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Review Article

Endotoxic Shock: Treatment with Potential Clinical Active Agents

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Abstract

Endotoxin (lipopolysaccharide) is the component of the outer membrane of gram-negative bacteria and is released into the circulation upon disruption of the intact bacteria. Endotoxin stimulates the release of inflammatory mediators (cytokines, nitric oxide etc.) giving rise to smooth muscle relaxation, vasodilation, and increased vascular permeability.

Endotoxic shock is a consequence of severe, generalized inflammatory response induced by bloodstream infection when humans are infected with gram-negative bacteria.

Treatment methods for endotoxic shock would be more effective if treatment is started before or at the onset of endotoxemia, as many of the required mediators are released within minutes of the onset. Such treatment methods may include supportive care of the endotoxemic patient, blood purification techniques, use of endotoxin synthesis inhibitors, anti endotoxin vaccines or anti endotoxin antibodies, blocking the interaction of endotoxin with target cells, and blocking endogenous mediators generated following endotoxin interaction with target cells using variety of potential therapeutic agents.

Amongst the potential therapeutic agents, norepinephrine is the first-line therapeutic agent for initial blood pressure management in endotoxic shock.

In the present article, attempt was made to provide an insight on endotoxin and endotoxic shock, non-therapeutic ways to manage the endotoxic shock as well as a number of chemical substances investigated as potential therapeutic agents.

Keywords: *Endotoxin; Endotoxic Shock; Potential Therapeutic Agents*

Introduction

Lipopolysaccharide (LPS) is an endotoxin that is probably the most important trigger of inflammatory response in gram-negative infection [1]. It is an essential component of the cell wall of gram negative bacteria and has a highly conserved structure [2]. LPS is structurally divided into three main parts, the O-antigen, the core oligosaccharide and Lipid A. The O-antigen is the outermost structure. The Lipid A molecule is the least variable component of LPS and anchors the LPS to the cell wall. Following the degradation of the cell wall, Lipid A is released from the bacterial cell and is responsible for the toxic effects of LPS on the human body. The regulated host response to LPS, rather than the LPS intrinsic properties is considered responsible for the potentially lethal effects attributed to such an infection [3].

Stimulation of endothelial cells by LPS leads to upregulation of several adhesion molecules (E-selectin, P-selectin, intercellular adhesion molecule-1, etc.), cytokine (IFN-α, INF-γ, IL-6) and chemokine (CCL2, CCL3, CCL5).

Endothelial dysfunction accompanied by barrier disruption will lead to increased vascular permeability which is critical to the pathogenesis of multi-organ failure [4].

The innate immune response based on recognition of pathogens structures, termed pathogen-associated molecular patterns (PAMPs) is the first line of defense against infections. The binding of PAMP (such as LPS) to pattern recognition receptors (PRRs), triggers off the proinflammatory and antimicrobial response [5].

The immune system identification of lipopolysaccharide following its release from the surface of bacteria can lead to (i) alteration of innate and adaptative immune system leading to the development of immune-paralysis (ii) general vasodilation of blood vessels throughout the circulatory system, (iii) triggering off a cascade of signalling pathways, leading to the release of several cytokines and chemokines [6].

One of the most resultant effects of immune system identification is decrease in blood pressure by increasing the production of nitric oxide (NO) as a result of up-regulation of inducible nitric oxide synthase (iNOS) in endothelial and smooth muscle cells. The decrease in blood pressure implies diverting blood away from essential organs such as the brain and heart (hypoperfusion), a process that can lead to death [7].

Endotoxemia has been implicated in clinical syndromes such as: invasive gram-negative infection [8], obstructive jaundice [9], liver disease [10], hemorrhagic diarrhea [11], and heat stroke [12].

Endotoxic shock is a complex phenomenon arising from systemic release of inflammatory mediators following endotoxin interactions with target cells (inflammatory cells, platelets, and vascular endothelium).

In humans, endotoxic shock is caused primarily by endotoxins released during severe Gram-negative bacterial infections and 30 - 50% mortality rate has been reported [13,14]. It may also have potential complications (namely abnormal blood clotting, brain damage, gangrene, heart failure, kidney failure liver failure, respiratory failure, and stroke.) that can be life-threatening and occasionally fatal. Age, onset of treatment, preexisting medical conditions are some of the factors that may influence the outcome of the patient conditions.

The symptoms of endotoxic shock may include chills or shaking, clammy, or sweaty skin, confusion and disorientation, cold, diarrhea, disseminated intravascular coagulation, fast heart rate, fever, hypothermia (low body temperature), hyperventilation (rapid breathing) lactic acidosis, low blood pressure, nausea and vomiting, oliguria, organ dysfunction secondary to perfusion abnormalities, pale skin, shortness of breath [6,15].

Diagnosis may involve examination of blood and urine cultures, carrying out a chest X ray imaging to exclude developing pneumonia, abdominal computed tomographic scan or magnetic resonance imaging scan if there is suspicion for intra-abdominal process [11].

Treatment

Numerous mediators involved in the body's response to endotoxin attack, make endotoxic shock treatment complicated. Currently, endotoxic shock management may involve:

(a) Supportive care- Entails the use of large amounts of intravenous (IV) fluids to treat dehydration, assist to increase blood pressure and blood flow to the organs.

Fluid resuscitation should be managed using balanced crystalloid solutions (lactated Ringer solution, plasma-lyte) or isotonic saline to reverse hypoperfusion and shock, improve cardiac output and tissue perfusion, and achieve a net-neutral or a slightly negative fluid balance [16,17]. Balanced crystalloids are preferred over isotonic solutions. Lactate clearance, dynamic preload responsiveness, composite of physical examination findings plus peripheral perfusion are key parameters to guide resuscitation [18].

(b) Blood purification techniques- To remove LPS from systemic circulation [18].

(c) Surgery- To remove a source of infection or infected tissue [18].

(d) Anti endotoxin vaccines- Prophylactic "vaccination" against LPS has been limited because of difficulty in predicting the time for endotoxemia onset as well as adverse effects arising upon exposure to small amounts of endotoxin [19].

(e) Anti endotoxin antibodies- Type-specific antibodies are the most protective antibodies against LPS from a given bacterium [20,21].

These antibodies are utilized with the view of interfering with injury by (i) Modulating neutrophil behavior to prevent release of arachidonic acid metabolites, free radical oxygen species, and proteases, (ii) Limiting the quantity of toxic substances released by neutrophils or other cells, tissues, or organisms, (iii) Decreasing neutrophil chemoattraction and aggregation in the pulmonary capillary bed [22,23].

(f) Interference with target cells- blocking the interaction of endotoxin with target cells by decreasing plasma endotoxin concentrations, inducing tolerance (causing cells not to respond to LPS), or interfering with endotoxin binding.

(g) Potential therapeutic agents- block endogenous mediators generated following endotoxin interaction with target cells.

Such potential therapeutic agents include antihistamines, calcium channel blockers, cardio-stimulants, cyclooxygenase blockers, corticosteroids, leukotriene blockers, opiate antagonists, oxygen radical scavengers, platelet activating factor blockers, tumor necrosis factor blockers and vaso-active agents.

Vasopressors (vasoactive agents)

They assist to support the patient's blood pressure during and after fluid resuscitation. Active agents investigated are dopamine, epinephrine, norepinephrine, and vasopressin. Previously, dopamine was the initial blood pressure agent of choice in endotoxic shock however, due to higher incidences of tachyarrhythmia and worsened mortality, norepinephrine was recommended to be used as a first-line agent [24].

Although, epinephrine never revealed a mortality difference when compared with norepinephrine; however, greater tachycardia and lactic acidosis associated with it reduced the clinical interest [25]. The inotropic property of epinephrine makes the active agent beneficial for endotoxic patients with hypotension and with evidence of cardiomyopathy and associated right heart dysfunction.

Vasopressin is a non-catecholamine molecule that directly acts on vasopressin1 (V1) and 2 (V2) receptors. Vasopressin when compared with norepinephrine had shown no overall mortality benefit [26]. Exogenous angiotensin II has been found to decrease catecholamine requirements in endotoxic patients [27].

Corticosteroids

When used in combination with antibiotics, corticosteroids have been found to improve long-term survival of endotoxemic patients. The major actions of corticosteroids occur at the level of protein transcription and translation. They act by blocking the synthesis of tumor necrosis factor (TNF) [28], inducing the synthesis (or release) of a protein, (lipocortin), which is phospholipase A2 inhibitor [29]. Typical examples are dexamethasone, methylprednisolone. Furthermore, systemic steroids such as hydrocortisone, fludrocortisones have

demonstrated decreased vasopressor requirements, decreased mortality and have combated the body's dysregulated response to endotoxemia [30,31].

Antibiotics and source control

The antimicrobial therapy should be narrowed based on the results of cultures analyses [32]. Typical examples include broad-spectrum penicillins namely piperacillin, tazobactam; cephalosporins such as imipenems; and polymyxin B etc.

The source of infection should be controlled at the earliest period by changing or removing IV and urinary catheters, endotracheal tubes, draining of abscesses, surgically excising necrotic and devitalized tissues (for example gangrenous gallbladder, necrotizing soft tissue infection).

Cyclooxygenase blockers

They have been found to prevent many early cardiovascular effects of LPS and delay death in severe acute endotoxemia. Potential active agents include aspirin, indomethacin, ibuprofen, flurbiprofen, and sodium meclofenamate. Ibuprofen acts by improving hemodynamics, reversing lactic acidosis, and increasing survival rate [33,34].

Leukotriene antagonists/lipoxygenase inhibitors

These have been investigated in experimental animals induced with endotoxic shocks. Potential agents studied include FPL55712 (a leukotriene receptor antagonist), SK+F 104353 (peptidoleukotriene receptor antagonist) and diethylcarbamazine (a lipoxygenase inhibitor). They were no significant effects on survival [35].

Cyclooxygenase/lipoxygenase inhibitors

Benoxaprofen which acts as both cyclooxygenase and lipoxygenase inhibitor was observed to exhibit some degree of activity against endotoxic shock in experimental animals [36].

Oxygen radical scavengers

A number of oxygen radical scavengers namely phenyl-t-butyl-nitrone, allopurinol, reduced glutathione, superoxide dismutase, and vitamin E were investigated. Only phenyl-t-butyl-nitrone and superoxide dismutase (with or without catalase) respectively showed some degree of activity (improved survival of endotoxic shock) in experimental animals [37,38].

Opiate antagonists

They act by blocking central opiate receptors, and reverse the autonomic effects of endogenous opiates; blocking peripheral opiate receptors; altering calcium flux and the cyclic adenosine monophosphate (cAMP) system; and also have effects on the y-aminobutyric and dopaminergic neurons [39]. Typical example is naloxone which is effective in reversing endotoxin-mediated hypotension by blocking β-endorphins [40,41]. Naloxone also has demonstrated in experimental animals a number of positive effects namely, decreased pulmonary platelet trapping, improved oxygenation and cardiovascular status, increased survival time, prevent hypoglycemia and hypoglycemia [42,43].

Antihistamines

They are considered as potential active agents on the basis that histamine causes hypotension and increased vascular permeability in endotoxemia. Increased survival has been observed in endotoxic rats with various doses of cimetidine, ranitidine, diphenhydramine, and with several combinations of histamine 1 (H_1) and histamine 2 (H_2) receptor blockers [44].

Calcium channel blockers

Calcium channel blockers act by preventing intracellular calcium overload in endotoxemia. They can also improve circulatory status secondary to vasodilation and have been found to improve survival in endotoxic experimental animals. Typical examples are verapamil, nifedipine and niadipine [45,46].

Pentoxifylline

It is another active agent that holds promise for the treatment of endotoxic shock. It has diverse anti-inflammatory properties that reduce lung edema and protein leak. The agent increases survival in experimental animals with acute lung injury and septic shock. Pentoxifylline also depresses neutrophil function in an inflammatory state, decreases neutrophil superoxide production, granulation, and adherence to endothelial cells [47].

Interleukin-l receptor antagonists

The antagonists have been found to reduce mortality in patients with sepsis syndrome from 44% to 16% [48,49].

Platelet activating factor antagonists

Platelet activating factor, is a potent phospholipid generated after phospholipase activation. Its actions namely chemotaxis, myocardial depression (bradycardia, reduced cardiac output), pulmonary alterations (increased airway resistance and reduced lung compliance), systemic hypotension, and neutrophil aggregation (resulting in thrombocytopenia and neutropenia) are relevant to the pathogenesis of shock [50,51].

Specific platelet activating factor receptor antagonists such as kadsurenone, triazolodiazepine analogue (WEB2086) and FR-900452 (specific antagonist) have been reported to prevent some endotoxin-induced changes and improves survival in experimental animals [50-53].

Discussion

Specifically, deleterious effect of endotoxin (lipopolysaccharide) to the host is the production of proinflammatory cytokinesis, which initiates a cascade of events that eventually results in irreversible tissue injury and lethal hypotension. Endotoxin is a structure composed of lipids and sugar complexes. Lipid A, the biologically active component of bacterial lipopolysaccharide (LPS) is responsible for much of the morbidity associated with gram-negative infections, including vascular collapse and death [54]. As the bacteria get into the body, the body natural defense cells (namely macrophages and monocytes) recognize the bacteria as foreign. The antigens in bacteria which include the O-antigen of LPS mediate the recognition process.

The degradation of bacteria by the defense cells culminates in the release of the endotoxins located within the bacteria into the circulation and exertion of their deleterious effects [55]. Also involved, is the release of substances by body defense cells to stimulate pathways that compound the negative effects of endotoxins Generally, the complement cascade causes vasodilation and inflammation. The inflammatory response is mediated through the release of substances such as the histamine, cytokines interleukins, nitric oxide, prostaglandins, reactive oxygen species (ROS) and tumour necrosis factor alpha (TNF-α). These substances in addition to inflammation, mediate the shock response [5].

The endotoxins release also activate coagulation pathway leading to aggregation of platelets, dilatation of the blood vessels and increased leakage of the vessel walls. The depletion, along with dilatation of blood vessels and increased leakage necessitate the occurrence of hemorrhages in bacterial infection. The critical aspect of treatment involves supportive care of the endotoxemic patients. Treatment is also envisaged to entail blocking the endogenous mediators released during interaction of endotoxin with target cells with a number

of active chemical substances namely: antibiotics, antihistamines, calcium channel blockers, corticosteroids, cyclooxygenase blockers, leukotriene blockers, opiate antagonists, oxygen radical scavengers, platelet activating factor blockers, tumor necrosis factor blockers etc.

Conclusion

Endotoxin (lipopolysaccharide) constitutes the outer leaflet of the outer membrane of most gram-negative bacteria. Lipopolysaccharide is composed of hydrophilic and hydrophobic polysaccharides of which Lipid A, the hydrophobic component is responsible for the major bioactivity. Immune cells recognize lipopolysaccharide as a pathogen-associated molecule through Toll-like receptor. Most enzymes and genes related to the biosynthesis and export of lipopolysaccharide have been identified in *Escherichia coli*, and are shared by most gram negative bacteria. Finally, although current treatment involves supportive care (including aggressive fluid resuscitation), antibiotics therapy, surgical excision of infected or necrotic tissue, drainage of pus, it is envisaged that some of these potential active agents investigated in animal and clinical trials would be of clinical relevance in improving the overall survival in patients with endotoxic shock.in the near future.

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