Biliverdin protects against polymicrobial sepsis by modulating inflammatory mediators

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The annual frequency of sepsis currently exceeds three quarters of a million cases, with an overall hospital mortality rate of ~30% (1, 3). Because severe sepsis is primarily a disease of the elderly, the occurrence of sepsis is predicted to increase as the nation ages. Various animal models of sepsis exist, but the cecal ligation and puncture (CLP) model is recognized to most closely mimic, both qualitatively and quantitatively, the clinical observations associated with polymicrobial peritonitis, bacteremia, and sepsis (16, 54). Just as in the clinical situation, death of the animal in the CLP model is caused by both the direct effects of the bacteria themselves and an overwhelming systemic inflammatory response to the polymicrobial pathogens (3).

The gastrointestinal tract plays a central role in sepsis, not only because it harbors various pathogens that actually outnumber the body’s own cells but also because it is a major target of invading bacteria. We have previously shown that the intestinal muscularis externa is an immunologically active tissue that dynamically participates in the secretion of numerous pro-inflammatory mediators in response to endotoxin (14, 15, 22). Furthermore, sepsis causes severe ileus, which compounds the intestinal inflammatory response and furthers the systemic release of luminal bacteria.

In recent years, it has become evident that the inflammatory response is followed by a counterregulatory anti-inflammatory reaction, which is intended to limit the destruction of “innocent bystander” cells to unbridled inflammation and bring the system back into homeostasis. Senescent erythrocytes, which have finished their 120-day mission of oxygen delivery, and various cytosolic proteins are abundant heme sources for macrophages (48). The catalysis of heme occurs through induction of the rate-limiting enzyme heme oxygenase (HO)-1, which results in the release of iron and the generation of biliverdin and carbon monoxide (CO) (34). In addition, HO-1 is highly regulated by stress and injury (53) in many organ systems, including the intestinal muscularis (37). Although an evergrowing body of literature demonstrates that HO-1 and CO have potent antioxidant, antiapoptotic, and anti-inflammatory properties (41, 44, 52), biliverdin and its reduction product, bilirubin, have traditionally been viewed solely as toxic waste products of heme catalysis. However, this view changed dramatically when biliverdin/bilirubin were found to potent antioxidants (40, 43, 50). The effectiveness of this HO-1 end product has been demonstrated in numerous inflammatory models [inflammatory bowel disease, intestinal ischemia-reperfusion, allogeneic transplantation, and acetaminophen-induced hepatotoxicity (8, 9, 19, 43)]. However, a potential beneficial effect of biliverdin/bilirubin in sepsis has not previously been investigated.

Because HO-1 induction has been shown to be protective to various cell types in the context of exogenous lipopolysaccharide (LPS) administration (6, 18, 38), we hypothesized that HO-1 exerts its anti-inflammatory and cytoprotective effects in part through the generation of biliverdin and its cyclic reduction into bilirubin by biliverdin reductase. With the use of the clinically relevant CLP model of polymicrobial sepsis, we...
examined the capacity of biliverdin treatment to blunt sepsis-induced intestinal dysmotility and muscularis leukocyte invasion and to determine its effects on muscularis pro- and anti-inflammatory molecular responses.

**MATERIALS AND METHODS**

**Animals.** Sprague-Dawley male rats (280–320 g) were purchased from Harlan Sprague Dawley (Indianapolis, IN) and maintained in a pathogen-free animal facility at the University of Pittsburgh with standard rat chow and tap water supplied ad libitum. They were allowed to acclimate at least 5 days before experimental manipulation. The University of Pittsburgh Institutional Animal Care and Use Committee approved the protocol.

Rats were anesthetized with a continuous isoflurane inhalation. Animals underwent aseptic midline laparotomy; the incision was removed, placed on sterile gauze outside of the abdominal cavity, kept wet with saline, partially ligated using a 4-0 silk tie, and punctured once with a 21-gauge needle, as previously described (16, 54). Rats were studied for molecular changes after 3 h and for functional motility alterations 24 h after CLP (n = 6 each). Age-matched sham controls underwent laparotomy without CLP and are referred to as controls.

**Biliverdin treatment.** Biliverdin (Frontier Scientific; Logan, UT) was dissolved in 0.1 N NaOH and adjusted to a final pH of 7.4 with HCl. After a dilution in PBS, 5 mg/kg biliverdin was injected intraperitoneally 8, 6, and 3 h before laparotomy, again just before closure of the laparotomy, and then 15 h postoperatively for motility studies. Sham control animals were given appropriate saline volumes at the same time points intraperitoneally.

**In vivo transit.** Gastrointestinal transit was measured in controls, biliverdin-treated controls, untreated CLP animals, and biliverdin-treated CLP animals 24 h postoperatively by evaluating the panenteric distribution of fluorescein-labeled dextran (molecular weight = 70,000) as previously described (25). For statistical analyses, the geometric center (GC) was calculated for the median distribution of labeled dextran along the gastrointestinal tract (35).

**Circular muscle contractility.** Twenty-four hours after CLP, animals were anesthetized with isoflurane and killed. The abdominal wound was reopened, and midjejunal circular smooth muscle strips were prepared (1 × 10 mm) and suspended in standard horizontal mechanical organ bath chambers that were continuously perfused with 37°C preoxygenated Krebs-Ringer bicarbonate buffer (KRB). In the organ chamber, each strip was allowed to equilibrate for 1 h. Strips were then incrementally stretched to the length at which maximal spontaneous contractile activity occurred (L₀). Dose-response curves were generated by exposing the strips to increasing concentrations of the muscarinic agonist Bethanechol (0.3–300 μmol/l) for 10 min with intervening 10-min wash periods. Contractile activity was calculated as grams per square millimeter per second by converting density, weight, and length of the strip to the cross-sectional area of the tissue.

**Leukocytic infiltration.** Segments of the small bowel were immersed in KRB in a Sylgard-lined petri dish, opened along the mesenteric border, and stretched to 150% of the length and 250% of the width. The mucosa and submucosa were removed, and the muscularis was fixed in 100% ethanol for 10 min. After being washed with KRB, the tissue was treated with Hanker-Yates reagent (Sigma; St. Louis, MO) for detection of polymorphonuclear neutrophils (PMNs) exhibiting myeloperoxidase (MPO) activity. Tissues were mounted on glass slides using Gel/Mount (Biomedia; Foster City, CA), coverslipped, and inspected by light microscopy (Nikon FXA; Huntley, IL) at a magnification of ×200. Numbers of PMNs exibiting MPO activity infiltrating the muscularis externa were determined from the mean counts collected from five optical fields.

**SYBR green real-time RT-PCR.** The time course of CLP-induced alterations in mRNA expression was analyzed using SYBR green two-step real-time RT-PCR (PE Applied Biosystems; Foster City, CA). Total mRNA extraction was performed as previously described using the guanidinium-thiocyanate phenol-chloroform extraction method (14). RNA pellets were resuspended in RNAse-free resuspension solution (Ambion; Austin, TX). After resuspension, DNase treatment was carried out (DNA-free reagent, Ambion), and equal aliquots (20 μg) of total RNA from each sample, quantified by spectrophotometry, were processed for cDNA synthesis.

Primers were designed according to published sequences or using Primer Express software (PE Applied Biosystems) (55, 57) and purchased from Life Technologies (Rockville, MD). GAPDH was used as an endogenous control. Sequences of the real-time PCR primers are listed in Table 1. The efficiency and equality of the real-time PCR primer pairs were determined by amplifying serial dilutions of muscularis cDNA. For each target gene, different MgCl₂ (2–5 μmol/l) concentrations were tested to optimize the PCR amplification. Agarose gel electrophoretic analysis was used to verify the presence of a single product and to ensure that the amplified product corresponded to the size predicted for the amplicon. Each sample was estimated in triplicate. The PCR mixture was prepared using SYBR green PCR Core Reagents (PE Applied Biosystems). PCR conditions on the ABI PRISM 7000 Sequence Detection System (PE Applied Biosystems) were as recommended by the manufacturer (see the User Guide, PE Applied Biosystems). Relative quantification was performed using the comparative cycle threshold method as described previously by Schmittgen et al. (47).

**NF-κB EMSA.** EMSA was performed using whole tissue extracts from the experimental groups as described above. Binding reactions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer Sequence</th>
<th>Source (Genbank Sequence or Citation)</th>
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</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>Forward: 5′-GCCCTCTGAGAAGACGCTGTA-3′</td>
<td>M26744</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Reverse: 5′-GAGCCGAGATCGCGATTAAT-3′</td>
<td>M57441</td>
</tr>
<tr>
<td>iNOS</td>
<td>Forward: 5′-GGGAGACCTTTTTCGACAC-3′</td>
<td>NM_012611</td>
</tr>
<tr>
<td>COX-2</td>
<td>Reverse: 5′-CCATGGCATATTTTGACCTG-3′</td>
<td>AF233596</td>
</tr>
<tr>
<td>IL-10</td>
<td>Forward: 5′-GGCAAGCTTTCGCGGAA-3′</td>
<td>Harness et al. (21)</td>
</tr>
<tr>
<td>HO-1</td>
<td>Reverse: 5′-CCATGCCCTACAAAGCGCT-3′</td>
<td>Yoshida et al. (56)</td>
</tr>
<tr>
<td>GAPDH</td>
<td>Forward: 5′-GCTCTGAGAAGATGTGAT-3′</td>
<td>NM_017008</td>
</tr>
</tbody>
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IL, interleukin; MCP, monocyte chemo attractant protein; iNOS, inducible nitric oxide synthase; HO, heme oxygenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.
were performed using 20 μg of extracted protein and radiolabeled DNA-binding elements. Levels of activated NF-kB were determined using the duplex oligonucleotide based on the NF-kB binding site upstream of the murine inducible nitric oxide (NO) synthase (iNOS) promoter (5). EMSA was performed on a 4% polyacrylamide gel as previously described (4). The level of transcription factor activation was quantitated using PhosphoImager analysis of gel shift band intensities.

Total antioxidant potential. The total antioxidant potential of the isolated muscularis externa was determined using a commercially available kit (TA-01 from Oxford Biomedical Research; Oxford, MI). The method colorimetrically measures the amount of Cu²⁺ derived from Cu²⁺ by the action of all antioxidant moieties in a sample. The Cu²⁺ that is produced by the reaction complexes with bathocuprine to form a stable compound that is proportional to the concentration of all antioxidants in the sample. The muscularis externa was stripped and immediately frozen from saline- and biliverdin (5 mg/kg)-pretreated animals with intraperitoneal injections 11, 8, 6, and 3 h before death. The injection schedule was designed to determine the muscularis antioxidant potential at a time point that coincided with the 3-h time point after CLP at which cytokine mRNA measurements were determined. The method colorimetrically measures the amount of Cu²⁺ derived from Cu²⁺ by the action of all antioxidant moieties in a sample. The Cu²⁺ that is produced by the reaction complexes with bathocuprine to form a stable compound that is proportional to the concentration of all antioxidants in the sample. The muscularis externa was stripped and immediately frozen from saline- and biliverdin (5 mg/kg)-pretreated animals with intraperitoneal injections 11, 8, 6, and 3 h before death. The injection schedule was designed to determine the muscularis antioxidant potential at a time point that coincided with the 3-h time point after CLP at which cytokine mRNA measurements were determined.

**RESULTS**

Gastrointestinal transit. We and others have shown that exogenous endotoxin and endogenous bacterial-induced sepsis by CLP alters gastrointestinal motility. The aim of the first series of experiments was to determine the potential beneficial effects of the HO-1 end-product biliverdin on preventing sepsis-induced ileus. Therefore, we measured in vivo gastrointestinal transit 90 min after oral fluorescein-labeled dextran administration in controls, sham surgery controls, biliverdin-treated sham surgery controls, untreated saline-injected CLP septic animals, and biliverdin-treated septic animals. Twenty-four hours after CLP-induced sepsis, transit measurements demonstrated a significant delay in the distribution of the nonabsorbable fluorescein-labeled dextran along the gastrointestinal tract (Fig. 1). The average transit GC for septic animals was calculated to be 5.9 ± 0.9 with a considerable amount of dextran retained in the stomach. In contrast, the fluorescein marker reached the terminal ileum in control and sham-operated animals as reflected by the GCs of 8.8 ± 0.2 and 8.9 ± 1.2. Biliverdin treatment of control animals had no significant effect on transit (GC = 9.1 ± 0.1). Treatment with biliverdin of the CLP animals prevented sepsis-induced ileus and improved gastrointestinal function, bringing the transit distribution pattern back to nearly the control distribution pattern (GC = 7.4 ± 0.7; Fig. 1).

Intestinal circular muscle contractility. The second experimental series was designed to determine the effect of intraperitoneal biliverdin treatment on the intestinal muscularis itself by measuring in vitro functional muscle strip contractile activity of the septic animal’s jejunal circular muscle 24 h after CLP. Superfusion of bethanechol (0.3–300 μM) elicited a concentration-dependent increase in muscle contractility. As shown in...
Fig. 2, CLP-induced sepsis resulted in a significant suppression of bethanechol-induced circular muscle contractions. Circular muscle contractility of septic animals was attenuated by 43% compared with controls at a bethanechol concentration of 100 μM. Contractility was significantly improved in biliverdin-treated CLP animals compared with untreated CLP animals (Fig. 2). As predicted by transit experiments, control intestinal contractility was not altered by biliverdin treatment alone (data not shown).

Leukocytic infiltration. Twenty-four hours after CLP, representative segments of the small intestinal muscularis were analyzed for the infiltration of MPO-positive leukocytes using Hanker-Yates histochemistry (Fig. 3A). In unoperated control animals, MPO-positive cells were only occasionally detected in the jejunal muscularis. CLP resulted in a significant recruitment of PMNs into the small intestinal muscularis. In agreement with the measured biliverdin-induced improvement in contractility, biliverdin treatment of CLP animals significantly decreased the recruitment of PMNs into the jejunal muscularis. These data are summarized in Fig. 3B for statistical analysis.

Molecular inflammatory responses. CLP-induced sepsis was a potent stimulus resulting in a significant increase in small bowel muscularis interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1 levels (Fig. 4). Biliverdin treatment of CLP animals significantly reduced the induction of IL-6 and MCP-1 (small intestine: 46% and 38%, respectively). We also quantitatively measured the effect of biliverdin on the induction of smooth muscle kinetically active mediators [cyclooxygenase (COX)-2 and iNOS]. CLP caused a significant mRNA induction of each of these inhibitors of smooth muscle contractility. Interestingly, at this particular time point, biliverdin treatment did not attenuate the induction of COX-2 and actually caused a significant increase in iNOS mRNA expression levels.

![Fig. 3](http://ajpgi.physiology.org/)
Previously, it has been shown that inhalation of CO, another HO-1 end product, can enhance the induction of the anti-inflammatory mediators IL-10 and HO-1 (37). Therefore, the modulatory effects of biliverdin on these anti-inflammatory pathways could be a potential mechanism(s) of action. Therefore, we also explored the effect of biliverdin on mRNA expression levels of the protective mediators IL-10 and HO-1 in the small bowel. The data demonstrated that CLP induced a significant increase in IL-10 and HO-1 message levels (Fig. 5). Biliverdin treatment resulted in an approximately threefold increase in IL-10 message compared with CLP alone but did not result in enhanced HO-1 expression. We were also interested in the effect of biliverdin treatment on biliverdin reductase, the enzyme important for the endogenous conversion of biliverdin to bilirubin. CLP caused a significant induction in biliverdin reductase mRNA in small intestinal muscularis extracts, but the exogenous administration of biliverdin did not alter the CLP-induced expression of this mRNA.

**Activation of NF-κB.** NF-κB comprises a family of transcription factors that act as regulators of proinflammatory mediators (30), but it has also recently been shown to be important in the resolution of inflammation and is a significant survival/reparative factor (13, 30). We hypothesized that biliverdin could potentially produce the above beneficial effects.
through the enhanced expression of NF-κB. Results from the EMSA of activated NF-κB are shown in Fig. 6. CLP caused a significant induction of activated NF-κB over control levels, and, as hypothesized, biliverdin caused a significant enhancement of this response (Fig. 6A; n = 3). Comparison of the levels of activated NF-κB in all four groups of animals (controls, control + biliverdin, CLP, and CLP + biliverdin animals) is shown in Fig. 6B (n = 3 for each group).

**Total antioxidant potential.** Biliverdin has known antioxidant properties, which in these experiments could directly limit the development of the inflammatory response within the intestinal muscularis. To investigate this possibility, we performed a total antioxidant analysis in the isolated muscularis after saline and biliverdin injections to match the time point of molecular analyses. The determined total antioxidant potential of the control muscularis externa was calculated to be 175.1 ± 4.09 μM, and the muscularis of the biliverdin-injected animals had a value of 182.4 ± 5.38 (total antioxidant potential·1 mg protein⁻¹·ml⁻¹). Although slightly higher, the total antioxidant potential of the muscularis from the biliverdin-injected animals was not significantly greater compared with the saline-injected animals (t-test = 0.16).

**DISCUSSION**

Despite the availability of potent antibiotics and intensive care support, the morbidity and mortality of sepsis remain high (1). Overwhelming proinflammatory and oxidative stress responses combined with diminished anti-inflammatory pathways are responsible for demolishing an organism’s homeostasis during sepsis. The therapeutic potential of anti-inflammatory mediators is only recently being explored, and little is known about their preemptive effects on the proinflammatory cascade. This study demonstrates the ability of exogenously applied biliverdin, an anti-inflammatory HO-1 end product, to interfere with the vicious proinflammatory cycle caused by sepsis in an animal model of endogenous sepsis (CLP). Our results show that the exogenous injection of biliverdin before CLP resulted in the amelioration of the sepsis-induced delay in the upper gastrointestinal transit. This improvement could be attributed in part to the molecular protection of the muscularis externa, as the CLP-induced suppression in intestinal motility was averted by biliverdin. Macroscopically, this preemptive protection of intestinal contractility was associated with a decrease in the recruitment of neutrophils into the intestinal muscularis.

To investigate the potential mechanistic actions of biliverdin, we focused on the expression of two main anti-inflammatory mediators, IL-10 and HO-1, because of their known protective roles in endotoxemia. Studies have shown that IL-10 protects mice from lethal endotoxemia (23) and lethal murine CLP-induced sepsis (28). IL-10 is a known inducer of HO-1 activity in macrophages, and IL-10-mediated protection against LPS-induced septic shock in mice is decreased by HO-1 inhibition. These data strongly suggest that HO-1 mediates a significant component of the anti-inflammatory action of IL-10 in vivo (31). The stress response protein HO-1 generates CO and biliverdin through heme metabolism in response to various oxidative agents. In other organs, several studies have reported that the induction of HO-1 before an injurious insult is protective against oxidative stress and inflammatory injury (20, 41, 42). Otterbein et al. (41) have shown that another HO-1 end product, CO, inhibits the expression of LPS-induced proinflammatory cytokines and increases LPS-induced expression of IL-10 in macrophages, suggesting that CO, as well as biliverdin, is involved in the anti-inflammatory action of HO-1. In the present study, treatment of septic animals with biliverdin significantly increased the CLP-induced expression of IL-10 mRNA and tended to increase HO-1 mRNA in muscularis extracts of the small intestine.

The anti-inflammatory properties of IL-10 in various inflammatory models of the intestine have been previously well demonstrated (2, 45). A known function of IL-10 is its ability to modulate the production of proinflammatory mediators like IL-6, TNF-α, and various chemokines (such as MCP-1) and prevent the generation of NO by LPS-activated monocytes/macrophages (12, 17, 24). IL-6 is a dependable indicator of sepsis severity because it remains elevated for a long period of time and reliably correlates with sepsis-induced mortality (11, 39). In this study, our data showed that IL-6 expression was significantly reduced by biliverdin, indicating that biliverdin treatment reduces the severity of the inflammatory response to polymicrobial sepsis.
A consequence of elevated expression of IL-6 is the induction of a cellular inflammatory response. Data indicate that the β-chemokine MCP-1 plays an essential role in the recruitment of monocytes to sites of injury (32), which, together with resident macrophages, are known to play a pivotal role in the intestinal pathophysiology of inflammatory bowel disease, irritable bowel syndrome, LPS-induced ileus, and postoperative ileus (5, 26, 29, 33). Our group has previously demonstrated that the regulation of leukocyte recruitment and subsequent intestinal smooth muscle dysfunction during LPS-induced endotoxemia is mediated through MCP-1 and that a major source of MCP-1 is the dense network of resident muscularis macrophages (51). In this study, we used MCP-1 mRNA as our marker of chemokine activity. As demonstrated above, biliverdin significantly reduced muscularis MCP-1 mRNA expression in CLP animals. On the basis of our previous study of MCP-1 neutralization, we hypothesized that the decreased induction of chemokines, such as MCP-1, resulted in the diminished recruitment of leukocytes into the septic jejunal muscularis. These data indicate that blunting of the induction of proinflammatory cytokines and chemokines by biliverdin plays a significant role in the observed improvements in motility. However, in the clinical realm, a decrease in MCP-1 could be a negative factor in an organism’s ability to contain and fight live bacterial infection.

Our group has previously demonstrated that prostanoids produced by COX-2 and NO produced by iNOS have potent inhibitory effects on intestinal smooth muscle contractility and that inhibition of the COX-2 enzyme or the selective knockout of the leukocyte-derived iNOS gene averts the development of postoperative ileus (27, 49). Additionally, CO treatment before intestinal manipulation decreased iNOS gene expression and NO production in mice (37). Interestingly, at the 3-h time point in this sepsis study, the HO-1 end-product biliverdin caused a significant increase in iNOS mRNA expression. These data suggest a different pathway or a different time frame for the actions of CO and biliverdin when interacting with pro- and anti-inflammatory mediators within the intestinal muscularis.

Many of the effects of HO-1 and its end product CO have been attributed to their modulation of NF-κB. In this study, we observed that the HO-1 end-product biliverdin significantly accentuated the CLP-induced activation of NF-κB. On one hand, this result could be seen as surprising because biliverdin/bilirubin have been demonstrated to be potent antioxidants; thus one would anticipate a decrease in NF-κB activation rather than an increase. Historically, the repression of LPS-induced NF-κB by HO-1 and CO has been shown to be important in moderating the inflammatory gene expression in RAW 264.7 mouse macrophages (46). And, a case has been made for NF-κB as the “bad guy” in hyperinflammatory conditions like sepsis, systemic inflammatory response syndrome, and multiple organ failure (10). More recently, on the other hand, NF-κB has been shown to be a significant prosurvival factor. In this context, increased NF-κB activation by HO-1 and CO has been shown to have significant antiapoptotic activity in tumor necrosis factor-α-stimulated cultured endothelial cells (4), because NF-κB functions as a promotor-specific activator of numerous survival genes. Furthermore, homodimers of NF-κB can also alter its transcriptional function such that it becomes a gene repressor rather than an activator (7). Most recently, it has been demonstrated that even NF-κB heterodimeric units can function as activators or repressors of gene transcription (7, 36). The scientific understanding of the functional role(s) of NF-κB is rapidly evolving. The functional activity of NF-κB in specific cell types, its response to specific stimuli, and possible time-dependent variations will need to be clarified. The muscularis extracts in this study contained many cell types (macrophages, smooth muscle, neurons, glia, endothelial cells, etc.). Although we measured a collective increase in NF-κB activity by biliverdin, it is certainly possible that NF-κB activity is not accentuated in all these individual cell types and could even be decreased in a particular cellular constituent of the septic muscularis externa. However, the accentuated activation of NF-κB could explain the measured increase in CLP-induced expression of iNOS mRNA in biliverdin-treated animals. Also, as shown above, the total antioxidant potential of the muscularis externa was not significantly greater in biliverdin-treated animals, a factor that could have participated in decreasing the activation of NF-κB.

In conclusion, the data presented in this study suggest that the protective effects of biliverdin administration occur by targeting selective elements within pro- and anti-inflammatory pathways. Biliverdin appears to act via an accentuated induction of IL-10 and the downregulation of inflammatory mediators such as IL-6 and MCP-1 with a subsequent reduction in leukocyte recruitment. Together, this inhibitory modulation of the CLP-induced proinflammatory response within the intestinal muscularis leads to an attenuation of the sepsis-induced suppression in intestinal motility. Hence, heme degradation products including biliverdin could provide new effective treatments to decrease the morbidity and mortality associated with sepsis, systemic inflammatory response syndrome, and multiple organ failure.

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REFERENCES

BILIVERDIN AND POLYMICROBIAL SEPSIS


