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Alternative Therapies for Septic Shock: Beyond Early Goal-Directed Therapy

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1. Introduction

Severe sepsis and septic shock are major concerns within our health care system, accounting for 2.26 cases per 100 hospital discharges (Angus et al., 2001). The incidence of sepsis has increased by 9% each year (Martin et al., 2003), and mortality ranges from 17.9% to 70% depending on severity of disease and factors such as age, sex, ethnic origin, and comorbidities (Angus et al., 2001; Martin et al., 2003; Alberti et al., 2002). The annual economic burden of severe sepsis in the United States is $17 billion (Angus et al., 2001).
Early goal-directed therapy is a stepwise approach to treatment of severe sepsis and septic shock and includes fluid resuscitation, optimizing hemodynamic parameters, early and appropriate antibiotic administration, and source identification and control (Figure 1). The appropriate use of EGDT has shown to significantly reduce mortality, demonstrating an absolute risk reduction in mortality of 16% compared to physician-driven treatment (Rivers et al., 2001). Beyond these recommendations, there are several adjunctive therapies which

Monitoring Parameter	**Intervention**	**Goal**
Central venous pressure (CVP)	Crystalloids (i.e. normal saline, lactated ringer's) and colloids (i.e. albumin)	CVP 8-12 mm Hg
Mean arterial pressure (MAP)	Vasopressors (i.e. norepinephrine, dopamine, vasopressin)	MAP ≥65 mm Hg
Central venous oxygen saturation ($Scv0_2$)	Packed red blood cells, ionotropes (i.e. dobutamine, milrinone)	Hematocrit ≥30%, $ScvO_2$ ≥70%
Cultures	Antimicrobial Agents	Early/appropriate therapy

Adapted from the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock (Dellinger et al., 2008).

Fig. 1. Early Goal-Directed Therapy.

have been studied; their use, however, is highly dependent upon severity of illness, response to EGTD, and patient-specific characteristics. The use of these adjunctive therapies is also limited by their evidence in the literature compared to other approaches such as fluid resuscitation and early and appropriate antibiotic administration.

The goal of this chapter is to discuss alternative pharmacologic therapies for the treatment of septic shock following the initiation and optimization of EGDT. The therapies discussed in this chapter are as follows: corticosteroids, activated protein C, immunoglobulin, statins, and toll-like receptor inhibitors.

2. Pathophysiology of sepsis

The rationale for use of targeted therapies in sepsis is based on pathophysiologic processes. As discussed in other chapters, sepsis results from the complex interaction between an infecting pathogen and host responses, including inflammation, coagulation and the immune system (Russel, 2006). The immune system, which consists of mucosal defences to prevent host tissue invasion, is comprised of endogenous bacterial flora and structural barriers, an early response mounted by the innate immune system, and a delayed response via the adaptive immune system (Nduka & Parrillo, 2009). The key concept in the development and progression from infection to sepsis to severe sepsis and septic shock is the disparity between the host response and the invading organism's virulence.

3. Corticosteroids

3.1 Mechanism of action

Adrenal insufficiency is a common finding in patients with severe sepsis and septic shock (Annetta et al., 2009). Previous literature has demonstrated that elevated baseline cortisol levels or inadequate response to stimulation via a corticotropin test are associated with higher mortality (Annane et al., 2000).

Secretion of cortisol is controlled by the hypothalamic-pituitary-adrenal (HPA) axis and stimulated by fevers, pain, hypoxia, hypoglycemia and alterations in blood pressure. Stimulation of the HPA axis causes the hypothalamus to release corticotropin-releasing hormone (CRH), which in turn stimulates the pituitary to release adrenocorticotropic hormone (ACTH) (Figure 2) (Schimmer & Funder, 2011). Release of ACTH causes the zona fasciculata of the adrenal cortex to release glucocorticoids, primarily cortisol. Cortisol then inhibits further release of CRH and ACTH via a negative feedback mechanism (Annetta et al., 2009).

Glucocorticoids have various effects on the body, mediating cardiovascular, metabolic, immunologic and inflammatory systems. Glucocorticoids are required for normal reactivity to α-mediated endogenous catecholamines (i.e norepinephrine, epinephrine) and angiotensin II (Chrousos, 2009). Not only do they stimulate the production of catecholamines, but they potentiate their actions through up-regulation of α-adrenergic receptors. Glucocorticoids also lead to inhibition of nitric oxide and prostaglandin synthesis, resulting in modulation of vascular permeability (Annetta et al., 2009; Marik et al., 2008). Metabolic effects of glucocorticoids include stimulation of gluconeogenesis and glycogenolysis resulting in increased blood glucose concentrations. Glucocorticoids activate proteinolysis in muscle and inhibit protein synthesis, resulting in increased free amino acid substrate for gluconeogenesis. Hyperglycemia is beneficial in stressful states such as sepsis

due to increased energy requirements (Pilkis & Granner, 1992). Glucocorticoids inhibit osteoblasts and activate osteoclasts, resulting in bone destruction. They also decrease calcium stores through inhibition of intestinal calcium uptake and increased urinary secretion by decreasing renal reabsorption (Annetta et al., 2009). Glucocorticoids have potent anti-inflammatory and immune-modulating effects. They decrease the amount and function of several immune cells, including T and B lymphocytes, macrophages, neutrophils, eosinophils, and monocytes. They also modulate the activity and production of cytokines [i.e interleukin-1 (IL-1), IL-2, IL-6 and tumor necrosis factor alpha (TNF-α)], chemokines and other inflammatory mediators, such as histamine and bradykinin. Lastly, glucocorticoids have anti-inflammatory effects via propagation of the release of anti-inflammatory factors (IL-10, IL-1 receptor antagonist and soluble TNF receptor) (Annetta et al., 2009; Marik et al., 2008; Fahey & Guyre, 1981).

Severe illness and stress activate the HPA axis. Once activated, serum levels of cortisol-binding globulin levels fall up to 50%, resulting in a significant increase in the amount of free cortisol (Ho et al., 2006). In critically ill patients this pathway may be impaired, resulting in adrenal insufficiency. Prevalence of adrenal insufficiency in septic shock has been reported in up to 60% of patients (Annane et al., 2006). The mechanism of action of HPA axis dysfunction is poorly-understood, but may include decreased production of CRH, ACTH, cortisol, and the dysfunction of their receptors. Accord to the American College of *Critical Care Medicine* guidelines, HPA axis dysfunction in the setting of critical illness is best-described as critical illness-related corticosteroid insufficiency (CIRCI) (Marik et al., 2008).

3.2 Pharmacology

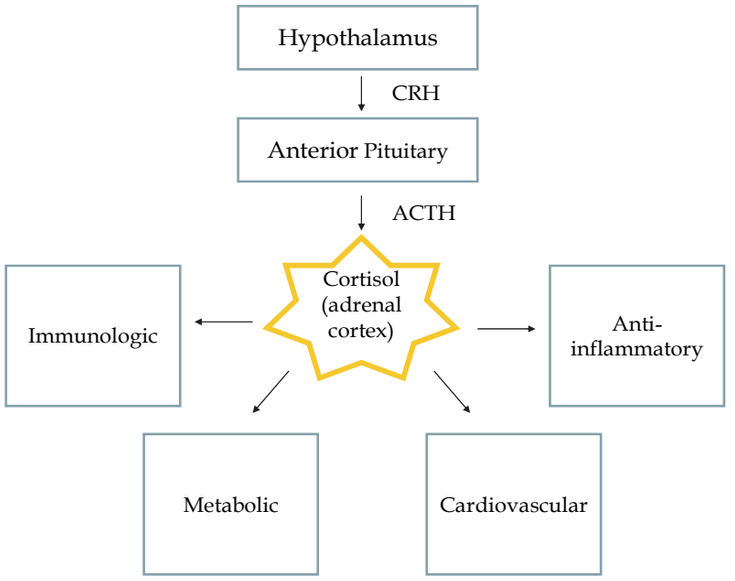
Many synthetic corticosteroids (e.g. dexamethasone, prednisone, etc.) have been developed to address pharmacological and therapeutic concerns, such as bioavailability and variable glucocorticoid and mineralocorticoid potencies (See Table 1). These agents are primarily used for their anti-inflammatory effects in disorders of various organ systems (Hydrocortisone prescribing information, 2010; Chrousos, 2008).

Hydrocortisone is the pharmaceutical product equivalent to cortisol; therefore, it is used as replacement therapy in adrenocortical deficiency states (Hydrocortisone prescribing information, 2010; Chrousos, 2008).

Hydrocortisone is available intravenously as the highly water-soluble hydrocortisone sodium succinate, which permits the immediate intravenous or intramuscular administration of high doses of hydrocortisone in a small volume of diluent. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Hydrocortisone is primarily bound to corticosteroid-binding globulin. Only 5% to 10% is unbound and biologically active. It is metabolized in the liver to inactive metabolites. Renal excretion of the administered dose is nearly complete within 12 hours (Hydrocortisone prescribing information, 2010; Schimmer, 2011).

Fludrocortisone is a synthetic corticosteroid with both glucocorticoid and mineralocorticoid activity; however, it has a much higher mineralocorticoid potency, producing marked sodium retention and increased urinary potassium excretion (Fludrocortisone prescribing information, 2009; Chrousos, 2008).

Following oral administration, 100% of fludrocortisone is detected in the serum, half of which is bound to plasma proteins. It is metabolized in the liver and excreted renally with a half-life of 3.5 hours (Fludrocortisone prescribing information, 2009).



CRH=corticotropin releasing hormone, ACTH=adrenocorticotropin hormone

Fig. 2. Corticosteroid mechanism of action.

		Relative potency to Hydrocortisone		Pharmacokinetics	
	Equivalent Glucocorticoid Dose (mg)	Glucocorticoid	Mineralocorticoid	Plasma half-life (minutes)	Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortisol)	20	1	1	90	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Mineralocorticoid					
Fludrocortisone	_	15	150	240	24-36
Aldosterone	–	0	400+	20	--
Reference: Adrenal Cortical Steroids. Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997					

Table 1. Corticosteroid Dosing and Equivalence

3.3 Clinical trials

Several clinical trials have been conducted assessing the use of steroid therapy in sepsis. In the last decade, four meta-analyses have been conducted to evaluate the benefit of corticosteroids in sepsis. The first two meta-analyses demonstrated high-dose corticosteroid use in sepsis and septic shock did not improve survival rates. (Cronin et al., 1995; Lefering & Neugebauer, 1995). The next two demonstrated long courses of low-dose corticosteroids to aid in earlier reversal of shock as well as a mortality benefit (Annane et al., 2004; Minneci et al., 2004).

The first landmark trial in recent years assessing the use of corticosteroids in septic shock was a randomized, placebo-controlled, double-blind, multicenter study assessing hydrocortisone 50 mg intravenous every 6 hours and fludrocortisone 50 μg by mouth daily for 7 days versus placebo in 300 patients with vasopressor-unresponsive septic shock (Annane et al., 2002). This study demonstrated significant shock reversal and a reduction in mortality in patients with relative adrenal insufficiency (non-responders to a corticotropin test). Adverse effects were similar between the two groups. The authors concluded that treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events (Annane et al., 2002).

The second clinical trial in recent years (the CORTICUS trial) was a randomized, placebo-controlled, double-blind, multicenter study assessing 251 patients that received hydrocortisone 50 mg intravenous every 6 hours for 5 days versus 248 patients that received placebo (Sprung et al., 2008). This study failed to show a mortality benefit with steroid therapy for patients in septic shock with relative adrenal insufficiency (non-responders to a corticotropin test). In the hydrocortisone group, shock was reversed earlier than in the placebo group; however, there were more episodes of superinfection, including new sepsis and septic shock. (Sprung et al., 2008). The external validity of this trial may be limited due to the inclusion of patients, regardless of their blood pressure response to vasopressors. This is an issue as patients with patients with blood pressures responsive to vasopressor therapy would likely not be candidates for steroid therapy.

3.4 Place in therapy

Based on the results of the aforementioned studies, there is much discord in regards to the optimal time to initiate corticosteroids for septic shock. Corticosteroids appear to reverse shock more rapidly, but effects on mortality are unclear and many adverse effects have been reported. Consensus guidelines suggest that intravenous hydrocortisone (200-300 mg daily in divided doses) be given only to adult septic shock patients unresponsive to fluid resuscitation and vasopressor therapy. The addition of oral fludrocortisone (50 μg daily) to corticosteroid therapy is considered optional if hydrocortisone is used (Dellinger et al., 2008; Marik et al., 2008).

3.5 Adverse effects

Complications associated with the use of corticosteroids are dependent upon dosage and duration of therapy. In critically ill patients, the most important adverse effects include immune suppression with an increased risk of infections (both typical and opportunistic), impaired wound healing, hyperglycemia, myopathies, hypokalemia, psychosis, HPA axis and GR suppression (Annetta et al., 2009).

4. Activated protein C

4.1 Mechanism of action

In sepsis, toxins and inflammatory cytokines (i.e. TNF-α and IL-1) cause direct activation of coagulation via up-regulation of tissue factor (TF) from monocytes and endothelial cells (Figure 3) (Bernard et al., 2001). TF leads to thrombin formation and fibrin clot. In addition inflammatory cytokines and thrombin can impair the endogenous fibrinolysis by stimulating the release of plasminogen-activator inhibitor 1 (PAI-1) from platelets and endothelial cells. PAI-1 is a potent inhibitor of tissue plasminogen activator, which lyses clots. Thrombin further potentiates the prothrombotic state when it activates thrombin-activatable fibrinolysis inhibitor (TAFI) (Toussaint & Gerlach, 2009; Dellinger, 2003; Bernard et al., 2001).

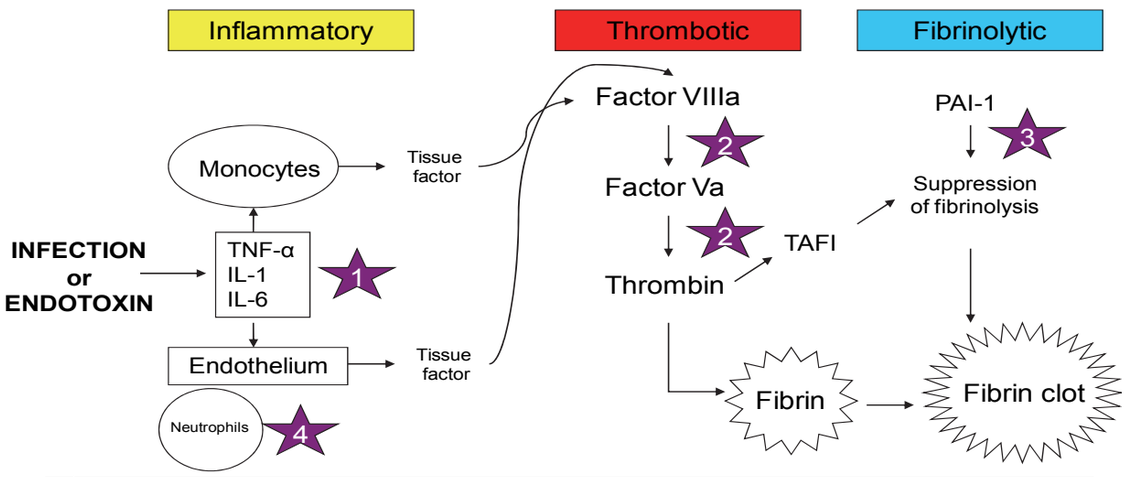


Fig. 3. Mechanisms of action of Activated Protein C

Protein C is activated when thrombin binds to thrombomodulin, which is impaired by the inflammatory response. Endothelial injury and pro-inflammatory cytokines decrease thrombomodulin levels resulting in activation of the coagulation cascade (Bernard et al., 2001). Coagulation in sepsis can lead to microvascular thrombosis, organ ischemia, multiorgan dysfunction, and death. Activated protein C is an anticoagulant and pro-fibrinolytic that exerts its effect through inactivation of clotting factors Va, VIIIa, and PAI-1, limiting the production of thrombin. A reduction in thrombin results in decreased activation of the coagulation cascade and also modulation of the systemic inflammatory response associated with sepsis (Toussaint & Gerlach, 2009; Dellinger, 2003; Bernard et al., 2001).

4.2 Pharmacology

Activated protein C is available pharmacologically as drotrecogin alfa. Following continuous intravenous administration of drotrecogin alfa at doses between 12

µg/kilograms (kg)/hour (hr) to 30 µg/kg/hr, steady state concentrations are reached within two hours. Drotrecogin alfa and endogenous activated protein C are inactivated by endogenous plasma protease inhibitors; therefore, no dosing adjustments are necessary for renal or hepatic dysfunction. The initial phase has a half-life of 13 minutes and the second phase half-life is 1.6 hours (Drotrecogin alpha prescribing information, 2008).

4.3 Clinical trials

Two major clinical trials have explored the mortality benefit of drotrecogin alfa in patients with severe sepsis and septic shock. The first, the PROWESS study, was a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 1690 patients with systemic inflammation and organ failure due to acute infection (Bernard et al., 2001). Patients received an intravenous infusion of either placebo or drotrecogin alfa at 24 µg/kg/hr for 96 hours. This study was terminated early due to an absolute reduction in mortality of 6.1% in the treatment group (P=0.005). The incidence of serious bleeding was significantly higher in the drotrecogin alfa group than in the placebo group. A limitation of this study is the inclusion of prospectively-defined subgroup analyses performed for various baseline characteristics [i.e Acute Physiology and Chronic Health Evaluation (APACHE II) score, age, sex, protein C deficiency]. Although the authors stated there were consistent treatment effects between these groups, this may be misleading as subgroup analyses, in general, lack an intent to treat group as well as have the potential for sampling bias and sample error.

In the recently –completed PROWESS-SHOCK trial, drotrecogin alpha failed to demonstrate a survival benefit. Preliminary analysis showed a 28-day all cause mortality rate of 26.4% in drotrecogin alpha group compared to 24.2% in placebo-treated patients (P=0.31). As a result, the manufacturer has announced a worldwide voluntary market withdrawal of drotrecogin alpha.

4.4 Place in therapy

Based on the results of the PROWESS trial, the Food and Drug Administration (FDA) approved drotrecogin alfa, but required a second study be conducted to evaluate its efficacy in patients with severe sepsis with a low risk of death. The ADDRESS study enrolled 2640 patients with severe sepsis and an APACHE II score <25 or single organ failure to receive the same intervention as above (Abraham et al., 2005). This trial was terminated early due to an increased risk of bleeding with no significant reduction in 28-day mortality (Abraham et al., 2005).

4.5 Adverse effects

As observed in clinical trials, bleeding is the significant adverse effect associated with administration of activated protein C (Bernard et al., 2001; Abraham et al., 2005).

5. Immunoglobulin

5.1 Mechanism of action

Intravenous immunoglobulin G (IVIG) contains IgG antibodies produced by B lymphocyte cells pooled from several thousands of blood donors. IVIG generates high

polyspecificity against bacterial, viral, parasitic and mycoplasma antigens and their toxins. It has been shown to be efficacious in various autoimmune and immunodeficiency diseases (Norrby-Teglund & Stevens, 1998). There are four subclasses of IgG (IgG1, IgG2, IgG3, and IgG4), of which IgG1 is the major component in IVIG preparations. IgA and IgM are also found in preparations of immunoglobulin; however quantities are minuscule compared to IgG. IgG1 has several functions within the immune system, including complement activation, tissue protection and virus inactivation. IgG1 also opsonizes bacteria, marking these cells for ingestion and phagocytosis (Knapp & Colburn, 1990).

Superantigens are a class of antigens that cause non-specific activation of T-cells, resulting in massive cytokine release. Patients infected with these antigens develop severe and rapidly-progressing sepsis (Ryan & Ray, 2010). Due to its ability to neutralize a broad range of superantigens and facilitate opsonization of streptococci (Norrby-Teglund & Stevens, 1998), IVIG therapy has been implicated in the treatment of septic shock secondary to group A Streptococci (GAS) infections, including necrotizing fasciitis and streptococcal toxic shock syndrome (STSS) (Darenberg et al., 2003). Both of these manifestations of GAS are severe, invasive infections with mortality rates up to 80% despite early and appropriate antimicrobial therapy (Davies et al., 1996).

5.2 Pharmacology

Immunoglobulin is available in subcutaneous and intravenous formulations. The bioavailability of subcutaneous immunoglobulin is approximately 73% compared to IVIG. After administration of IVIG (0.1–2 g/kg), serum concentrations rise, then fall rapidly in the first 1 to 7 days due to diffusion into lymph and extracellular fluid compartments (Immunoglobulin prescribing information, 2010). IVIG catabolism occurs slowly thereafter. The half-life of IgG is dependent on the half-lives of the IgG subclasses (Knapp & Colburn, 1990). There are several commercial preparations of IVIG available that contain varying amounts of IgG subclasses. Therefore, the half-life is dependent upon the product used, which report half-lives ranging between 25-48 days (Bonilla, 2008).

5.3 Clinical trials

There is a preponderance of literature available on the use of IVIG for treatment of severe sepsis and septic shock. However, many of these studies are observational in nature and limited in the number of participants and statistical power.

In order to assess the overall mortality benefit of IVIG therapy in severe sepsis and septic shock, a meta-analysis of 14 randomized controlled trials between 1988 and 2006 was conducted (Laupland et al., 2007). Most of these studies were small, ranging from 21 to 653 participants, comprised primarily of surgical intensive care unit patients with gram-negative infections. The median dose of IVIG was 0.92g/kg, with an interquartile range (IQR) from 0.75 to 1.0 g/kg, and half of the studies used preparations of IVIG that where enriched with IgA and/or IgM. Overall, there was a significant mortality benefit associated with use of IVIG in adults with sepsis. However, this effect was lost when only the high-quality studies where included in the analysis. High quality studies were considered those with adequate blinding, allocation concealment, and those that used intention-to-treat analysis. The authors concluded that further research is needed to determine the mortality benefit of IVIG in severe sepsis and septic shock (Laupland et al., 2007).

One study included in the above meta-analysis focused specifically on patients with STSS. This was a randomized, placebo-controlled, double-blind, multicenter study of 21 patients, of

whom 10 received IVIG and 11 received placebo (Darenberg et al., 2003). This study was terminated prematurely due to slow patient recruitment, which was thought to be secondary to a low incidence of STSS in the participating centers. A dose of 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3 was used. Though not statistically significant, the primary endpoint of mortality at 28 days was found to be 3.6-fold higher in placebo group (1 patient, IVIG vs. 4 patients, placebo). Patients in the treatment group also had a significant decrease in the sepsis-related organ failure assessment (SOFA) score at days 2 and 3. This study is limited by the number of patients enrolled; however it demonstrates that further research should be conducted to determine the benefit of IVIG therapy in STSS.

5.4 Place in therapy

The sepsis guidelines recommend that IVIG be used in children with sepsis and septic shock; however, there are no formal recommendation for the use of IVIG in adults. (Dellinger et al., 2008) The aforementioned meta-analysis demonstrated a mortality benefit with IVIG therapy as an adjuvant to standard of care. However, at this time further research is needed to determine which patients would benefit most from IVIG therapy. Though high quality studies are limited, there may be a mortality benefit in using IVIG in patients with STSS. The theoretical benefit of IVIG in septic patients infected with superantigen-generating pathogens is supported by one small study; however, larger, well-designed studies are needed. At present IVIG should be considered in patients with rapidly progressing sepsis due to confirmed or suspected GAS.

5.5 Adverse effects

The most common adverse reactions observed in ≥5% of the patients were headache, pyrexia, fatigue, rigors, nausea, chills, dizziness, vomiting, migraines, pain in extremities, urticaria, and cough. Hypersensitivity reactions have also been observed, so epinephrine should be readily available when administering. IVIG can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with IVIG (Immunoglobulin prescribing information, 2010).

Caution should be used in patients with acute or chronic renal failure, as over 100 cases of renal failure associated with IVIG have been reported. Patients predisposed to acute renal failure include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion feasible (Bonilla et al., 2008; Immunoglobulin prescribing information, 2010).

Aseptic meningitis has also been associated with IVIG use. There appears to be an increased risk of aseptic meningitis in patients with a history of migraines. Possible inciting factors include the IgG itself, various stabilizing products within each of the preparations, cytokine release triggered by the therapy, or cerebrovascular sensitivity (Sekul et al., 1994).

6. Statins

6.1 Mechanism of action

Statins are a class of lipid-lowering agents which inhibit the enzyme 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Traditionally, they have been indicated for primary and secondary prevention of cardiovascular disease due their effects on

reducing atherosclerosis. Endogenous cholesterol production starts from the precursor acetyl-CoA, which then is converted to hydroxymethylglutaryl-CoA (HMG-CoA). HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate in the rate-limiting step of cholesterol synthesis. Mevalonate is then converted to cholesterol through several steps. Inhibition of HMG-CoA reductase has been shown to reduce total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, triglycerides, and increase high-density lipoprotein (HDL) cholesterol (Goa et al., 2008; Terblanche et al., 2006).

Independent from their lipid-lowering effects, statins exert various pleiotropic effects. They play a role in immune modulation, resulting in attenuation of the immune response. In animal models, statins have been shown to reduce leukocyte recruitment, adherence, and transmigration in a time-dependent manner (Goa et al., 2008; Diomede et al., 2001). Statins also cause a significant reduction of leucocytes adhesion to endothelium by down-regulation endothelial cell adhesion molecules on the cell surface (Goa et al., 2008; Pruefer et al., 2002). Finally, statins affect monocyte function. In a double-blind, placebo-controlled study of 20 healthy male volunteers, simvastatin was shown to attenuate up-regulation of toll-like receptors (TLR) 2 and 4 on the surface of monocytes by more than half after a lipopolysaccharide challenge. Blocking TLR expression was associated with decreased concentrations immune cytokines, such as TNF-a and monocyte chemoattractant protein-1 (Goa et al., 2008; Niessner et al., 2006).

Statins also inhibit pro-inflammatory markers, decreasing response to activation of the inflammatory cascade. In animal studies, statins were shown to reduce exudate production of interleukin-6 (IL-6) and monocyte chemotactic proteins (Diomede et al., 2001), as well as TNF-a, IL-8 and other inflammatory mediators involved in sepsis (Grip et al., 2002). Statins, particularly atorvastatin (Goa et al., 2008), have been shown to reduce serum concentrations of C-reactive protein (CRP), which is a major acute phase reactant in humans. CRP is produced mainly in the liver in response to IL-6. Statins decrease IL-6-induced CRP production through inhibition of protein geranylgeranylation within the hepatocytes (Arnaud et al., 2005).

Statins also modulate the coagulation cascade. They reduce monocyte tissue factor (TF) expression, decrease concentrations of von Willebrand factor, increase the expression and functional activity of thrombomodulin which in turn binds to thrombin to activate protein C, reduce levels of plasminogen activator inhibitor-1 (PAI-1) and increase tissue-type plasminogen activator (tPA), and reduce platelet aggregation, and reduce conversion of prothrombin to thrombin leading to a decrease in levels of fibrinogen. (Goa et al., 2008; Steiner et al.,2005; Bickel et al., 2002; Terblanche et al., 2006; Shi et al., 2003; Bourcier & Libby, 2000).

Endothelial cell dysfunction is central to the development of sepsis. Statins prevent this by increasing expression of endothelial nitric oxide synthase (eNOS), in conjunction with down-regulation of inducible nitric oxide synthase (iNOS). eNOS is activated to produce endothelium-derived NO for controlling vasomotor activity. This decreases occurrence of hypotension and attenuates resistance to vasoactive agents in patients with septic shock (Goa et al., 2008; McGown & Brookes, 2007).

6.2 Pharmacology

There are six different pharmacologic preparations of statins, each with varying dosing and relative potency (Table 2) (Goa et al., 2008; Pharmacist's Letter, 2009). Lovastatin, pravastatin

sodium, and simvastatin are fungal-derived agents, whereas atorvastatin calcium, fluvastatin sodium and rosuvastatin are fully synthetic compounds (Goa et al., 2008). Statins are only available orally; therefore these agents cannot be administered to patients that do not have oral or enteral access for medication administration. Following absorption, statins undergo extensive first-pass extraction in the liver, thus the availability of drug in systemic circulation is variable. Most of the agents are metabolized in the liver through the cytochrome P450 (CYP 450) system; therefore, careful examination for drug interactions is warranted. Pravastatin is metabolized hepatically via sulfation; therefore, it may be considered over other agents for patients on concomitant substrates or inhibitors of CYP3A4 or CYP2C9. Statins have variable renal elimination. (Goa et al., 2008; Simvastatin prescribing information, 2011; Lovastatin prescribing information, 2010; Pravastain prescribing information, 2011).

Statins*						
Drug	Dose (mg)	Equivalent Dose (mg)	Bioavailability (%)	Protein Binding (%)	Metabolism	Half-life (hr)
Atorvastatin	10-80	20	12	98	CYP3A4	13-16
Fluvastatin	20-80	--	24	98	CYP2C9	1-3
Lovastatin	20-80	80	5	>95	CYP3A4	2-3
Pitavastain	1-4	--	80	96	UGT1A3, UGT2B7	11
Pravastatin	10-40	80	20	43-67	sulfation	2-3
Rosuvastatin	10-40	5	20	90	CYP2C9	19
Simvastain	10-80**	40	5	95-98	CYP3A4	1-3

* Goa,2008; Pharmacist's Letter, 2009
**Simvastain 80 mg is no longer recommended by the FDA unless previously maintained on this dose of > 1 year

Table 2. Statin Dosing and Equivalence

Though statins undergo hepatic metabolism, patients with renal dysfunction should exercise caution when using statins. They are also contraindicated in patients with active liver disease, including unexplained persistent elevations in hepatic transaminases (Simvastatin prescribing information, 2011).

All statins are pregnancy category X, meaning that they are contraindicated in women who are or may become pregnant. Cholesterol and cholesterol derivatives are needed for normal fetal development, and congenital abnormalities have been reported (Simvastatin prescribing information, 2011).

6.3 Clinical trials

There is much literature demonstrating the lipid-lowering properties of statins, but randomized, controlled trials examining their pleiotropic effects for treatment of severe

sepsis and septic shock are limited. Several retrospective and prospective observational studies have been conducting to explore infection-related mortality and incidence of hospitalization from sepsis in patients receiving statins. These studies have yielded mixed results (Almog et al., 2007; Gupta et al., 2007; Majumdar et al., 2006).

In order to clarify the effects of statin use in patients with sepsis, a recent meta-analysis was conducted. Twenty studies were included in the analysis, of which 18 were cohort studies, 1 matched cohort study with 2 case-control studies, and 1 randomized control trial (Janda et al., 2010). Meta-analysis for various infection-related outcomes favored use of statins for 30-day mortality, in-hospital mortality, pneumonia-related mortality, bacteremia-related mortality, sepsis-related mortality, and mixed infection-related mortality. The analysis was limited by the cohort design of the selected studies and the degree of heterogeneity among them, necessitating further randomized controlled studies (Janda et al., 2010).

One prospective, randomized, double-blind, placebo-controlled trial of 150 patients on preexisting statin therapy requiring hospitalization for infection compared atorvastatin 20 milligrams (mg) to placebo ((Kruger et al., 2011). No difference was found in progression of sepsis during hospitalization. The rate of decline of severe sepsis was similar between the groups. There was also no difference in mortality between the two groups; however, most of the study patients were not critically ill. Investigators concluded that this study does not support a beneficial role of continuing pre-existing statin therapy in patients with sepsis. Cessation of statin therapy was not associated with adverse effects secondary to rebound inflammation (Kruger et al., 2011).

6.4 Place in therapy

Currently sepsis consensus guidelines make no mention of statins as an adjunctive therapy for treatment of severe sepsis and septic shock. Conflicting data precludes a definitive recommendation for continuing pre-existing statin therapy in patients admitted with severe sepsis or septic shock. In patients with patent oral or parenteral access for medications, continuing statin therapy may be considered.

6.5 Adverse effects

Statins are safe in the majority of patients receiving them; however, in recent years attention has been drawn to their ability to cause myopathies progressing to rhabodomyolysis and liver dysfunction. These adverse effects are of particular concern in patients that develop sepsis because liver failure is a common complication of sepsis and drugs used in treating sepsis, such as steroids and neuromuscular blocking agents, can also cause myopathies (Goa et al., 2008; Pasternak et al., 2002).

Elevated liver transaminases occur in 0.5 to 2% of patients taking statins and are dose-dependent; however, progression to liver failure due to statins is very rare. Reversal of elevated transaminases frequently occurs with reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin. Cholestasis and active liver disease are contraindications to statin use, but exacerbation of liver disease by statins has not been shown (Pasternak et al., 2002).

Myopathies are characterized by non-specific muscle aches or joint pain, usually without elevations in creatinine kinase (CK). Rarely, patients on statins may develop muscle aches and pains associated with elevated CK, generally >10 times the upper limit of normal (ULN). Failure to discontinue statin therapy can lead to rhabdomyolysis, myoglobinuria,

and acute renal necrosis. In 2001, cerivastatin was withdrawn from the market due to reports of serious myopathy, including 31 reports of death from rhabdomyolysis in the United States (Pasternak et al., 2002). More recently, the Food and Drug Administration (FDA) has put out a recommendation to limit the use of simvastain 80 mg due to risk of muscle injury (FDA Consumer Health Information, 2011).

In 2002, the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute issued a clinical advisory on the use and safety of statins. It recommends that all patients initiated on a statin should have liver transaminases checked after 12 weeks of therapy, then annually. CK should be monitored at baseline, and then muscle symptoms should be evaluated 6 to 12 weeks after initiation. If symptoms are present, a CK should be obtained. This statement also highlighted patients at risk for developing myopathies, including patients >80 years, small body frame and frailty, multisystem disease, multiple medications, post-operative period, and specific concomitant medications (i.e. fibrates, azoles, macrolides, cyclosporine, protease inhibitors, verapamil and amiodarone) (Pasternak et al., 2002).

7. Toll-like receptor inhibitors

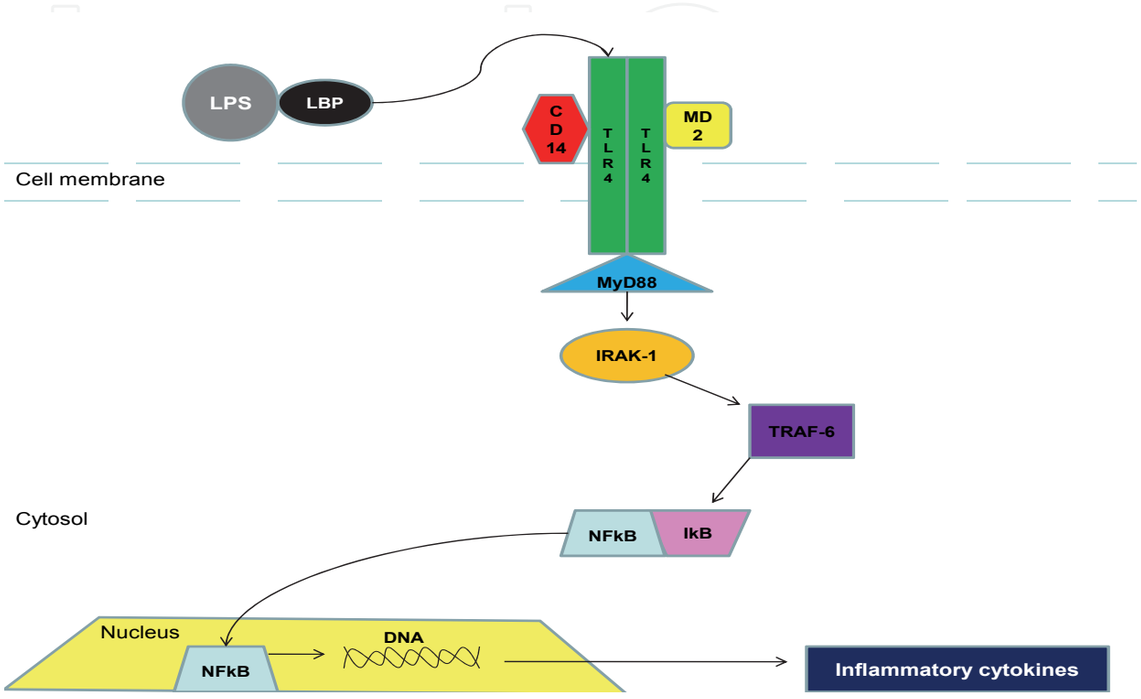
7.1 Mechanism of action

Key components of the innate immune system are pattern recognition receptors (PRRs), such as toll-like receptors (TLRs). These agents act as sentinels against damage-associated molecular pattern molecules (DAMPs), alarmins, and invading organisms carrying pathogen-associated molecular patterns (PAMPs) (Zhu & Mohan, 2010). PAMPs are a diverse set of microbial molecules which contain different recognizable biochemical features that alert the organism to intruding pathogens. Alarmins are non-infectious endogenous molecules that signal tissue and cell damage. Both alarmins and PAMPs are a subgroup of DAMPs (Bianchi, 2007). Once TLRs sense DAMPs, the innate immune response and antigen-specific adaptive immune response are activated. An intracellular cascade of signaling molecules occurs that ultimately activates the transcription factors, nuclear factor- κB (NF-κB) and interferon regulatory factors (IRFs). These transcription factors lead to expression of various inflammatory cytokines, interferons, and chemokines (Zhu & Mohan, 2010).

There are at least 10 types of TLRs that have been identified in humans. Bacterial flagellin and Toxoplasma profilin are recognized by TLR5, TLR11 and TLR12. Bacterial lipopeptides are recognized by TLR1, TLR2 and TLR6. Lipopolysaccharide (LPS), found in the outer membrane of gram-negative bacteria, and endotoxin are recognized by TLR4 (Zhu & Mohan, 2010). Pharmacologic agents targeting individual TLRs are being developed in order to prevent activation of the immune response associated with DAMP binding. Of particular interest in sepsis are TLR2 and TLR4 because expression of these PRRs is increased on monocytes in healthy volunteers undergoing an LPS challenge (Wittbole et al., 2005), and in patients with sepsis (Harter et al., 2004).

TLR4 binds with MD2, an extracellular accessory protein, which form a complex that interacts with LPS (Figure 4) (Wittebole, et al., 2010). Eritoran is a LPS antagonist that binds to the TLR4-MD-2 complex, rendering it unable to illicit the immune response. Resatorvid is another agent that inhibits TLR4 signaling by binding directly to a specific amino acid in the TLR4-intracellular domain, thus is a TRL4 antagonist (Wittebole, et al., 2010).

Other medications that are currently marketed for other indications have been found to interact with TLRs in animal studies. Agents such as chloroquine, ketamine, nicotine and statins have various immunologic properties through their interactions with TLRs (Wittebole, et al., 2010), but few studies exist to determine the clinical relevance of these interactions in humans.



LPS=Lipopolysaccharide, LBP=Lipopolysaccharide-binding protein, TLR-4=toll-like receptor 4, MD2=myb regulated gene, MyD88=myeloid differentiation primary response gene, IRAK-1=interleukin-1 receptor associated kinase, TRAF-6=TNFa receptor associated factor, IkB=inhibitory kappa B proteins, NFkB=nuclear factor kappa B, DNA=deoxyribonucleic acid

Fig. 4. Toll-like receptor 4 mechanism of action

7.2 Pharmacology

Eritoran has been studied as an intravenous infusion in a phase I study. Following administration, it has a relatively low volume of distribution and a long half-life, up to 62.7 hours. Eritoran is highly bound to lipoproteins and is cleared hepatically (Rossignol et al., 2004).

7.3 Clinical trials

Of all of the agents that have TLR-modulating properties, eritoran has been studied the most extensively. In a laboratory study, eritoran caused a dose-dependent inhibitory effect on IL-6 and TNF-α production in LPS-stimulated human monocytes from healthy volunteers (Czeslick et al., 2006). Another group of healthy volunteers were challenged with 4 ng/kg of LPS. All eritoran doses, from 50 mcg to 250 mcg, achieved statistically significant reductions in elevated temperature, heart rate, C-reactive protein levels, white

blood cell count, TNF-*a* and IL-6 levels compared to placebo. In doses >100 mcg/kg, eritoran ameliorated LPS-induced fever, chills, headache, myalgia, and tachycardia (Lynn et al., 2003).

A recent prospective, randomized, double-blind, placebo-controlled, multicenter, ascending-dose phase II trial was conducted in 293 patients who were randomized either eritoran high dose (105 mg), eritoran small dose (45 mg) or placebo. A trend towards a lower mortality rate was observed in patients at highest risk of mortality by APACHE II score quartile in the eritoran 105 mg group. A trend toward a higher mortality rate was observed in subjects in the lowest APACHE II score quartile for the eritoran 105 mg group. Number of adverse events was similar among all treatment groups (Tidswell et al., 2010).

A phase III study comparing eritoran 105 mg to placebo in patients with severe sepsis was conducted; however, due to fact that the study did not meet its primary endpoint of reduction of 28-day all-cause mortality Eisai Inc. will not submit marketing authorization applications. The pharmaceutical company will continue an analysis of the data and determine next steps.

Resatorvid was studied in a randomized, double-blind, placebo-controlled study of patients with severe sepsis and related respiratory or cardiovascular failure. Unfortunately, this study was ended prematurely due to insufficient cytokine suppression (Wittebole et al., 2010).

7.4 Place in therapy

Though eritoran and resatorvid are not currently marketed and are still under investigation for use in severe sepsis and septic shock, pharmacologic agents targeting TLR2 and TLR4 remain promising interventions.

7.5 Adverse effects

Eritoran was well tolerated in clinical trials. Anemia, diarrhea, insomnia, acute renal failure, phlebitis and rash were observed more frequently in the group receiving eritoran compared to the group receiving placebo. Serious adverse events included cardiac arrest, hepatobiliary events, multiorgan failure, sepsis, atrial fibrillation, respiratory failure and deep vein thrombosis (Tidswell et al., 2010).

8. Conclusion

Despite initiation of EGDT, severe sepsis and septic shock remain a major cause of mortality and economic burden in the United States. Each of the therapies discussed above can be considered after optimization of EGDT once the etiology and severity of sepsis is determined.

Though the use of corticosteroid remains controversial, hydrocortisone can be considered in patients that are hemodynamically unstable despite adequate fluid resuscitation and vasopressor therapy. It is unclear at this time if there is a role for IVIG in all patients with severe sepsis and septic shock. Because IVIG neutralizes superantigens and opsonizes streptococci, patients with confirmed or suspected group GAS infections may benefit from therapy. Continuation of pre-existing statin therapy can be considered in patients with severe sepsis and septic shock with intact oral or enteral access. Finally, while there are currently no available toll-like receptor inhibitors marketed in the United States,

interventions at the cellular level in sepsis are still in their infancy of investigation and present promising adjunctive therapies.

Drug	Mechanism	Dose	Adverse Effects
Corticosteroids	Metabolic, cardiovascular, immunologic and anti-inflammatory properties	Hydrocortisone 200-300 mg/day divided in 3-4 doses	Immune suppression, increased risk of infections, impaired wound healing, hyperglycemia, myopathies, hypokalemia, psychosis, HPA axis and GR suppression
Activated Protein C	Anticoagulant and pro-fibrinolytic	24 mcg/kg/hr infusions for 96 hours	Bleeding
IVIG	IgG antibodies; neutralize superantigens, opsonize streptococci	Doses vary; For STSS – 1 g/kg on day 1, 0.5 g/kg on day 2 &3	Headache, pyrexia, fatigue, rigors, nausea, chills, dizziness, vomiting, pain in extremity, urticaria, cough, hypersensitivity reactions, renal failure, aseptic meningitis
Statins	Immunologic, anti-inflammatory, and anticoagulant properties	Vary depending on agent (see table 2)	Myositis, rhabdomyolysis, elevated liver transaminases
TLR modulators	Direct or indirect TLR inihibition	Eritoran 105 mg intravenous	Anemia, diarrhea, insomnia, acute renal failure, phlebitis and rash, cardiac arrest,atrial fibrillation, respiratory failure, deep vein thrombosis

Table 3. Summary of Interventions

Sepsis is a complex physiologic process that involves activation of the inflammatory system and coagulation cascade, thereby creating multiple outlets for possible therapeutic intervention. At this time, more research is warranted to determine the most optimal therapeutic regimen based on individual patient factors, such as etiology, severity of illness and comorbid conditions.

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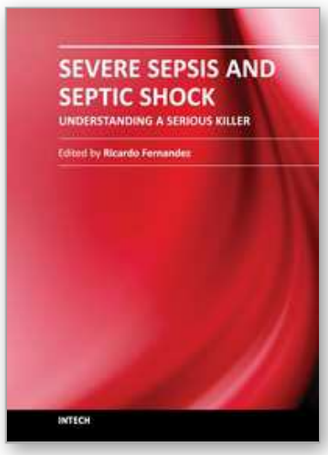

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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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