr>
<tr>
<td></td>
<td>Dopamine to maintain NAP &gt;5 mmHg after fluid challenge</td>
<td>No norepinephrine or dopamine (+/- inotropes) if central venous infusions can be administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>Supplemental oxygen where available</td>
<td>Support guided by clinical assessment and Pao2</td>
<td>Arterial blood gas monitoring</td>
<td>Arterial blood gas monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More complex ventilation strategies (PEEP, low-volume lung-protective ventilation if indicated)</td>
<td>More complex ventilation strategies (PEEP, low-volume lung-protective ventilation if indicated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-invasive ventilation</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>Sedation</td>
<td>Analgesia available</td>
<td>For ventilated patients, regular administration of sedatives with dosing according to protocol based on sedation scale</td>
<td>For ventilated patients, intermittent or continuous dosing of sedatives according to protocol based on sedation scale</td>
<td>For ventilated patients, intermittent or continuous dosing of sedatives according to protocol based on sedation scale</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>Refer if required, where possible</td>
<td>Peritoneal dialysis</td>
<td>In temporary haemodialysis or CVVH</td>
<td>Intermittent haemodialysis or CVVH if unstable</td>
</tr>
<tr>
<td>Other management recommendations</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Stress ulcer prophylaxis</td>
<td>Stress ulcer prophylaxis</td>
<td>Stress ulcer prophylaxis</td>
<td>Stress ulcer prophylaxis</td>
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<tr>
<td></td>
<td>DVT prophylaxis</td>
<td>DVT prophylaxis</td>
<td>DVT prophylaxis</td>
<td>DVT prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Basic glycaemic control (&lt;200 mg/dL)</td>
<td>Basic glycaemic control (80-200 mg/dL)</td>
<td>Basic glycaemic control (80-200 mg/dL)</td>
<td>Basic glycaemic control (80-200 mg/dL)</td>
</tr>
<tr>
<td>Other issues</td>
<td>Public awareness and prevention</td>
<td>Integration of critical care services into health system</td>
<td>Medical/specialist supervision (+/- &quot;closed&quot; intensive care model)</td>
<td>Medical/specialist supervision</td>
</tr>
<tr>
<td></td>
<td>Staffing and training</td>
<td>Basic staffing and training</td>
<td>Specialist nursing training</td>
<td>Specialist nursing training</td>
</tr>
<tr>
<td></td>
<td>Public awareness and prevention</td>
<td>Community support and education</td>
<td>&quot;Closed&quot; intensive care model</td>
<td>&quot;Closed&quot; intensive care model</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Public awareness and prevention</td>
<td>Public awareness and prevention</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; CVVH, continuous veno-venous haemofiltration; DVT, deep venous thrombosis; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; Pao2, saturation of oxygen in arterial blood flow.

doi:10.1371/journal.pmed.0259173.0001
CONCLUSION

Severe sepsis is a commonly occurring complication of many conditions. It occurs in all fields of medicine and has a complex pathophysiology. It is still, however, poorly diagnosed and managed. This has resulted in an international effort to create an easy to follow treatment plan. The Surviving Sepsis Campaign was thus formed. This is a committee of experts that develop an approach to managing sepsis. Due to constant changes in medical practices, advancement in science, new discoveries and new patient studies, the Campaign’s Guidelines are reviewed constantly.

Many limitations to the SSG do exist. They have been designed in settings where resources are abundant. The implementation of the guidelines, in their entirety, has been limited to these areas as well.

Experts have tried to create alternative management options for low income, resource limited countries.

With all these different expert opinions on management, one idea is still put through by everyone: the creation of protocol-based treatment for sepsis, results in improvement in outcomes and a reduction in cost of patient care. They also recommend the formation of protocols based on each area’s resources and local expert advice.
Box 3. Severe sepsis bundles

Sepsis resuscitation bundle: Tasks to be completed within 6 hours of presentation
1. Measure serum lactate.
2. Obtain blood cultures before antibiotic administration.
3. Administer broad-spectrum antibiotics within 3 hours from time of presentation for ED admissions and 1 hour for non-ED ICU admissions.
4. In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dL):
   a. Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent).
   b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg.
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dL):
   a. Achieve central venous pressure (CVP) ≥ 8 mm Hg.
   b. Achieve central venous oxygen saturation (ScvO₂) ≥ 70% (or SvO₂ ≥ 85%).

Sepsis management bundle: Tasks to be completed within 24 hours of presentation
1. Administer low-dose steroids for septic shock in accordance with standardized ICU policy.
2. Standardized ICU protocol.
3. Maintain glucose control greater than or equal to the lower limit of normal, but < 150 mg/dL (8.3 mmol/L).
4. Maintain inspiratory plateau pressures < 30 cm H₂O for mechanically ventilated patients.

Surviving Sepsis Guidelines – management bundles
Early goal directed targets

Table 5 Goal-directed therapy: a summary of clinical targets

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous pressure</td>
<td>8–12 mm Hg (≥ 8 mm Hg in spontaneously breathing patient, ≥ 12 mm Hg in ventilated patients)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>Between 65 and 90 mm Hg</td>
</tr>
<tr>
<td>Central venous oxygen saturation</td>
<td>≥ 70 mm Hg</td>
</tr>
<tr>
<td>Urine output</td>
<td>≥ 0.5 ml kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>≥ 30%</td>
</tr>
</tbody>
</table>
### Useful lab tests in Sepsis

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>Leukocytosis or leukopenia</td>
<td>Endotoxemia may cause early leukopenia</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Thrombocytosis or thrombocytopenia</td>
<td>High value early may be seen as acute-phase response; low platelet counts seen in overt DIC</td>
</tr>
<tr>
<td>Coagulation cascade</td>
<td>Protein C deficiency; antithrombin deficiency; elevated D-dimer level, prolonged PT and FTT</td>
<td>Abnormalities can be observed before onset of organ failure and without frank bleeding.</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>Elevated from baseline</td>
<td>Doubling-indicates acute renal injury</td>
</tr>
<tr>
<td>Lactic acid level</td>
<td>Lactic acid &gt; 4 mmol/L (36 mg/dL)</td>
<td>Indicates tissue hypoxia</td>
</tr>
<tr>
<td>Liver enzyme levels</td>
<td>Elevated alkaline phosphatase, AST, ALT, bilirubin levels</td>
<td>Indicates acute hepatocellular injury caused by hypoperfusion</td>
</tr>
<tr>
<td>Serum phosphate level</td>
<td>Hypophosphatemia</td>
<td>Inversely correlated with proinflammatory cytokine levels</td>
</tr>
<tr>
<td>C-reactive protein (CRP) level</td>
<td>Elevated</td>
<td>Acute-phase response</td>
</tr>
<tr>
<td>Procalcitonin level</td>
<td>Elevated</td>
<td>Differentiates infectious SIRS from noninfectious SIRS</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate transaminase; DIC, disseminated intravascular coagulation; PT, prothrombin time; FTT, partial thromboplastin time; SIRS, systemic inflammatory response syndrome.
APACHEII scoring for disease severity in ICU patients

**SEPSIS RESUSCITATION BUNDLE**

The goal is to perform all indicated tasks 100% of the time within the first 6 hours of identification of severe sepsis.

The tasks are:

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic, *within 3 hrs of ED admission* and *within 1 hour of non-ED admission*
4. In the event of hypotension and/or a serum lactate > 4 mmol/L
   - a. Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
   - b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L
   - a. Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
   - b. Achieve a central venous oxygen saturation (ScvO2) ≥ 70 % or mixed venous oxygen saturation (SvO2) ≥ 65 %

**SEPSIS MANAGEMENT BUNDLE**

Efforts to accomplish these goals should begin immediately, but these items may be completed within 24 hours of presentation for patients with severe sepsis or septic shock.

1. Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. *If not administered*, document why the patient did not qualify for low-dose steroids based upon the standardized protocol.
2. Administer drotrecogin alfa (activated) in accordance with a standardized ICU policy. *If not administered*, document why the patient did not qualify for drotrecogin alfa (activated).
3. Maintain glucose control ≥ 70, but < 150 mg/dl
4. Maintain a median inspiratory plateau pressure (IPP) *< 30 cm H2O* for mechanically ventilated patients

*For questions or concerns, please contact the Critical Care Fellow On-Call.*

Cooper

University Hospital
<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+4</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>+2</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>+4</td>
<td>Points</td>
</tr>
<tr>
<td>Temperature - rectal (°C)</td>
<td>≥41°</td>
<td>39 to 40.9°</td>
</tr>
<tr>
<td>Mean Arterial Pressure - mm Hg</td>
<td>≥160</td>
<td>130 to 159</td>
</tr>
<tr>
<td>Heart Rate (ventricular response)</td>
<td>≥180</td>
<td>140 to 179</td>
</tr>
<tr>
<td>Respiratory Rate (non-ventilated or ventilated)</td>
<td>≥50</td>
<td>35 to 49</td>
</tr>
<tr>
<td>Oxygenation: A-aDO2 or PaO2 (mm Hg)</td>
<td>≥500</td>
<td>350 to 499</td>
</tr>
<tr>
<td>a. FIO2 ≥0.5 record A-aDO2</td>
<td>7.6 to 7.69</td>
<td></td>
</tr>
<tr>
<td>b. FIO2 &lt;0.5 record PaO2</td>
<td>41 to 51.9</td>
<td></td>
</tr>
<tr>
<td>Arterial pH (preferred)</td>
<td>≥7.7</td>
<td>7.5 to 7.59</td>
</tr>
<tr>
<td>Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)</td>
<td>≥52</td>
<td>32 to 40.9</td>
</tr>
<tr>
<td>Serum Sodium (mEq/l)</td>
<td>≥180</td>
<td>160 to 179</td>
</tr>
<tr>
<td>Serum Potassium (mEq/l)</td>
<td>≥7</td>
<td>6 to 6.9</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>≥3.5</td>
<td>1.5 to 2.0</td>
</tr>
<tr>
<td>Double point score for acute renal failure</td>
<td></td>
<td>1.0 to 1.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≥60</td>
<td>50 to 55.9</td>
</tr>
<tr>
<td>White Blood Count (total/mm3) (in 1000s)</td>
<td>≥40</td>
<td>20 to 35.9</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS) Score = 15 minus actual GCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Total Acute Physiology Score (sum of 12 above points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Age points (years) &lt;44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Chronic Health Points (see below)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total APACHE II Score (add together the points from A+B+C)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES

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