REVIEW ARTICLE

Septic Shock - A Clinical Perspective

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Septic shock is a universally occurring serious clinical conundrum produced by micro-organisms, their toxins or both invading the blood stream of the host. Sepsis and it's sequelae-severe sepsis and septic shock are characterised by a systemic response of the host to infection mediated by endogenous mediators which may lead to a generalised inflammatory reaction in organs remote from the initial insult and eventually to end organ dysfunction and /or failure.

Sepsis [I rot-Greek] with its squelae is a potent killer worldwide with 30% of patients dying within the first month of diagnosis and 50% within 6 months. The number of sepsis is estimated to be growing by 1.5% per annum which can cause an addition of one million cases /year in USA alone by 2020, leading to an increase in total mortality and burden on health care resources. The growing use of invasive procedures, increasing number of elderly and high risk individuals with cancer and HIV, problems of hospitalisation and resistance to antibiotics contribute to the above increase in the incidence of sepsis.

Sepsis may be caused by both gram-positive and gram negative bacteria, virus or fungi and can occur as a continuum of four stages -

1) SIRS (Systemic inflammatory response syndrome) –Criteria here is the presence of two or more of the following: Body temp.>38/<36 degrees; H.R>90/min; RR>20/min or arterial PaCo2<32mm Hg ;WBC >12000/ mm3 or <4000/mm3 or immature forms >10%. Recently, revision of sepsis definitions has removed these criteria while retaining the concept as most of the trials in the last 15 years have been predicted on patients having two/ more of these.
2) Sepsis - .SIRS + a documented infection site.
3) Severe Sepsis - Sepsis + associated organ dysfunction,,.hypoperfusion abnormalities /hypotention. Hypoperfusion abnormalities include but are not limited by lactic acidosis, oliguria and acute alteration in mental status.
4) Septic shock -Sepsis induced hypotention despite fluid resuscitation + hyoperfusion abnormalities.

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PATHO-PHYSIOLOGY

Sepsis or septic shock typically begins with a nidus of infection within the body within which the organism replicates and eventually releases the mediators of shock such as complement derived anaphylotoxins, kinins, prostaglandins, leucotriens, thromboxane, platelet aggregating factor, histamine, myocardial depressant factor, tumour necrosis factor, endotoxin (lipopolysaccharide) etc. These result in a) direct myocardial effects such as depression &dilatation and b) peripheral effects like vasodilatation, vaso-constriction,, leucocyte aggregation and vascular endothelial dysfunction. Consequently maldistribution of blood,lactic acid production and increase in mixed venous o_2 occur. The end result of all this will be severe multiorgan failure, severe decrease in systemic vascular resistance, fatal myocardial depression in majority of patients. But it should be remembered that very early resuscitation can reverse cellular damage leaving bacteraemia as a secondary phase.

In recent times, the role of micro circulation and its endothelium has captured the lime light in the context of sepsis. The micro circulatory endothelium is about 4000 – 7000 m^2 (largest organ in the body). Because it is the divide between the flowing blood within and extra-celluar space beyond, the endothelium forms an interface between inflammation and coagulation. It mediates and controls exchanges between plasma and interstitial fluid; regulates the vasomotor tone by releasing vasodilating and vasoconstricting substances; maintains an anti-coagulant state and regulates transmigration of leucocytes into surrounding tissues. It also plays a central role in the regulation of microcirculatory perfusion by sensing flow, metabolic and other regulatory substances to alter arteriolar tone and capillary recruitment.

In sepsis, inflammation of microcirculation with a damaged endothelium makes the normally water tight vessels porous allowing large amounts of protein rich fluid to leak into the subcutaneous tissues with enormous tissue edema and intravenous dehydration. The derailed endothelium starts liberating procoagulant factors causing activation of the coagulation cascade leading to clogging of the micro vessels with thrombi. There is also failure of endothelium to perform its regulatory function with a severe disturbance of its nitric oxide system. The smooth muscle cells of arterioles lose their adrenergic sensitivity and tone. Increased rigidity of red cells increases blood viscocity. The endothelial glycocalyx which is a layer covering endothelium and responsible for maintainance of vascular tone, machanotransduction, transport along the vessels as well as organ blood flow and red cell velocity is said to be destroyed.

The end result of the above derangements, is arteriolar hypo-responsiveness to vasoconstrictors and vasodilators despite elevated catacholamines, reduced number of perfused capillaries and obstruction of venules by sequestered neutrophils. The shutdown of microcirculation leads to shunting of blood and oxygen to the venous side which is seen as a deficit of O_2 extraction by the tissues despite an apparently normal delivery.

The downstream global derivatives of microcirculatory dysfunction which manifest as higher lactate levels (reflecting anaerobic metabolism hence used to detect patients with normal nacrohaemodynamics with altered microcirculation), normal or higher SvO_2 (because of the shunting) and raised gastric or sublingual Pco_2 (anaerobic metabolism causing production of acids which are buffered by bicarbonate ions leading to increased CO_2 tension in tissues) are indirect measures of the same.

MANAGEMENT

Early intervention is essential for the successful treatment of septic shock. Because of an inadequate

understanding of sepsis in humans, sepsis has been described as the graveyard of pharmaceutical discovery as most drugs that appeared promising on the basis of in-vitro and animal models have proved ineffective in humans emphasising a need for resuscitation at both macro and microcirculatory levels. At present the following goal directed strategies form the mainstay of management of septic shock.

Initial Resuscitation

Organ failure is the result of inadequate oxygenation by a disturbed microcirculation and poor perfusion as well as impaired mitochondrial function leading to compromised oxygen utilization.

It should also be remembered that :

Oxygen delivery (DO_2)= Cardiac output x O_2 content

i.e. DO_2 = CO x [(O_2 Saturation x Hb Level x 1.36) + O_2 dissolved in plasma].

The cardiovascular function can be optimised by the correction of hypovolaemia and use of inotropes and vasopressors.

Correction of Hypovolemia

Hypovolaemia can be relative (vasodilatation) or absolute (abnormal capillary permeability). Fluids are the mainstay of resuscitation and may be used in the form of crystalloids or colloids.

Crystalloids Vs Colloids

Characteristics	Crystalloids	Colloids
Volume of infusion	Larger	Smaller
Duration of plasma stay	Shorter	Sustained
Hemodynamic effects	Transient	Sustained
Peripheral edema	Common	Uncommon
Pulmonary edema	Similar potential	
Intracranial pressure	May ↑	May ↓
Coagulopathy	Uncommon	Common
Cross matching	Unaffected	Impaired
Osmotic diuresis	Absent	Present
Renal function	GFR ↑	May ↓
Cost	Cheap	Expensive

The clinician has to consider different properties and side effects of available solutions and specific patient characteristics including hemodynamic stability, coagulation profile and renal function before choosing the fluid . Some fluids like hydroxy ethyl starch solutions or haemoglobin are said to have specific effects on microcirculation in septic patients but need further studies.

Fluid challenge test:

	CVP (cm of H_2O)	PCWP (mm of Hg)	Infusion
Start	< 8	< 10	200ml/10min
	8 – 12	10-14	100ml/10min
	≥12	≥14	50ml/10min
During Infusion	>5*	>7*	stop
After 10 min	≤2*	≤3*	continue
	>2 - ≤5*	>3 - ≤7*	Wait for 10 min
	>5*	>7*	stop
After waiting	Still >2*	Still>3*	Stop
	≤2*	≤ 3*	Repeat

* Rise above the baseline reading

When uncertain about the status of circulating volume, a fluid challenge test may be used by infusing a pre-determined volume of fluid and measuring the response of the filling pressure. Large changes in pressure results with small changes in volume with overfilling of ventricles due to non compliance. The aim of fluid administration is to restore normovolaemia and optimise haemaocrit with close monitoring of the patient [pulse, capillary filling,temperature. Also needed are MAP ≥ 65 mmHg,CVP ≥ 8 mmHg (≥ 12mmHg if mechanically ventilated), O_2 saturation (Cvo 2 ≥ 70%, mixed venous ≥ 65%), urine output ≥ 0.5ml / kg / hr.].

Composition of some commonly used I.V. Fluids (Crystalloids)

Sl. No.	Solution	Tonicity mosm/L	Na^+ meq/L	Cl^- meq/L	K^+ meq/L	Ca^{2+} meq/L	Mg^{2+} meq/L	Glucose g/l	Lactate meq/L	pH
1	5%Dextrose in H_2O (D_5W)	253 (Hypo*)	—	—	—	—	—	50	—	4
2	Normal Saline** (NS)	308 (Iso)	154	154	—	—	—	—	—	5

*5% D is isotonic when administered but as glucose is relatively quickly removed from blood (metabolism and intracellular shift) the effect of infusion is hypotonic. Dextrose is d-glucose.

**If osmolality is calculated by ionic dissociation, NS (0.9%) is actually hypertonic with respect to Na and especially to Cl. NaCl has a relative osmolality of 1 as compared with that of Na and Cl, the value of which is 2. Hence though referred to as being isotonic with blood in clinical context, it is a technical inaccuracy.

3	Lactated Ringers (R L)	273 (Iso)	130	109	4	3	—	—	28	6.5
4	D_5NS	560 (Hyper)	154	154	—	—	—	50	—	—

Physiochemical properties of various Colloids

Sl. No.	Colloids	Mw*	Mn•	Mw/ Mn	Colloid %	Na^+ mmol /L	Cl^- mmol /L	K^+ mmol/L	Ca^{2+} mmol/L	Citrate mmol/L	others	pH
1	Succinylated gelatin	35,000	22,600	1.5	4	154	125	0.4	0.4	-	Gelatin 40g	7.4
2	Urea linked gelatin (Haemaccel)	35,000	24,500	1.4	3.5	145	145	5.1	6.26	-	Gelatin 35g	7.4
3	Dextran - 70 in 0.9 % Nacl	70,000	39,000	1.9	6	154	154	—	—	-	dextran	4.5-5.7
4	Human albumin solution	69,000	69,000	1	4.5	varies	varies	Less than 2	—	4–10	Albumin 40-50g	7.4
5	Hydroxyethyl starch 450 / 0.7	4,50,000	70,000	6.4	6	154	154	—	—	-	Starch 60g	5.5
6	Normal plasma	-	-	-	5	135-145	97-110	3.5-5.5	2.5-2.6	-		7.35-7.45

Note: Mw* - Molecular weight (Weight average)-determines the viscosity.
Mn• - Molecular weight (Number average)-determines the oncotic pressure.

Inotropes and / or vasopressor usage

Hypotension in septic shock can occur from inadequate pump function or vasodilatation which cannot be corrected with fluid therapy alone and needs inotropes and/or vasopressors. An agent with inotropic property such as dopamine [low dose-dopaminergic β_1, $(\alpha+\beta_2)$; high dose – dopaminergic $\alpha\beta_1$ (β_2)] or dobutamine [β_1 (β_2) (α)] especially in patients with myocardial dysfunction become relevant if the patient is cool pheripherally [large core to body temperature difference] and has signs of poor organ perfusion and / or low B.P., whereas an agent like noradrenalin [α (β_1)] fits the need in a vasodilated patient with hyperdynamic circulation to raise the blood pressure. A combination of inotrope and vasopressor (dobutamine and noradrenalin) have also been used. Epinephrine [β_1 β_2 α] has not been recommended as initial vasopressor but is to be used as the alternative agent when blood pressure is poorly responsive to norepinephrine or dopamine. The so called renal dose of dopamine is no longer entertained. Vasopressin (a peptide harmone stored in post. pituitary) has received a lot of attention in recent times in the context of septic shock as the condition may have a relative deficiency of the same. Vasopressin mediates vasoconstriction via V_1 receptor

activation of vascular smooth muscle and its use is associated with a decreased need for other vasopressors. Hence it may be a useful strategy to use low dose vasopressin (0.01-0.04 U/min). As it seems act as a pure vasopressor in the context of vasodilatory shock, a decrease in cardiac output should be watched for. Further trials are said to be needed. Milrinone in low dose with it's alternate route of inotropy may be effective if catecholamine responsiveness is inadequate. Levosimendan - a newer vasoactive drug acting by Ca^{++2} sensitization in the myocardium and the opening of K_{ATP} channels in the vascular smooth muscle cells is shown to improve cardiac dysfunction and also improve tissue PO_2 in sepsis. Inotropes have to be given through central veins with direct arterial blood pressure monitoring.

Ideally, patients should have achieved the targeted intravascular volume status before the initiation of vasopressors to avoid aggravation of organ ischaemia.Use of all inotropes/vasoactive drugs is potentially dangerous and can cause dysrhythmias or myocardial ischaemia. Although specific targets are suggested, therapy for each patiet must be highly individualised and dynamic. Each agent has to be titrated to effect, carefully guided by clinical and haemodynamic monitoring to achieve optimisation of critical organ and tissue perfusion.

Diagnosis

Immediate sampling of at least two blood cultures (one drawn percutaneously and another through each vascular access device if in for > 48 hours) together with other appropriate cultures with appropriate diagnostic imaging is necessary for the identification of causative organism.

Antibiotic therapy

Broad spectrum antibiotics should be given within the first hour following recognition of sepsis, zeroing down to targeting the causative organism(s) on receipt of culture /sensitivity report. Daily assessment with the treatment lasting for 7 to 10 days (longer in case of undrainable infection foci, immunological deficiency or slow response) is necessary.

Identification and Elimination of Septic focus

After initial resuscitation, the septic nidus may be identified by suitable investigations, imaging and eliminated by appropriate surgical methods (infected pancreatic necrosis-exception).

Ventilatory strategies

Often Acute lung injury and ARDS can be the sequelae of septic shock with problems of pulmonary gas exchange. Hence it is recommended that one should use low tidal volumes (6 ml/kg), limit plateau pressure to< 30 cm H_2O with permissive hypercapnia and pressure control rather than volume control (lower peak inflation pressure for same TV)and PEEP.Oxygen should be used carefully with consideration for dosage and monitoring to prevent hypoxic tissue injury or the deleterious effects of hyperoxia. One should use a weaning protocol and a spontaneous breathing trial (SBT) regularly to judge the potential for discontinuation of mechanical ventilation.

Ventilator associated pneumonia (VAP) is a frequent complication by aspiration of regurgitation material around ETT. Following recommendations are to be considered

- Aseptic technique of suctioning
- A semi-recombent position of nursing
- Early nasogastric feed to prevent gastric mucosal damage. This is lowers risk of infection decreasing bacterial translocation and limiting systemic inflammatory response to bacterial toxins, improves survival and is cheap. Diminished bowel sounds should not prevent a trial of enteral feeding. Most patints will tolerate it if a small bowel tube is used.(Paretentaral feeding should be used only if enteral feeding is not possible despite best efforts).
- Proper cuff inflation.
- H_2 receptor antagonists and proton pump inhibitors

are recommended by some studies while another school of thought advocates avoidance of the same because of the disadvantage of bacterial overgrowth due to decreased gastric acidity leading to VAP. Sucralfate has been suggested as a cheaper alternative.

Corticosteroids

Usage is an immunomodulatory therapy which has been recommended in the physiological or low doses in vasopressor-resistant septic shock based on a landmark multi-centric,randomised,double-blind and placebo controlled trial of Ananne et.al in 2002.Corticosteroids could reduce excessive inflammatory reaction in sepsis by inhibiting the pro-inflammatory cytokine like factor- NF-kB; promoting production of anti-inflammatory cytokines such as IL-4 and IL -10; enhancing adrenergic receptor activity; increasing myocardial contractility and by inhibiting inducible nitric oxide synthetase- a vasodilator molecule along with a diminished production of PG-E and prostacycline resulting in an overall increase in blood pressure. Other postulated machanisms of corticosteroids affecting vascular tone are signal transduction, influencing Na^{++} and Ca^{++} transport, modulation of adreno-angiotensin, endothelin and mineralocorticoid receptors etc. Intravenous hydrocortisone is recommended in adult septic shock with hypotension responding poorly to fluids and vaso-pressors in a dose of 50mg IV every 6 hours (total - 200 to 300mg/day) for 7 days. Fludrocortisone(optional) has also been used-50mg orally / day for 7 days. However lowdose steriod therapy has again become controversial with the non-reproducibility of beneficial effect in a large multicentered, randomised study.

Recombinant human activated Protein C (RhAPC) - (C_{1786} H_{2779} N_{509} O_{519} S_{29M})

Normally protein-C,a vitaminK dependent protein factor synthesised in the liver, circulates in the blood as an inactive zymogen and is converted to the activated form by thrombin-thrombomodulin complex. Studies have reported lower levels of APC in septic patients, the levels having a predictive value for the outcome in these patients. Drotrecogin Alfa (activated) [Xigris] is a recombinant version of the above and was developed as the result of the realisation of the link between the coagulation system and inflammatory response.It aims at therapy to target the pivot of sepsis-the endothelium. Hailed as a breakthrough in the treatment of septic shock, it was licensed by FDA in 2001 followed by other countries worldwide. It is antithrombotic, profibrinolytic and anti-inflammatory and synergy between these qualities are said to be responsible for its clinical efffects. It is also suggested that restoration and preservation of microcirculatory blood flow prevents reperfusion injury while anti-inflammatory effects prevent organ dysfunction and failure. It has ioo% bio-availability (intravenous use only) and is inactivated by endogenous protease inhibitor.

Evidence concerning its use is based primarily on clinical trials – PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis). The drug is recommended for adult patients with sepsis induced organ dysfunction associated with clinical assessment of high risk of death, most of whom will have APACHE II ?25 or multi-organ failure if not contra-indicated. It is to be given as multiple dose infusion covering a total period of 96 hours. Dosage is calculated as per the formula:

Dose = Mg of Drotrecogin Alfa = Patient weight in kg x 24 mcg / hr x hours of infusion / 1000. In the majority of patients,the plasma levels of the drug decrease to undetectable levels within two hours after cessation of infusion.

Controversies - relate to

- Changes made to the protocol mid way through the trial PROWESS
- Risk of serious bleeding
- FDA labelling restricting use based on APACHE II scores
- High cost

Contraindications

- Active internal bleeding
- Recent (< 3 months) haemorrhage or stroke
- Recent (< 2 months) intracranial or intraspinal surgery or severe head injury
- Trauma with increased risk of life threatening bleed
- Presence of epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation
- Known hypersensitivity to rhAPC

So careful risk /benefit assessment is required before the use of the drug as also careful monitoring.

Blood Products :

Red cells to target a Hb of 7-9g/dl/ in adults should be given. A higher haemoglobin is required in special circumstances – myocardial ischaemia, severe hypoxemia, cyanotic heart disease, lactic acidosis and acute haemorrhage. Erythrocyte usage has to be guided as per the baseline haematocrit with an eye on storage time and presence or absence of residual leucocytes in the transfused product. Erythropoietin usage should only be for other accepted reasons and not for sepsis related anaemia. FFP is advocated only if there is bleeding or planned invasive procedure. Antihrombin therapy is not recommended .Platelets are to be used when counts are Ω 5000/ mm^3 regardless of bleeding, 5,000- 30,000/ mm^3 with significant bleeding risk. Higher counts > 50,000/ mm^3 are typically required for surgery or invasive procedures.

Sedation : Protocols should be set to achieve target sedation levels with break-up aimed to reduce total sedation load and reduce weaning duration. Neuromuscular blockers are to be avoided as far as possible.

Glucose protocols : Hyperglycaemia and insulin resistance is common in critically ill patients even if they have not had diabetes previously.Tight control of glucose has been found to reduce the mortality rate in studies. However, it poses several logistic problems including increased nursing time, additional blood sampling and risk of hypoglycaemia. Glucose calorie source and a validated dose protocol of insulin as necessary are to be used to maintain blood glucose level between 70 to 150mg/dl.

Renal replacement therapy : Continuous veno-venous haemofiltration or intermittent haemodialysis may be required in patients with septic shock because ionic channels in tubular epithelium of renal medulla are highly sensitive to episodes of hypotension and hypoxia leading to ARF. Indications for renal replacement therapy are

- Severe refractory hyperkalaemia
- Severe metabolic acidosis
- Decreased/absent urine output(obstructive causes to be ruled out)
- Symptomatic uraemia.

DVT prophylaxis : Is also an area of consideration and may need use of either low dose unfractionated heparin or low molecular weight heparin and / or compression stockings or intermittent compression device unless contraindicated.

Anti endotoxin strategies :

Endotoxin, the key initiator of sepsis binds to Liposaccharide binding protein (LBP) which can transfer endotoxin to lipoproteins (resulting in endotoxin inactivation). There are excess of endotoxin binding sites normally but are reduced in active illness. Experimental studies show that HDL can block the effects of endotoxin. Study with an emulsion of phospholipid which is a predominent lipid in HDL is said to lower serum endotoxin. Phase two clinical trials with the emulsion are ongoing

Apoptosis inhibition, high mobility Group B -1 protein, Poly (ADP) ribose Polymerase/ synthetase are other interesting avenues for the future.

SURVIVING SEPSIS CAMPAIGN (SSC)

S.S.C is a worldwide programme which developed as a collaboration of European Society of critical care medicine, International sepsis forum and society of critical care medicine with additional contribution from 13 other professional bodies. Surviving sepsis campaign has three phases.

Phase-1 : In 2002 a consensus was reached at the congress of ESICM among international experts for a focussed and combined action against sepsis and to reduce the related mortality by 25% over a 5 year period (Barcelona Declaration). It had a 5 point, later 6 point global action plan regarding Awareness, Diagnosis, Treatment, Education, Counselling and Referral about septic patients.

Phase-2 : Severe sepsis bundles came into existence. The bundles are a concentration of concepts and recommendations by SSC in 2004. Bundle is a group of therapies built round the best evidence based guidelines which when implemented together, produce greater benefit in terms of outcome than individual therapeutic interventions. Bundle science is the result of integration of medical science and improvement work. A sepsis bundle must fulfill the following criteria.

- Bundle is a set of 4-5 evidence based interventions and should have been accepted in clinical practice
- Investigation needs to be completed in the same time and space.
- Completion of each intervention can be determined by a Yes or No
- Completion of whole bundle can be determined by a Yes or No

It is also important to redesign delivery system to ensure that the interventions in the bundle are delivered and to measure outcomes to acertain the effects of the changes in the delivery system. Hospitals are advised two different sepsis bundles each requiring a specific time frame.

Sepsis Resuscitation Bundle

The aim here is to complete all prescribed tasks 100% within 6 hours of severe sepsis identification.

- Bundle element 1 : Measure serum lactate.
- Bundle element 2 : Obtain blood cultures prior to antibiotic administration.
- Bundle element 3 : Administer broad spectrum antibiotic intravenous as early as possible.
- Bundle element 4 : In the event of hypotension and /or serum lactate > 4 mmmol/l
  - o Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
  - o Apply vasopressor for hypotension not responding initial fluid to maintain a MAP > 65mm Hg.
- Bundle element 5 : In the event of hypotension and /or serum lactate > 4 mmmol /L
  - o Achieve a CVP of ? 8mm Hg
  - o Achieve a central venous oxygen saturation? 70% or mixed venous saturation ? 65%.

Sepsis Management Bundle

The aim here is to complete the evidence based goal within 24 hours in patients with severe sepsis, septic shock and / or lactate > 4mmol/L.

- Bundle element 1 : Adminster low dose steroid by a standard policy. If not administered, document why patients did not qualify for it.
- Bundle element 2 : Administer rhAPC as per standard ICU policy. If not given, document why the patient did not qualify for it.
- Bundle element 3 : maintain blood glucose ≥ 70, but ≤ 150mg /dl.
- Bundle element 4 : Prevent excessive inspiratory plateau pressure (IPP <30 cm H2O) for mechanically ventilated patients.

SSC has an international registry into which providers can recruit and enter patients / and monitor their institutions performance.

Phase 3 : The present phase targets the implementation of a core set of previous recommendations in hospitals environments where change in behaviour and clinical impact have been measured.The guidelines given earlier are aimed to be achieved involving not only criticare medical personnel but also the staff working outside criticare for early identification and management of these patients.

Lastly, an open mind for limitation of support with inappropriateness of continued aggressive therapy, through advanced planning encompassing discussion of likely outcomes and pragmatic goals of treatment with patients and relatives is also part of the whole programme.

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