Endotoxin in Human Disease*
Part 2: Biologic Effects and Clinical Evaluations of Anti-endotoxin Therapies

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ARDS = adult respiratory distress syndrome; BPI = bactericidal permeability-increasing protein; LPS = lipopolysaccharide; LVSWI = left ventricular stroke work index; MDF = myocardial depressant factor; PTA = polymyxin, tobramycin, amphotericin; RBF = renal blood flow; SGD = selective gut decontamination; TNF = tumor necrosis factor

In part 1 of this article, we outlined the biochemistry, assay, and possible role of endotoxin in a number of disease states. In this concluding section, the systemic and organ-specific pathophysiologic effects of endotoxin are discussed in greater detail. In the light of recent understanding of these pathophysiologic effects and their mechanisms, clinical investigation has been directed at methods of neutralizing endotoxin or attenuating various cascades initiated by endotoxin. Accordingly, a discussion of potential therapies directed against endotoxin that have undergone clinical evaluation is included.

**Systemic Effects of Endotoxin**

The most salient feature of human septic shock is hypotension in the face of a high cardiac output. In animals, endotoxin produces an initially different picture: hypotension with low cardiac output, due initially to an increase in venous capacitance. However, fluid administration in endotoxin-treated animals overcomes these effects and incompletely restores the arterial pressure; cardiac output increases above normal values. Without such fluid administration, endotoxin leads to a more rapid demise. With fluid administration, shock is forestalled but a diffuse capillary leak becomes apparent. Thus, endotoxin plus fluid in animals closely approximates the clinical appearance of septic shock. High-output hypotension results physiologically from a high venous return while dilation of resistance vessels lowers systemic vascular resistance.

In consequence, normal or abnormal hearts generally attain supernormal cardiac outputs in sepsis.

Since arterial and venous dilation are responsible for the changes noted above, one can incorrectly conclude that vasodilation is the primary vascular change in sepsis. In fact, vasoconstriction is also seen in animal models. For example, hepatic vein sphincter constriction in the endotoxin-treated dog causes mesenteric pooling of blood and contributes to falling venous return. Moreover, pulmonary vascular resistance increases early in sepsis in a variety of animals. Rat mesenteric arterioles constrict early in sepsis, and later become hyporesponsive and dilated.1 Even late in sepsis, the prevalence of hypotension does not imply that vessels are uniformly dilated, but merely that the flow resistance and capacitance vessels are dilated. Changes in distributive vessels (small arterioles and precapillary sphincters) cannot be readily assessed using hemodynamic measurements.

Sepsis causes widespread tissue dysfunction. If there is a unifying explanation for this, it must hold features that can be shared among all organs and tissues, across tissue planes and system boundaries. Two classes of hypothesis have been advanced for this: toxic explanations and distributive explanations. Toxic explanations suppose that damaging elements (for example, neutrophils, complement, cell-derived free radicals, cytokines) exert local cellular damage anywhere they can travel. Distributive explanations propose that failure of local blood flow (due, for example, to microembolization, thrombosis, or vascular dysregulation) results in deprivation of nutrients or buildup of waste products. In reality, elements from both classes of explanation may be intertwined, as in reperfusion injury damage where metabolic xanthine accumulation fuels xanthine oxidase to create damaging free radicals.2

The normal microcirculation functions to match blood flow to local oxygen demand by autoregulatory vasodilation. Interference with vasodilatory mechanisms may thus impair tissue blood flow regulation,)
resulting in local areas of hypoperfusion regardless of total blood flow. Tissue oxygen extraction ability offers one measure of the efficiency of blood flow matching; normal tissues and even whole animals can extract up to 70 percent of the delivered oxygen from arterial blood without reduction in their normal oxygen uptake. Endotoxin and experimental bacteremia have been shown to alter this balance, so that tissues become hypoxic by the time only 50 percent of the oxygen has been extracted, an extraction inefficiency that has been termed pathologic supply dependency of oxygen utilization. This oxygen extraction defect affects different tissues differently: intestinal oxygen extraction is dramatically impaired, while skeletal muscle oxygen extraction is only minimally affected. Interestingly, endotoxin ablated the normal hyperemic response to transient occlusion (often used as a rough measure of autoregulation) in the intestine but not in the muscle, suggesting a correlation between this measure of autoregulation and oxygen extraction ability.

Oxygen extraction measurements are frequently made in patients who have a pulmonary artery catheter allowing thermodilution cardiac output measurements and arteriovenous content difference measurements. Computation of oxygen delivery (cardiac output &times; arterial oxygen content) and oxygen uptake (cardiac output &times; arteriovenous oxygen content difference) is straightforward, and several investigators have noted that changes in oxygen delivery are correlated with changes in oxygen uptake. This suggests that oxygen uptake is supply-limited, despite the fact that these patients often have an oxygen extraction ratio in the 20 to 30 percent range. Unfortunately, many of these observations are confounded by the fact that a potentially error-prone variable (cardiac output) is used to compute both the oxygen uptake and delivery, so that a false statistical correlation may easily arise. The clinical relevance of these observations remains controversial and cannot be accepted as de facto evidence for or against distributive defects in sepsis. Regardless of the efficiency of oxygen extraction in sepsis, it is sensible to restore oxygen extraction to normal levels and to use organ function (mentation, urine output) to guide titration of therapies for sepsis-related hypoperfusion.

A common, in fact defining, metabolic abnormality of sepsis syndrome and septic shock is lactic acidosis, taken by many clinicians to signal anaerobic metabolism resulting from hypoperfusion of one or more tissue beds. While lactic acidosis seen under conditions of low flow shock (eg, cardiogenic shock) is almost certainly the result of anaerobic metabolism, existing data do not prove a similar pathophysiology in sepsis. Septic postoperative patients with metabolic acidosis and elevated serum lactate levels exhibit parallel elevations of serum pyruvate such that lactate:pyruvate ratios were not different from nonseptic postoperative patients. This suggested that lactic acidemia in these patients was likely related to preferential shunting of amino acids into a pyruvate-pathway rather than to anaerobic glycolysis which should increase the lactate:pyruvate ratio. In a canine model of high output hypoperfusion resulting from endotoxin infusion and volume resuscitation, Curtis and Cain studied oxygen delivery, oxygen uptake, and lactate flux of the whole body and regional circulations (isolated hind limb and gut). Regional and whole body lactate production rose significantly following development of a high output circulation. Administration of dichloroacetate, a pyruvate dehydrogenase inhibitor, normalized lactate levels without influencing oxygen delivery and uptake relations. These results suggest that lactic acidemia is not a marker for tissue hypoxia in sepsis. Even if lactic acidosis in sepsis is not a marker for anaerobic metabolism and is rather an epiphenomenon deriving from altered amino acid metabolism, it is nonetheless an important prognostic factor, since patients with high initial lactate levels which fail to correct early in the course of therapy have diminished survival.

Impaired thermoregulation is one of the defining characteristics of sepsis. Endotoxin has long been known to induce fever when injected into human volunteers. Interleukin 1, occasionally referred to as endogenous pyrogen, is believed to change the hypothalamic thermoregulation setpoint, leading to fever.

**Organ Effects of Endotoxin**

**Myocardium**

Data from both animal models and human clinical investigations suggest that systolic ventricular function is impaired following endotoxin infusion and in sepsis. Ognibene et al compared 14 critically ill patients without evidence of sepsis to 21 patients with septic shock and 21 patients with sepsis syndrome without frank shock. Following volume infusion, left ventricular stroke work index (LVSWI) increased less in septic shock than in shock of other cause. The septic patients without shock exhibited an intermediary increase in LVSWI, greater than septic patients with shock, but less than the patients without sepsis.

The following explanations have been proposed as to how sepsis impairs myocardial contractility: (1) sepsis induces generation of a myocardial depressant factor (MDF), (2) sepsis decreases intracellular calcium levels, and (3) sepsis causes myocardial ischemia. While these mechanisms are intriguing, they may be of minimal clinical significance since the circulation in these patients often maintains a high
flow state. Thus, if a component of systolic dysfunction exists, it is often reversible by infusion of catecholamines such as dobutamine, although the benefits of driving a high flow to higher levels in these patients is unproven. Patients whose ventricular dysfunction is profound and do not develop a high output state may, however, represent a subset with poor prognosis. Some data have also suggested that diastolic dysfunction may also contribute to reduced myocardial performance in sepsis.

Lungs

Acute lung injury frequently complicates sepsis, and sepsis syndrome is one of the most commonly identified antecedents to the adult respiratory distress syndrome (ARDS). In animal models, a number of physiologic abnormalities are consequent to endotoxin infusion, including increased pulmonary vascular resistance, endothelial cell injury with leak of protein-rich fluid into the lung interstitium and alveoli, and attenuation of hypoxic vasconstriction. Endotoxemia does appear to predict the development of ARDS but is neither sensitive nor specific for ARDS. Parsons et al noted that endotoxin was detected in 74 percent of patients at risk who subsequently developed ARDS and was present in 64 percent of patients with established ARDS. Only 22 percent of the at-risk population who did not develop ARDS had detectable circulating endotoxin levels. Suffredini et al recently studied 26 normal human volunteers who were injected with 4 ng/kg of purified Escherichia coli endotoxin, while hemodynamics were continuously monitored. As in prior studies, lipopolysaccharides (LPS) led to a flu-like illness with headache, malaise, nausea, fever, and myalgia. Oxygen consumption and delivery increased significantly at 3 h, while extraction fell. Cardiac output rose, and PaO₂ dropped in saline solution-resuscitated subjects. Lung scans performed at 3 h suggested that increased pulmonary capillary permeability caused the hypoxemia.

Kidney

Renal failure is a common complication of septic shock. In a large recent series, 81 of 200 gram-negative bacteremic patients developed renal failure. The most frequent injury described is acute tubular necrosis. Possible etiologies of tubular injury during the course of sepsis include hypovolemia in the early phases of the syndrome, alterations in intrarenal blood flow, or direct effects from the humoral cascade triggered by endotoxin. A number of animal studies have demonstrated reductions in renal blood flow (RBF) following endotoxin infusion or induction of infection, however RBF remains the same or increases in similar models if hypovolemia is avoided.

Lucas et al studied 61 septic patients and found mild reductions in glomerular filtration rate despite increased RBF. The fraction of the cardiac output perfusing the kidneys in septic patients exceeded expected norms. Urine volume remained high as did urinary sodium. Cessation of volume infusion led to increased urinary concentrations and reduced urinary sodium values suggesting intact tubular function. These data suggest that much of the renal dysfunction seen in endotoxemia results from the functional hypovolemia accompanying the early capillary leak and altered vascular responses of this syndrome.

Brain

The effects of endotoxin or endotoxin-mediated cascades on the brain remain poorly studied. As for renal function, separation of hemodynamically-mediated from toxic effects is likely important. Data obtained in several animal models suggest that endotoxin infusion results in increased permeability of the blood brain barrier. Several studies have shown reductions in cerebral blood flow in animal models of endotoxic shock, though the contribution of hypovolemia is not well defined. There is some suggestion that hyperperfusion of the central nervous system may be disproportionate to the observed hypotension. The pathologic correlates of endotoxic shock in animal models include periventricular leukomalacia, cerebral white matter changes, and multiple diffuse infarcts.

In humans, data are equally scant. Roughly, 30 percent of patients with gram-negative shock will have a prominent encephalopathy. Some have suggested this relates to abnormalities of amino acid metabolism and/or enhanced penetration of amino acids into the central nervous system, disturbing the normal balance of neurotransmission. While an interesting hypothesis, available data do not permit partitioning of cause between metabolic abnormalities, hemodynamic changes, or other consequences of sepsis in explaining the frequently observed abnormalities of cortical function in these patients.

Gastrointestinal Tract

One important function of the gastrointestinal tract is to serve as a barrier to luminal gut flora and endotoxin, and to the extent that these gut contents enter the portal circulation, to clear them without ill effect. Aberrations in gut permeability and in hepatic clearance have been noted in endotoxemia. The mechanism(s) of endotoxin-mediated increases in gut permeability have remained controversial, though most data have suggested a reduction in mesenteric blood flow, perhaps coupled to increased metabolic demand results in loss of gut barrier function.
Increased gut permeability could result in an increased delivery of endotoxin to hepatic reticuloendothelial cells. In processing endotoxin, these cells produce tumor necrosis factor (TNF) and thus, set into motion the cascade previously described. Accordingly, the gastrointestinal tract, via increases in intestinal permeability coupled to diminished hepatic clearance, may be pivotal in the development of endotoxemia and humoral cascades that lead to multiple systemic and specific organ dysfunctions.66-71

Therapies Designed to Block the Effects of Endotoxin

Antibiotics, surgical drainage of infected collections, and supportive care are the mainstays of treatment for sepsis and related endotoxemia. Nevertheless, these therapies prove insufficient in many cases, and so investigations have focused on direct intervention in the excessive host responses characterizing sepsis. One therapeutic strategy is to suppress host responses by blocking cytokine release or action (eg, IL1 receptor antagonists or steroids), or by inhibiting downstream mediators (eg, ibuprofen or nitroprigiline). Among the above examples, steroids confer no benefit in treating sepsis, and the others remain open to question. A second approach is to reduce endotoxin levels or endotoxin activity directly.

Polymyxin

Polymyxin, a cyclic polypeptide antibiotic, has antimicrobial activity against a broad variety of gram-negative pathogens but is also known to bind endotoxin.72 The latter effect enables polymyxin to prevent many of the humoral and pathophysiologic effects delineated above,73,74 and polymyxin pretreatment has been shown to attenuate septic hemodynamics and reduce mortality in animal models.75,76 However, neutrocytic and nephrotoxicity of parenteral polymyxin preclude its general clinical use. Nonetheless, low doses of polymyxin B have been given to a few burned patients; although there was a suggestion of improvement, the patient number was too small to determine significance.79 A potentially less toxic polymyxin B nonapeptide has been developed but has yet to be tested in human subjects.80

Pheresis

Plasmapheresis has been investigated as a means to reduce levels of endotoxin or subsequently released mediators. By passing the plasma over specialized columns, such as polymyxin-sepharose, one might selectively deplete endotoxin from blood. Cohen et al81 reported that plasmapheresis recovered 94 percent of injected LPS from blood of endotoxin-treated rats, and that such therapy protected the rats from leukopenia, thrombocytopenia, and death. Similarly, Nasawa et al82 reported that hemofiltration with a polymyxin-impregnated fiber improved survival in dogs with gram-negative bacteremia.

Plasmapheresis with specialized column exchange has not been reported in human subjects, although conventional plasmapheresis has been used. In an uncontrolled study, Bjorvatn et al83 reported four meningococccemic patients who underwent plasma/leukopheresis; all four survived, an improvement when compared to historic control subjects at their institution. Plasmapheresis has been reported to decrease endotoxin levels in septic patients.84 These results are intriguing but too limited to support pheresis for clinical use outside research protocols.

Bactericidal Permeability-Increasing Protein

When neutrophils are activated during infection, they display a variety of binding proteins on their surface which facilitate binding of a microbe and its subsequent phagocytosis, including bactericidal permeability-increasing protein (BPI). First isolated from neutrophil azurophilic granules in 1978,85 BPI has a molecular structure similar to lipopolysaccharide-binding protein (LBP) and a molecular weight of 50 to 60 kd. The BPI binds to the surface of bacteria, altering membrane permeability and killing the bacteria.86 This protein also binds to the lipid A domain of endotoxin, and attenuates TNF release.87 The gene for BPI has recently been cloned,88 and this naturally occurring protein may have direct clinical utility.

Anti-endotoxin Antibodies

Optimaly, antibodies against endotoxin would bind and inactivate endotoxins from many bacterial species, using conserved portions of lipopolysaccharide as the immunogen. Also, immunotherapy directed at endotoxin would be effective only if initiated before organ damage has progressed to a point of self-perpetuation or irreversibility. Unfortunately, meeting these theoretical requirements is not always practical. Interpretation of the published human trials should be conducted with this standard in mind (Table 1).89-95

After demonstrating benefit from passive immunization with antiserum to LPS in animal models,96,97 Ziegler et al91 randomized 212 gram-negative bacteremic patients to receive routine medical therapy with or without antiserum to J-5 E coli LPS. Of 109 patients with gram-negative bacteremia in the control group, 42 died. Only 23 of 103 patients in the J-5 antiserum group died. The improvement in mortality was greater in those subjects with shock (77 percent mortality in control subjects, 44 percent in the treatment group).

In 1985, Baumgartner et al92 prospectively randomized 262 patients with sepsis to receive J-5 antiserum or routine medical management. Only 2 of 16 patients in the J-5 group who developed Gram-negative bacte-
remia died, whereas 9 of 23 in the control group died. These differences reached statistical significance (p<0.05), but no difference was noted in the remaining patients who did not have gram-negative bacteremia.

In 1988, a third study\textsuperscript{45} compared purified J-5 IgG versus pooled immunoglobulin in septic shock patients. Mortality in both patient groups was the same (50 percent). Unfortunately, no control group was included in this study.

These early studies suggesting clinical efficacy of antibody therapy were followed by the development and evaluation of monoclonal antibodies to endotoxin. HA-1A (Centoxin) is a human monoclonal IgM that was designed to bind the lipid A domain of endotoxin. This antibody was developed using the lipid A portion of J-5 E. coli and was engineered in a stable heteromyeloma cell line. E-5 (Xomen) is a monoclonal IgM produced in murine ascites using J-5 E. coli LPS as the immunogen.

After animal studies of HA-1A suggested efficacy\textsuperscript{86,90} and preliminary human studies showed an adequate safety profile,\textsuperscript{100,101} a large multicenter trial was undertaken in human subjects. Ziegler et al\textsuperscript{42} studied 543 patients with septic shock randomized to receive HA-1A or best medical therapy. No difference in outcome was found between groups. Of the randomized patients, 200 had positive blood cultures for gram-negative bacteria. Of these 200, 95 received placebo, 105 received HA-1A. The two groups were similar with regard to severity of disease (APACHE score) and underlying chronic disease processes. Overall, 45 of 93 placebo-treated patients followed to discharge survived. Of 103 followed to discharge in the HA-1A treated group, 65 survived. This difference in mortality was statistically significant. Warren et al\textsuperscript{102} have offered the following criticisms of this study.

1. Even though treatment and placebo groups had similar APACHE scores, other measures of severity of illness not included in APACHE scoring were more prevalent in the placebo-treated group (disseminated intravascular coagulation, renal failure, hepatic failure, respiratory failure, polymicrobial sepsis).

2. More patients in the placebo group received inappropriate antibiotics, and when these patients were excluded from analysis, there was no difference between HA-1A-treated and placebo-treated patients.

3. At sites with overall high mortality from sepsis, treatment with HA-1A appeared to have a greater effect than at low mortality sites.

4. Benefit from HA-1A was clear only in the gram-negative bacteremic individuals \textit{with} shock, and not in those \textit{without} shock. The mortality is greater in septic shock and thus a larger patient sample might be required to show significance in sepsis without shock.

5. Four patients in the placebo-treated group died unrelated to sepsis. However, the FDA had agreed to analyze death from all causes rather than those resulting from complications of sepsis.

6. This study was not designed to examine a subgroup such as patients with gram-negative bacteremia but rather the efficacy of therapy in all patients meeting entrance criteria. Accordingly, the retrospective definition of subgroups demonstrating significant differences in outcome was scientifically flawed.

In addition to these issues, the binding characteristics of HA-1A have been called into question.\textsuperscript{103-106} Moreover, animal studies have either failed to show benefit from HA-1A\textsuperscript{103-104} or have shown increased mortality.\textsuperscript{107} For these reasons, HA-1A has not been FDA approved. Another large human trial is underway, enrolling patients with septic shock of presumed gram-negative source.

After preliminary safety studies,\textsuperscript{108,109} Greenman et al\textsuperscript{26} studied 486 patients with sepsis randomized to receive placebo or E-5. A total of 316 of these patients subsequently had blood or body fluid cultures positive for gram-negative bacteria. No difference in mortality was found between all patients entered in the study, nor in the patients with shock and gram-negative infection. Only the subset with gram-negative sepsis without shock benefited from treatment with E-5. In follow-up to this initial study,\textsuperscript{96} 847 patients receiving E-5 were reported; in this larger group there was no survival benefit demonstrated in any patient group. However, multiple system organ failure may have been attenuated in treated patients.\textsuperscript{110}

Evaluation of these two monoclonal antibodies rep-

### Table 1 - Therapeutic Trials of Anti-endotoxin Antibody

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Treatment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaffin and Lachman</td>
<td>PNR</td>
<td>22</td>
<td>Pooled IgG</td>
<td>19/22 clinically improved, 3 died</td>
</tr>
<tr>
<td>Schedel et al*</td>
<td>PRC</td>
<td>55</td>
<td>Pooled IgG</td>
<td>Improved survival in septic shock</td>
</tr>
<tr>
<td>Ziegler et al*</td>
<td>PRC</td>
<td>304</td>
<td>J-5</td>
<td>Improved survival in GNR bacteremia</td>
</tr>
<tr>
<td>Baumgartner et al*</td>
<td>PRC</td>
<td>262</td>
<td>J-5</td>
<td>Reduced shock in GNR bacteremia</td>
</tr>
<tr>
<td>Calandra et al*</td>
<td>PRC</td>
<td>100</td>
<td>J-5 IgG</td>
<td>No difference vs pooled IgG</td>
</tr>
<tr>
<td>Ziegler et al*</td>
<td>PRC</td>
<td>543</td>
<td>HA-1A</td>
<td>Improved survival in GNR bacteremia</td>
</tr>
<tr>
<td>Greenman et al*</td>
<td>PRC</td>
<td>486</td>
<td>E-5</td>
<td>Improved survival in GNR sepsis without shock</td>
</tr>
<tr>
<td>Wenzel et al*</td>
<td>PRC</td>
<td>847</td>
<td>E-5</td>
<td>No difference</td>
</tr>
</tbody>
</table>

PNR = prospective non-randomized; PRC = prospective controlled; GNR = Gram-negative rod.
resents the most comprehensive studies in sepsis. Both failed to demonstrate a reduction in mortality for the entry cohort of patients with septic syndrome or septic shock. Since clinicians currently have no way of predicting which patients with septic syndrome on admission will subsequently be proven to have gram-negative bacteremia, and these were the only patients who might benefit from these antibodies, it is not clear how to identify potential candidates for this therapy. A clinically useful endotoxin assay might aid in selecting patients, although patients without systemically detectable endotoxemia may still derive benefit. More than 400,000 patients develop sepsis each year (30 to 40 percent related to gram-negative bacteremia). At a projected price of over $3,000 per dose, if all septic patients were given antibody with the intent of helping the subgroup with gram-negative bacteremia that might benefit, the health care budget would increase by over $1.2 billion. This would underwrite a therapy that would prevent death in at most 4 percent of those treated. Therefore, the promise of these new therapies is attended by problematic questions of drug efficacy, timely patient identification, and cost-benefit ratio.

Selective Gut Decontamination

Since the bowel serves as a reservoir for gram-negative organisms and endotoxin, it is tenable that antimicrobials could be used to diminish gut burden and hence delivery of bacteria and their products to the circulation. Stoutenbeek and van Saene recently reviewed the data regarding selective gut decontamination (SGD). He performed a meta-analysis of six European studies in which critically ill patients received enteral polymyxin, tobramycin, and amphotericin (PTA). These studies utilized historic control subjects or concurrent treatment designs. Two of these showed reductions in mortality when compared to historic control subjects. All showed dramatic reductions in colonization and secondary respiratory infections in treated subjects. Stoutenbeek et al had also shown decreases in secondary infection and late mortality in trauma patients treated with PTA. The infection, but not the mortality, results were confirmed by the above and subsequent studies.

Blair et al prospectively randomized 331 critically ill patients to receive either PTA and 4 days of cefotaxime or standard therapy. Of the 126 patients in the PTA group, 21 developed secondary infection, whereas 40 of 131 in the control group developed secondary infection. Respiratory infection was the most common cause of excess infections in the non-treated group. Respiratory colonization decreased in treated patients, whereas fecal colony counts were not affected. No difference in mortality or hospital stay was shown between groups.

In the largest study to date, Gastinne et al prospectively randomized 445 critically ill mechanically ventilated, non-trauma patients to receive colistin/tobramycin/amphotericin or placebo paste applied to the oropharynx and administered via nasogastric tube. There was no difference in the rate of mortality, secondary pneumonias, or multiple organ failures. These investigators concluded that the excessive cost of this modality outweighed the potential benefits.

The efficacy of SGD in critical illness is unproved at this time. Indeed, these studies suggest that any benefits derived from SGD may relate to the prevention of oropharyngeal colonization and the subsequent development of pneumonia rather than to an effect on the lower gastrointestinal tract. This speculation is supported by other investigations that have described a reduction in colonization rates and nosocomial pneumonia in patients treated with a paste applied to the oropharynx.

Enteral Nutrition

Increased gut bacterial burden, increased gut permeability, and diminished hepatic clearance of endotoxin are likely common in critical illness, and they may conspire to produce endotoxemia. Accordingly, a number of investigators have questioned whether enteral feeding improves gut contents and integrity. Studies in animal models have suggested that gut villous atrophy occurs in animals that are deprived of enteral nutrition and that atrophy may correlate with increased permeability. Specifically, Alverdy et al found more bacterial translocation from the gut to the portal circulation in parenterally fed than in enterally fed rats. Moore et al randomized 75 patients with abdominal trauma to receive enteral or parenteral nutrition. Albumin and transferrin levels significantly increased in the enteral group and decreased in the parenterally fed group. The parenterally fed group also had statistically more abdominal abscesses and pneumonia when compared to the enterally-fed group. No differences in mortality were noted. Herndon et al also suggested a beneficial effect of enteral versus parenteral feedings in critically ill human subjects.

These data suggest but do not prove that enteral feeding attenuates the course of critical illness when compared to parenteral nutrition. The role of endotoxin translocation is unclear. Nevertheless, enteral nutrition is well-tolerated by critically ill patients, and it may limit complications of critical illness—perhaps by reducing gut permeability to endotoxin.

Conclusions

Abundant in vitro and in vivo observations suggest that endotoxin contributes to human disease. Gram-negative sepsis, liver disease, burns, and bowel dis-
Endotoxin in Human Disease, Part 2 (Manthous, Hall, Samsel)

Diseases are common clinical scenarios in which endotoxin likely plays a pathogenic role. Conceptually, therapy with antibodies against endotoxin seems well founded, yet clinical results are disappointing. Serious questions remain. Do the antibodies reliably bind LPS and attenuate host mediator response? Does LPS binding turn off mediator cascades, and if so, is there some critical point in time after which the cascades will proceed without endotoxin? Does the immune system respond to LPS? Furthermore, we do not know which patients (and which diseases) will benefit from such therapy, and how do we select them?

As we have come to realize that many diseases derive from deleterious host responses, we have taken the first steps at interrupting these mechanisms. Insofar as these early efforts will afford a greater understanding of the pathogenesis of such diseases, such advances may lead to clinical applications that will amend our armamentarium against disease. Thus, an understanding of the role of endotoxin in human disease promotes a familiarity with this potential frontier.

REFERENCES

20 Bryce-Smith R, Coles DB, Cooper KE, Cranston WI, Goodale F. The effects of intravenous pyrogen upon the radiant heat induced vasodilatation in man. J Physiol 1959; 145:77-84
35 Meyrick B, Brigham KL. Acute effects of E. coli endotoxin on the pulmonary microcirculation of anesthetized sheep: structure-function relationships. Lab Invest 1983; 48:438-70
36 Snell JS, Ramsey LH. Pulmonary edema as a result of endotoxemia. Am J Physiol 1969; 217:170-75
40 Parsons PE, Worthen GS, Moore EE, Tate RN, Henson PM. The association of circulating endotoxin with the development of the adult respiratory distress syndrome. Am Rev Respir Dis 1989; 140:294-301
67 Bulkley GB, Kvietys PR, Parks DA, Perry MA, Granger DN. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. Gastroenterology 1985; 89:552-57
71 Fink MP. Why the GI tract is pivotal in trauma, sepsis and MOF. J Crit Illness 1991; 6:253-76
72 Morrison DC, Jacobs DM. Binding of polymyxin B to the lipid A portion of bacterial lipooligosaccharides. Immunochim 1976; 13:813-18
75 Corrigan JJ, Kiernan JF. Effect of polymyxin B sulfate on


77 Hughes B, Madan BR, Paratt JB. Polymyxin B sulphate protects cats against the haemodynamic and metabolic effects of E coli endotoxin. Br J Pharmacol 1981; 74:701-07

78 From AHL, Fong JSC, Good RA. Polymyxin B sulfate modification of bacterial endotoxin: effects on the development of endotoxin shock in dogs. Infect Immun 1979; 23:660-64


97 Braude AI, Douglas H, Davis CE. Treatment and prevention of intravascular coagulation with antiserm to endotoxin. J Infect Dis 1973; 128 Suppl:S157-64


105 Heumann D, Baumgartner JD, Jacot-Guillarmod H, Glauser MP. Antibodies to core lipopolysaccharide determinants: absence of cross-reactivity with heterologous lipopolysaccharides. J Infect Dis 1991; 163:762


107 Quezado ZMN, Natsone C, Banks SM. A human IgM monoclonal antibody (Mab) against endotoxin (HA-1A) decreased survival in a canine model of gram-negative bacterial septic shock. Clin Res 1991; 40:286A


111 Stoutenbeek CP, van Saene HKF. Infection prevention in
113 Ledingham MeAI, Alcock SR, Eastaway AT, McDonald JC, McKay IC, Ramsay G. Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime, and microbial surveillance for prevention of acquired infection in intensive care. Lancet 1988; 1:785-90
118 Stoutenbeek CP, Zandstra DF, van Saene HKF. The impact of an integrated trauma service on the late mortality from multiple organ failure and sepsis in severely injured patients. In: Infection prevention in multiple trauma patients by selective decontamination of the digestive tract (SDD) [Thesis]. University Groningen, 1987; 69-85
129 Moore FA, Moore EE, Jones TN, McCroskey BL, Petersen VM. TEN versus TPN following major abdominal trauma-reduced septic morbidity. J Trauma 1989; 29:916-23