Whole gut washout for severe sepsis: Review of technique and preliminary results

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Background. The purpose of this study was to determine the safety and feasibility of whole gut washout for severe sepsis in human beings.

Methods. High-volume polyethylene glycol-3500 was administered to patients with severe sepsis. Body temperature, white blood cell count, and ventilatory indexes were recorded 24 hours before and 24 hours after whole gut washout.

Results. A significant decrease in febrile response was observed after gut washout with polyethylene glycol. Improvements in PaO₂, positive end-expiratory pressure, and peak airway pressure were observed. The washout was well tolerated in all but one patient.

Conclusions. High-volume whole gut washout for severe sepsis appears safe in critically ill patients and may offer some promise in reducing enterogenic inflammation after catabolic stress. (Surgery 1997;121:89-94.)

The possibility that luminal intestinal flora play a significant role in sepsis syndrome must be recognized. Over the course of time, treatment modalities such as positive pressure ventilation, antibiotic therapy, total parenteral nutrition, and vasoactive agents may severely compromise the functional microecologic unit that colonizes the intestinal tract. Under these circumstances the proliferation of microbes that have developed virulence strategies to deal with their changing intestinal environment may result in histologically elusive inflammation, which not only affects the intestinal tract itself but through autocrine and neurocrine mechanisms may also affect remote organ function. Animal models have established that catabolic stress can both severely perturb the luminal microbial flora and impair normal defense strategies that contain these mucosal pathogens. Although animal studies suggest that a gut-driven proinflammatory state may cause multiple organ failure, human models have uniformly failed to substantiate the existence of this phenomenon. The use of whole gut lavage described herein appears to have resulted in substantial changes in the clinical courses of patients with sepsis syndrome. These cases suggest, but by no means prove, that alteration in the luminal environment of the intestine may affect remote organ function. Although the case reports that follow present only anecdotal evidence that manipulation of the gut luminal environment attenuates the clinical manifestations of sepsis syndrome, they do provide practical and useful information on the technique that may be studied in detail.

MATERIAL AND METHODS

The purpose of our study was to determine the feasibility and logistics of whole gut washout in the critically ill patient with sepsis syndrome. The five patients described here were admitted to the University of Chicago Medical Center between 1993 and 1996. Patients were eligible for whole gut washout if they had no evidence of mechanical intestinal obstruction and if they had fulfilled criteria for sepsis syndrome as recently outlined by Casey et al., including fever over 38.3°C, evidence of cardiopulmonary response (tachypnea, tachycardia), and an abnormal white blood cell count.

Whole gut washout protocol. Six patients were entered into the study and five completed the protocol. One patient did not tolerate the infusion and thus was eliminated from the study. A well-positioned enteral access tube was placed in the jejunum several centimeters below the ligament of Treitz either nasoenterically or through a surgical jejunostomy. Nasogastric tubes were placed on continuous suction throughout the infusion protocol. Two doses of lactulose (30 ml) were administered 2 hours before washout to promote colon output. Infusion time varied between 6 and 12 hours. The intestinal lavage solution consisted of polyethylene glycol-3500 (PEG) GoLYTLEY. PEG infusion was begun at 100 ml/hr for 1 hour and rapidly advanced to 500 ml/hr. Infusions were intermittently increased to 500 ml/hr to promote stool output. The infusion was maintained...
at this rate until the stool effluent was clear. A plain abdominal x-ray film was obtained every 6 hours during infusion to detect colonic distension. Once the stool output became less thick, a rectal tube was used.

**Statistical analysis.** Twenty-four hours before lavage, maximal body temperature and white blood cell count were recorded. In addition, ventilatory indexes including peak airway pressure (PAP), positive end-expiratory pressure (PEEP), PaO₂, and FIO₂ were recorded. Data were pooled and expressed as the mean value ± standard deviation before and after the washout protocol. Data were analyzed for statistical significance by using a sum rank analysis with SigmaStat software (Version 1.0; Jandel, San Rafael, Calif).

**CASE REPORTS**

**Patient no. 1.** A 60-year-old man otherwise healthy, underwent a curative gastrectomy for a superficial adenocarcinoma discovered incidentally on upper endoscopy. The patient was discharged on postoperative day 6 and returned 24 hours later after he vomited ingested food. A chest x-ray film revealed right lower lobe atelectasis possibly caused by aspiration. The patient was afebrile and asymptomatic; there was no shortness of breath and blood gases were normal. The patient was placed on broad spectrum antibiotics, and a nasogastric tube was inserted. Three days later the patient began having spiking temperatures to 39° C. On postadmission day 4 the patient was regularly spiking temperatures to 41° C. His mental status was markedly altered, and he was admitted to the intensive care unit. A chest x-ray film revealed resolution of the right lower lobe process; however, developing pulmonary edema predominated the radiographic picture. Twenty-four hours after admission to the intensive care unit and after placement of invasive monitoring and intubation for persistent hypoxemia, the patient’s clinical picture was consistent with low pressure permeability pulmonary edema with severe hypoxemia. The patient’s ventilator settings were tidal volume of 700 ml, respiratory rate of 20 breaths per minute, PEEP of 12.5 cm H₂O, and an FIO₂ of 0.8. A chest radiograph revealed persistent and progressive evidence for pulmonary edema. Pulmonary artery pressures and cardiac outputs continued to display evidence of low-pressure pulmonary edema. All culture data, including urine, sputum, and blood, were negative. A computed tomography (CT) scan was taken of the patient’s abdomen, and was negative. The following day the patient was taken to the operating room for enteral access. General exploration did not reveal any intraabdominal disease, and a feeding jejunostomy was placed. The next day the patient remained persistently febrile. Ventilator parameters continued to display evidence of poor pulmonary compliance and severe hypoxemia. At this time an intestinal lavage solution, PEG, was infused into the jejunum at a rate of 100 ml per hour and rapidly increased to 300 ml per hour. Within 4 hours the patient began to have dense stool output. Approximately 8 L of stool effluent was passed during the next 12 hours, completely clearing the patient’s small bowel and colon of luminal debris. His persistently febrile course rapidly diminished as the diarrheal effluent began to clear. The PEG was discontinued, and enteral feedings were begun. The patient’s mental status improved, and he was weaned from the ventilator. The patient remained afebrile for the remainder of his hospital stay. Antibiotics were discontinued on the second day after the gut washout, and the patient eventually was discharged in excellent condition.

**Patient no. 2.** A 42-year-old woman was admitted to the emergency room in septic shock. The patient was rapidly resuscitated and taken to the operating room, where she was found to have a perforated diverticular abscess. The abscess appeared to have been present for many days and had now freely perforated into the peritoneal cavity. A loop of distal small bowel that was draped over the abscess cavity was completely necrotic. Resection of the distal small bowel was completed and both ends were brought up as stomas, leaving a proximal ileostomy in continuity with the upper gastrointestinal tract and a distal ileal mucus fistula, which was approximately 8 cm proximal to the ileocecal valve. The sigmoid colon was divided proximal to the diverticular abscess, and an end descending colostomy was created. The sigmoid colon could not be removed because it was markedly inflamed and completely adherent to the lateral wall of the peritoneal cavity. Gross fecal contamination was found throughout the peritoneal cavity, which was then copiously irrigated and packed open. A nasoenteric feeding tube was placed far below the ligament of Treitz and sutured transmurally into the wall of the intestine to secure its position. Throughout the procedure the patient remained on high dose epinephrine and her systolic pressure varied between 60 and 70 mm Hg. Forty-eight hours after exploration, the patient remained persistently febrile, spiking intermittent temperatures between 40° and 42° C. The patient was both ventilator and pressor dependent.

Whole gut lavage was begun through both the feeding tube and the distal ileum. Approximately 10 L intestinal output was passed during the next 18 hours. A marked diminution in the patient’s febrile response was noted as the effluent from both ostomy sites began to clear. PEG therapy was withdrawn 24 hours after its initiation. A marked improvement of both ventilatory and oxygenation support was noted.

**Patient no. 3.** An 18-year-old woman who had undergone an appendectomy for perforated appendicitis with generalized peritonitis had severe adult respiratory distress syndrome (ARDS) with poor dynamic compliance. She required acute vasoactive pharmacologic support. At 1 week after exploration and appendectomy the patient remained persistently febrile in the 40° to 41° C range. Despite numerous negative CT scans and antibiotic regimen changes, the patient’s persistently febrile course and ARDS were not improving. Urine, sputum, and blood cultures were negative. A high-volume infusion of PEG at approximately 200 ml per hour was begun through a feeding tube. Eighteen hours after the infusion of this solution, the patient’s diarrheal effluent was clear. The patient rapidly defervesced, and 24 hours later her radiographic ARDS picture had improved. She was extubated 72 hours after initiation of the PEG therapy and remained afebrile thereafter. The patient was ultimately discharged in good health.

**Patient no. 4.** A 48-year-old woman, who had undergone three previous operations for complications of peptic ulcer disease, underwent a total gastrectomy with Roux-en-Y recon-
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Abbreviations

Table I. Ventilatory and fever indexes 24 hours before and after gut washout

<table>
<thead>
<tr>
<th>Parameter</th>
<th>24 hr before</th>
<th>24 hr after</th>
<th>( p ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Pao}_2 ) (mm Hg)</td>
<td>75.8 ± 1.6</td>
<td>129 ± 19.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( \text{FiO}_2 ) (%)</td>
<td>0.66 ± 0.1</td>
<td>0.32 ± 0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>( \text{Paco}_2/\text{FiO}_2 )</td>
<td>125 ± 21.2</td>
<td>271.2 ± 56.7</td>
<td>0.09</td>
</tr>
<tr>
<td>PEEP (cm H2O)</td>
<td>9.5 ± 0.9</td>
<td>6.5 ± 0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAP (cm H2O)</td>
<td>53.2 ± 3.7</td>
<td>30.4 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum temp (°C)</td>
<td>39.7 ± 0.2</td>
<td>37.7 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White blood cell count (10^3 cells/mm^3)</td>
<td>19.6 ± 1.5</td>
<td>17.8 ± 2.8</td>
<td>0.2</td>
</tr>
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*Significance measured by rank-sum analysis.

RESULTS

The results are summarized in Table I. All five patients experienced a rapid decline in temperature after the infusion protocol. This was particularly striking in patients 1 and 4 (Fig. 1).

DISCUSSION

Recent studies on the pathophysiology of severe sepsis syndrome consistently show that an infectious source is identified in less than 50% of cases. Although newly identified proinflammatory chemokines may play a major role in sepsis syndrome of unknown cause whether they are a cause or consequence of systemic inflammatory response syndrome is not clear. The manipulation of gut contents appears to have a suppressive effect on the systemic inflammatory response in various animal models of sepsis. Whereas a gut-derived septic state driven by the intestinal microflora is an attractive explanation for culture-negative septic-like states in critically ill patients, this hypothesis has not been proved in human beings. Nonetheless, several investigations have attempted to manipulate the gut microflora in human beings to both invoke the gut hypothesis of sepsis and offer a potential treatment strategy. One such approach is antibiotic decontamination of the gut. Despite numerous trials, selective antibiotic decontamination of the gastrointestinal tract in the critically ill patient has failed to substantially alter the natural history of sepsis syndrome.

The concept of whole gut washout for sepsis is not new. Whole gut washout has been used in several animal and human studies with positive results. Animals treated with PEG and subjected to inflammatory lesions induced by trinitrobenzene sulfonic acid, a model of ulcerative colitis, each had positive weight gain and attenuation of the histologic colon lesion score, and a significant diminution occurred in the gut luminal levels of prostaglandin E\(_2\), thromboxane A\(_2\), and leukotriene B. This was in sharp contrast to the control group,
whose members did not receive PEG, and in whom weight loss was significant, colon lesion scores were much greater, and mean luminal levels of proinflammatory prostaglandins were significantly elevated. Furthermore, this study showed that colony-forming units of both Bacteroides and Clostridium species were significantly lower in the PEG-treated animals. A second animal report showed similar findings in a model of ischemia/reperfusion to the splanchnic bed. Animals were randomly assigned to be fed normally or to receive a bowel preparation with PEG 24 hours before the study. In addition to the PEG, normal saline solution was added to the bowel preparation. All animals were subjected to 60 minutes of superior mesenteric artery occlusion followed by 120 minutes of reperfusion. Significant attenuation of the deleterious hemodynamic effects from ischemia/reperfusion were found in the PEG- and saline-treated animals. These included a significant attenuation in the decrease in cardiac output and superior mesenteric artery blood flow. Attenuation of the histologic lesion was also exhibited in animals treated with gut lavage. Thus use of PEG and intraluminal fluid appeared to protect against the cardiovascular compromise and tissue destruction during small bowel ischemia/reperfusion in this model.

Only a single human study that has examined whole gut washout as a method of treating systemic toxemia presumed to be of intestinal origin is available. This
Table II. Multiple pharmacologic effects of PEG on bacterial mucosal cell interactions

<table>
<thead>
<tr>
<th>Action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks toxin receptors on intestinal epithelia</td>
<td>17</td>
</tr>
<tr>
<td>Stabilizes F-Actin, a key component of the epithelial barrier</td>
<td>14</td>
</tr>
<tr>
<td>Surfactant-like properties, prevents bacterial adherence to mucosa</td>
<td>15</td>
</tr>
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The study was performed in patients who were hospitalized for exacerbation of Crohn’s disease and in whom systemic signs of toxicity were present. These investigators used 0.9% normal saline infusate warmed to 37°C. An extremely high flow rate at 9 L per hour was used to achieve efficient washing of the entire intestinal tract. Remarkably, this was extremely well tolerated in the nine patients studied. Plasma endotoxin and febrile responses were followed in patients randomized to either high-saline lavage or conventional treatment. A statistically significant decrease in plasma endotoxin concentration was observed after whole gut irrigation, in sharp contrast to the plasma endotoxin levels in untreated controls. To our knowledge, this is the only report that shows that whole gut lavage may be an effective treatment modality for systemic endotoxemia. It is possible that the simple reduction of the total mass of bacteria and soluble proinflammatory luminal macromolecules may decrease enterogenic inflammation in patients with sepsis syndrome. However, other mechanisms may be operative during whole gut washout with PEG. Reported pharmacologic effects of PEG could be responsible for attenuation of enterogenic inflammation (Table II). PEG can act like physiologic surfactants, which may stabilize the epithelial barrier, and can also prevent bacterial adherence to mucosal epithelia—an event shown to be important for proinflammatory signaling by bacteria. PEG also has been shown to bind to toxin receptors on epithelia and may block signal transduction pathways elicited by luminal toxins. Despite these provocative observations, no information on these effects is available in vivo.

The most dramatic finding in the five patients studied was the rapid decline in the temperature curve after high-volume cleansing of the gastrointestinal tract. The fever curves shown in Fig. 1 show the dramatic diminution in temperature in patients treated with whole gut washout. Although it could be argued that the rapid decreases in these patients temperatures were unrelated to the lavage, the observations are quite striking. As the rapid flow of stool effluent began to clear, a marked improvement in each patient’s febrile response could be seen. Although the case number is small and therefore by no means proves the efficacy of this therapy, the treatment appears simple, safe, and promising. However, despite the encouraging preliminary data in this pilot report, future trials of this approach will be necessary to confirm safety and determine efficacy.

Several practical points regarding this therapy should be mentioned. First, it is of the utmost importance to protect the airway during high-volume intestinal infusion of PEG. Because many of the intensive care unit patients are intubated, this is a lesser concern. Nonetheless, it is our protocol to place a nasogastric tube on continuous suction during the infusion of PEG to ensure that if intestinal stasis results, upper gastrointestinal fluid is immediately evacuated. Second, there must be a significant commitment to these patients by physicians to continue to evaluate the progress of the intestinal washout. Continuous repositioning of the patient is often necessary, as continued reexamination of the patient’s abdomen for rapidly developing distention. It is our protocol to obtain an abdominal x-ray film to determine whether colonic distention is becoming excessive. It is also our protocol not to discontinue therapy if the colon becomes distended but rather, to immediately perform colonoscopy and completely empty the colon of air and fluid. However, the logistics of whole gut lavage can impose significant obstacles during the practice of this technique. If colonoscopy is not immediately available and if close observation by trained personnel is not possible, then this therapy is not recommended.

In summary, whole gut washout for severe sepsis is a technique that can be performed safely in patients who are critically ill. It may offer some promise in elucidating the mechanism by which the intestinal tract elicits systemic inflammation during conditions of severe catabolic stress. Future trials will be necessary to test the efficacy of whole gut washout in the critically ill.

REFERENCES