Use of Immunoglobulins in Prevention and Treatment of Infection in Critically Ill Patients: Review and Critique

Giorgio Zanetti, Michel P. Glauser, and Jean-Daniel Baumgartner

From the Division of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

The study of the use of standard intravenous immunoglobulin (IVIG) preparations as adjunctive therapy for seriously ill patients is motivated by the need to restore immunoglobulin G depleted because of trauma or surgery and/or by the need to provide patients with specific antibodies to various microorganisms. Whereas no clinical studies have shown that standard IVIG has therapeutic efficacy, some data suggest that its prophylactic use is beneficial. Antisera or IVIG prepared from individuals who are hyperimmunized with the biologically active, highly conserved core portion of the endotoxin of gram-negative bacteria confer variable degrees of protection in animal models and clinical trials. Two clinical trials with use of monoclonal antibodies to core lipopolysaccharide have been completed. Only subsets of patients with gram-negative sepsis were protected by the monoclonal antibodies, but the results of the studies were discrepant in regard to the specific characteristics of patients who benefited from the administration of these antibodies. Further studies will be necessary to establish whether this therapy can be recommended for critically ill patients.

Critically ill patients are at high risk for infection as a result of several immunologic dysfunctions. Decreased levels of IgG have been reported in such patients, especially after trauma and surgery [1]. Moreover, the efficacy of their neutrophils undergoes a decline with respect to exhibition of chemotaxis, opsonic activity, and ability to kill bacteria. In addition, such patients are exposed to a wide variety of organisms in the hospital environment, a circumstance which further increases the probability of infection. The administration of intravenous immunoglobulin (IVIG) to critically ill patients might enhance host defense by restoring IgG and/or by providing patients with specific antibodies to various microorganisms or constituents of microorganisms. IVIG might also attenuate the inflammatory process engendered by the host response to bacterial products such as endotoxin. Two approaches have been used in the administration of IVIG for treatment of critically ill patients: (1) administration of standard IVIG (nonspecific use) and (2) administration of whole plasma, immunoglobulin preparations, or monoclonal antibodies (MoAbs) directed against the endotoxin constituent of gram-negative bacteria (specific use).

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Reprints and correspondence: Prof. Michel P. Glauser, Division of Infectious Diseases, Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

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Nonspecific Use of IVIG

Treatment of infections. IVIG can be administered to patients therapeutically for infections. In an unblinded, randomized, controlled clinical trial with 104 surgical intensive care patients, Just and colleagues [2] administered four 100-mL doses of IVIG (Pentaglobin; Biotest Pharma, Frankfurt, Germany) over 2 days in conjunction with antibiotics to 50 patients at the first sign of infection. Fifty-four control patients received antibiotics alone. The mortality attributed to infections and the overall mortality of the IVIG and control groups did not differ. The IVIG reportedly was effective for patients preoperatively classified as "high risk," but since this result was obtained in only one of several subgroups, the data should be interpreted cautiously. In a multicenter, unblinded, randomized, controlled clinical trial among 288 patients with fibrinopurulent peritonitis, Jesdinsky and co-workers [3] administered 10 g of an IVIG preparation (immunoglobulin 7S human iv; Armour Pharmaceuticals, Eschwege, Germany) to 145 patients; a control group that consisted of 143 patients was not treated. The study failed to demonstrate the efficacy of IVIG therapy, however. One possible explanation for such a result is that the amount of specific antibodies might have been insufficient to confer protection against the large number of pathogenic bacteria.

Prophylactic use of IVIG. IVIG can also be administered prophylactically. Two reports of studies using this approach have been published. Duswald and colleagues [4] administered 2.5 g of IVIG (Intraglobulin; Biotest Pharma) to 150 critically ill patients, but the investigators observed no protective effects with respect to wound infection, urinary tract infection, or pneumonia. Glinz and associates [5] administered 36 g (12 g on days 0, 5, and 12 after admission to the inten-

sive care unit) of IVIG (Sandoglobulin; Sandoz, Basel, Switzerland) to 150 patients and observed a decrease in the incidence of pneumonia. This benefit was not unequivocally proven, however, since pneumonia was mainly defined radiologically and microbiologic documentation was questionable.

Recently, Cometta and co-workers [6] completed a blinded, placebo-controlled clinical trial with two IVIG preparations. A 400 mg/kg dose of standard preparation (Gammagard; Hyland Therapeutics Division, Glendale, CA) was administered to 109 patients when they were admitted to the surgical intensive care unit and once a week thereafter. A second preparation of IVIG, which was enriched with antibodies to the core lipopolysaccharide (LPS) of *Salmonella minnesota* R595 (Re LPS) (see next section), was administered to 108 patients. The titer of the antibodies to core LPS in this preparation was eightfold higher than that in the standard IVIG. A control arm of 112 patients received albumin. The standard IVIG preparation accounted for a reduction in the number of patients who developed infections during the course of the study (36%, versus 53% in the control group; $P < .05$). The reduction was caused by a significant decline in the number of cases of pneumonia ($P < .05$).

Therefore, it appears that standard IVIG can have a protective effect when administered to high-risk surgical patients as a prophylactic measure. Indeed, detailed analysis of the results showed that both the stay in the intensive care unit and the entire duration of hospitalization were shorter for those patients who received standard IVIG than for those who received albumin. It is surprising that the IVIG enriched with antibodies to the endotoxin core failed to protect the patients from infection. The preparation conferred no protection against gram-negative sepsis, septic shock, or focal infections; the reason for this is unclear.

Antibodies to Gram-Negative Bacteria

It is well known that the toxicity of gram-negative bacteria is caused by the toxic LPS, called endotoxin, that constitutes the outer bacterial membrane. The endotoxin molecules consist of the toxic moiety, a lipoidal acylated glucosamine disaccharide (lipid A), which is linked to a polysaccharide side chain (called O antigen) through an intermediate oligosaccharide region, the core. Antibodies to the intact LPS are produced mainly in opposition to the side chains, which are highly antigenic. Because side chains vary widely between strains, these antibodies have a very narrow specificity. By contrast, the core is highly conserved and is very similar in different strains.

In the 1970s, Braude et al. [7], Ziegler et al. [8], and McCabe [9] all hypothesized that by stimulating production of antibodies to the highly conserved core moiety of LPS, one could obtain cross-reacting antibodies that would protect against a wide variety of gram-negative bacteria. This was ultimately accomplished by using the *Escherichia coli* mutant J5, a rough mutant of *E. coli* 0111:B4 that lacks the enzyme uridine 5′-diphosphonate-galactose 4-epimerase; this defect prevents attachment of the side chains to the core. Therefore, in the J5 strain, the polysaccharide side chains of the endotoxin are missing and the core is exposed. In animals, immunization with LPS from *E. coli* J5 or with whole *E. coli* J5 bacterial cells results in high titers of antibody to epitopes of the LPS core [10]. Another rough mutant that has been studied for its ability to stimulate production of antibodies to the core region is an Re mutant of *S. minnesota*.

Researchers have postulated that antibodies elicited by these two rough mutants should afford protection against a wide range of gram-negative bacteria by a mechanism requiring two steps: (1) these antibodies recognize epitopes of the core region shared by the LPS of pathogenic gram-negative bacteria, and (2) the postulated binding neutralizes the endotoxic properties of LPS, i.e., leads to a suppression or attenuation of the release of mediators such as cytokines. However, neither of these two hypothetical steps has been unequivocally demonstrated. The following sections review what has been learned from studies in which the J5 mutant and other rough mutants were used.

Studies with animals. Ziegler and colleagues have shown that granulocytopenic rabbits challenged in the conjunctival sac with *Pseudomonas aeruginosa* develop a massive, lethal pseudomonal infection [11] and that these rabbits could be protected with *E. coli* J5 antiserum. Some of their results with use of purified immunoglobulins from human volunteers immunized with *E. coli* J5 are reproduced in table 1 [12]. Braude et al. [7], McCabe [9], and other researchers [8, 13–18] have also found that animals were protected when they were actively or passively immunized with the rough mutant J5 of *E. coli* or with an Re rough mutant of *S. minnesota*.

Some investigators, however, were unable to obtain similar results [19–28]. For instance, Greisman and Johnston [27] found that mice inoculated with LPS from *S. minnesota*, *Salmonella typhimurium*, *E. coli* 0127, or *E. coli* 0111 were not protected by either of the two antisera to the J5 and Re mutants; the mortality among these mice was even greater than the mortality for mice that received only saline. The study revealed that only antibody to the strain-specific LPS was protective (table 2).

Thus, the results of animal studies described in this section

Table 1. Level of protection of neutropenic rabbits from lethal pseudomonal bacteremia after intravenous administration of immunoglobulin from humans immunized with *E. coli* J5.

Source of immunoglobulin	No. of deaths/no. of rabbits treated (%)*
Nonimmunized human	12/14 (86)
Immunized human	3/14 (21)

NOTE. Reprinted with permission from [12].
* $P = .001$ (χ^2 test).

Table 2. Level of protection (in terms of mortality) noted in mice after pretreatment with various preparations* and inoculation with 230 μg of LPS from *S. typhimurium*.

Pretreatment preparation (0.5 mL)	Percentage of deaths/ no. of mice inoculated
Saline	52/25
Antiserum to *E. coli* J5†	75/12
Preimmune serum†	64/11
Antiserum to *E. coli* J5‡	83/12
Preimmune serum‡	83/12
Antiserum to *S. typhimurium*	0/25§

NOTE. Adapted with permission from [27].
* The *E. coli* J5 antisera were prepared by using the method of Braude et al. [7].
† Serum from rabbit 25.
‡ Serum from rabbit 26.
§ $P < .0005$, compared with the other trials.

Table 3. Mortality among patients with gram-negative bacteremia after administration of control serum from nonimmunized donors or antiserum from donors immunized with *E. coli* J5.

	No. of deaths/no. of patients treated (%) in group receiving indicated therapeutic serum		
Patient group	Control serum (mean titer, 1:6)	Antiserum (mean titer, 1:32)	*P* value
All patients	38/100 (38)	22/91 (24)	.04
Patients in profound shock	26/34 (76)	17/37 (46)	.009

NOTE. Adapted with permission from [36].

show that only some researchers have been successful in demonstrating that antibodies to core glycolipids can be protective. There is no simple explanation for the discrepant results of studies with various preparations of antibodies to core LPS. The precise specificities as well as the mode of action of the antibodies tested have not been clarified. Moreover, the animal models studied, the mode of challenge, and the nature of LPS or of bacteria used for challenge are parameters that all could have an impact on the protective efficacy of these preparations [29].

However, these considerations cannot explain all the discrepancies in data; varying results were sometimes obtained despite the use of similar antibodies, similar animal models, and similar bacterial or LPS challenges [8, 9, 26, 27, 30]. Therefore, it can be postulated that additional, unknown negative or positive factors sometimes operate. For instance, an artifact (now well recognized) can result when the antibody preparation to be tested is contaminated by LPS. Minute amounts of LPS administered prophylactically induce a state of tolerance to LPS and protect animals against subsequent bacterial or LPS challenges [31, 32]. Since antibodies tested in studies of protection almost uniformly are administered before bacterial or LPS challenge, the occurrence of such an artifact in many earlier-reported experiments cannot be ruled out. Moreover, the interpretation of data from experimental studies of protection with use of rabbit antisera may depend on whether preimmune and immune sera came from the same rabbit or from different rabbits [27]; it has been shown that sera from nonimmunized rabbits, unlike other sera, may have a natural protective power against challenge with gram-negative bacteria or LPS.

Similarly, in studies of protection with use of MoAbs, the degree of purification is critical to the results. Indeed, ascitic and hybridomal fluids can contain various proteins and peptides, such as cytokines, some of which might be able to bind to LPS or to induce some tolerance to LPS in experimental animals. Most experimental studies of protection that have been reported, including those by Teng et al. [30] and Young et al. [33], have involved ascitic or hybridomal fluids. Experimental variability might account for important differences in survival rates noted from one experiment to another, so the reporting of only part of the experiments might introduce some element of bias [34, 35]. In conclusion, the precise description of the control preparation and of the preparation containing antibody is critical for the interpretation of experimental data from studies with animals.

Clinical studies. As was the case with the animal studies described in the previous section, only some of the data from clinical studies indicated that patients could be successfully treated or protected with administered antibodies.

In 1982 Ziegler and co-workers [36] reported a pioneering randomized, blind, controlled study of patients with gram-negative bacteremia who received either serum from healthy volunteers who had been vaccinated with heat-killed *E. coli* J5 or control serum obtained from the same donors before immunization. There was a fivefold difference in the mean titers of antibody to the LPS of *E. coli* J5 in the control and immune serum. These sera were administered to 304 patients, 191 of whom had gram-negative bacteremia. The results (table 3) led to the conclusion that human *E. coli* J5 antiserum substantially reduces mortality due to gram-negative bacteremia and septic shock. Regarding the mode of protection, Ziegler et al. [36] hypothesized that antibodies to *E. coli* J5, which were present in the serum after immunization, became bound to some part of the endotoxin core of pathogenic gram-negative bacteria and sterically prevented lipid A from reacting with mediators of shock in blood and tissue fluid. This hypothesis could not be convincingly confirmed, however, since the outcome could not be significantly correlated with the level of antibody to *E. coli* J5 measured in the serum administered to patients.

In a randomized, double-blind, prophylactic trial, Baumgartner and colleagues [37] were able to show that plasma from volunteers immunized with *E. coli* J5 protected surgical patients who were at high risk for gram-negative infection from shock and death. On admission to the intensive care

Table 4. Prophylaxis of surgical patients for gram-negative shock with plasma from nonimmunized donors or from donors immunized with *E. coli* J5.

Patient group	No. of patients treated with plasma from indicated type of donor		*P* value
	Non-immunized	Immunized	
All patients	136	126	. . .
with focal GN infections	55	45	NS
who developed GN shock	15	6	.049
who died of GN shock	9	2	.033
Patients who underwent abdominal surgery	83	71	. . .
who developed GN shock	13	2	.006
who died of GN shock	9	1	.017

NOTE. GN = gram-negative; NS = not significant. Adapted with permission from [37].

unit, patients received plasma harvested from donors who had been immunized against *E. coli* J5; the control group received plasma taken from these same donors before immunization. Six of 126 patients (4.8%) who received plasma from immunized donors and 15 of 136 patients (11.0%) in the control group developed gram-negative shock; the numbers of related deaths in each group were two (1.6%) and nine (6.6%), respectively ($P < .05$, one-tailed Fisher exact test). The difference between the two groups was observed mainly in patients who underwent abdominal surgery (table 4). Although administration of plasma with antibodies to *E. coli* J5 failed to decrease the incidence of gram-negative infection, it greatly reduced the most serious consequences of such infections. As was noted in the report by Ziegler et al. [36], protection was related to immune plasma, not to specific levels of antibody to core LPS in a given plasma (D. Heumann and J-D Baumgartner, unpublished data).

Two other studies, however, have failed to demonstrate that any beneficial effect results from the administration of *E. coli* J5 antiserum. McCutchan and colleagues [38] studied neutropenic patients as well as patients receiving bone marrow transplants. These patients were given *E. coli* J5 antiserum as a prophylactic measure. The results did not suggest that the antiserum prevented gram-negative bacteremia or the occurrence of fever that, for at least some of these patients, was considered to be caused by release of endotoxin from the gut. One possible explanation for this failure to demonstrate such a beneficial effect could be the low power of the study, since the number of infections due to gram-negative bacteria was small. Recently, we conducted a blind study in which 73 children with purpura fulminans received either control plasma (33 patients) or plasma with antibodies to the core LPS of *E. coli* J5 (40 patients) (E. Girardin and J-D Baumgartner, submitted for publication). There was no difference in mortality between the two groups, a fact suggesting that the plasma from donors immunized with *E. coli* J5 was not effective in the treatment of meningococcal septicemia.

As already noted, in both successful clinical studies with *E. coli* J5 antiserum [36, 37], the protection remained of unclear origin because outcome could not be convincingly correlated with the level of antibodies to the core LPS of *E. coli* J5 ([36] and D. Heumann and J-D Baumgartner, unpublished data). In addition, it was found that in 70 volunteers who donated their plasma for one of these studies [37], immunization with *E. coli* J5 vaccine (provided by E. J. Ziegler) induced a modest threefold increase in antibodies to the LPS of *E. coli* J5 but no increase in antibodies to Re LPS or to lipid A [39]. Thus, the protection afforded by *E. coli* J5 antiserum could not be attributable to antibodies to the LPS of *E. coli* J5, to Re LPS, or to lipid A.

IVIG enriched with antibodies to the LPS core has been purified from serum of immunized volunteers or from serum of donors with naturally acquired high levels of antibodies to LPS. Calandra and colleagues [40], in a randomized, double-blind trial, compared the efficacy of IVIG collected from volunteers who were immunized with *E. coli* J5 with that of standard IVIG (Sandoglobulin) in the treatment of 71 patients with gram-negative septic shock. There was a 2.2-fold increase in titer of antibody to the LPS of *E. coli* J5 in the preparation from the hyperimmunized donors compared with that in the standard IVIG. No difference between the two groups in terms of mortality was reported.

As previously noted, Cometta and co-workers [6] compared IVIG that contained antibodies to core LPS, which was collected from blood donors with naturally high levels of Re antibodies, with standard IVIG or placebo in a prophylactic double-blind study. In contrast to the efficacy of standard IVIG, no protection was afforded by the IVIG with core LPS antibodies. One hypothetical explanation for the ineffectiveness of IVIG with antibodies to core LPS is that IgM antibodies, which were absent from IVIG preparations, might be necessary for protection [15]. However, since the precise specificity and the mode of action of antibodies to core LPS are unknown, there is no strong basis for such a claim. Although some experimental data suggested that IgM-enriched serum fractions were more effective than IgG-enriched fractions [15], other studies had found that IgG antibodies were as effective or even more effective than IgM [17, 41].

This review of the clinical trials performed with antisera or polyclonal immunoglobulin reveals that, among six studies, four were unsuccessful in demonstrating the efficacy of the administered preparations. The data emphasize the need for an understanding of which factors were responsible for the protective effects noted in the successful studies with serum or plasma and, in addition, which of these factors were absent from the unsuccessful studies with plasma or immunoglobulin preparations.

Studies With Monoclonal Antibodies

In recent years, several MoAbs have been developed that recognize various epitopes of the core region of endotoxin [30, 33, 42–52]. Two of these MoAbs, both of the IgM class, have been tested for treatment of patients with gram-negative infections.

First, Young and associates [33] made murine MoAbs to the endotoxin core of the J5 mutant of *E. coli* and of the Re mutant of *S. minnesota*. They immunized BALB/c mice against these bacterial strains and could produce IgM MoAbs to Re LPS or lipid A. The ability of these MoAbs to prevent or treat infection was then tested in female mice. The authors found that these antibodies were not protective when administered alone [33], but one of them, an IgM MoAb to lipid A called E5, appeared to be synergistic with antibiotics in experimental studies of prophylactic or therapeutic methods.

For instance, mice were injected with a dose of live serum-resistant bacteria (three challenge organisms were used) that would be expected to kill 80%–100% of the animals. Two hours after onset of infection, a mixture of antibiotics was injected intramuscularly; control mice received saline. After an additional 2 hours, the MoAb E5 was injected intravenously.

There were four treatment groups, with 14 mice per group and per challenge organism. Group A received antibiotics alone; 45% survived (results of challenges with the three organisms were pooled). Group B received antibiotics and MoAbs; 64% survived ($P < 0.05$, one-tailed, in comparison with group A when the results of the three bacterial challenges were combined). For group C (which received MoAbs and saline) 29% survival was noted, and for group D (which received saline alone) 24% survival was noted.

In another experiment, the MoAb E5 was used for the treatment of infections due to two strains of *P. aeruginosa* in mice. Again, E5 alone had no protective effect, but when the results for the two strains were combined, treatment with E5 and antibiotics was significantly more effective than treatment with antibiotics alone. These studies suggested, therefore, that E5 might have a protective effect in some experimental conditions. However, definitive conclusions are difficult to draw because ascitic fluid, not purified antibody, was used and because individual experiments had to be pooled to obtain statistically significant differences.

In a clinical study of the MoAb E5 [53], patients with a suspected gram-negative septic syndrome were randomly assigned to receive intravenously either the antibody (2 mg/kg daily for 2 consecutive days) or an identical volume of saline. Of the 468 evaluable patients, 316 had a documented gram-negative infection. No decrease in mortality was observed in this group of patients. However, when the results in subgroups were analyzed, there was a statistically significant decrease in mortality among the 137 patients who were not in shock when enrolled in the study ($P = .03$), whereas the 179 patients who were in shock were not protected. Shock was defined as refractory hypotension; patients with organ failure or disseminated intravascular coagulation were not considered to be in shock if they had a systolic pressure >90 mm Hg. Among patients who were not in shock, a comparable reduction in mortality occurred in the bacteremic group as well as the nonbacteremic group. Administration of E5 was safe in that <2% of patients developed allergic adverse effects. Because the results of this study suggested that E5 was effective only in a subgroup of patients who were not in shock (an unanticipated finding), a confirmatory multicenter study has been initiated.

The second MoAb, subsequently designated as HA-1A, was produced by Teng and co-workers [30] from a hybridoma obtained by fusing B lymphocytes from human spleen with heteromyeloma cells. The researchers used splenocytes taken from one patient with Hodgkin's disease who was undergoing splenectomy and who had previously been vaccinated with the J5 mutant of *E. coli*. They reported that the MoAb reacted in vitro with many unrelated species of gram-negative bacteria. Moreover, the MoAb in hybridomal fluid was shown to be protective against endotoxin in the dermal Shwartzmann reaction in rabbits and against gram-negative bacteremia in mice. Protection appeared to be specific for gram-negative bacteria because the MoAb to *E. coli* J5 failed to protect against the pneumococcus, a gram-positive organism that lacks endotoxin. The results of ELISAs and binding inhibition experiments led to the conclusion that the MoAb specifically recognized lipid A [54].

These experimental observations could not be reproduced, however. Indeed, using purified MoAb instead of crude hybridomal fluid, we could not demonstrate that HA-1A could be protective [26] in models very similar to those used by Teng et al. [30]. In addition, in contrast to type-specific LPS antibodies, HA-1A did not suppress LPS-induced secretion of tumor necrosis factor in mice, a circumstance suggesting that HA-1A was not able to prevent LPS from reaching its target on macrophages [26].

Moreover, it was found that purified HA-1A bound moderately to lipid A and Re LPS but poorly to LPS from pathogenic, smooth, gram-negative bacteria. It bound to a large range of gram-negative bacteria and also to gram-positive bacteria, fungi, and lipids unrelated to lipid A, including cardiolipin and lipoproteins (use of such controls has not been previously reported [30, 54]). This broad binding pattern suggested nonspecific interactions with hydrophobic constituents and may bring into question the specificity of HA-1A for lipid A (D. Heumann and J-D Baumgartner, unpublished data).

Ziegler and colleagues [54] administered HA-1A (or albumin as a control preparation) to patients with a presumptive diagnosis of gram-negative sepsis. The patients were randomized to receive a single dose of HA-1A (100 mg intravenously) or a similar volume of human albumin. Of the 543

patients, 317 had microbiologically documented gram-negative infections; for 200 of the 317 patients, blood cultures were positive at the time of randomization. HA-1A did not reduce the mortality in the overall study population or among the 117 patients with nonbacteremic gram-negative infections. However, there was a significant decrease in mortality among the subgroup of patients with gram-negative bacteremia ($P = .014$); the decrease in mortality was most obvious among the 101 patients who were in shock when enrolled in the study.

Detailed analysis of these data indicated that, by chance, differences in risk factors between placebo and HA-1A recipients might have been present in the subgroup of 200 patients with gram-negative bacteremia at the time of randomization. Indeed, a total of 101 serious complications (e.g., disseminated intravascular coagulation, adult respiratory distress syndrome, acute hepatic failure, and acute renal failure) [54] were noted at entry in the 95 placebo recipients (mean, 1.06 per patient); 85 such complications were noted in the 105 HA-1A recipients (mean, 0.81 per patient) ($P = .07$ by comparison of Poisson distributions). The 16 additional serious complications in the placebo group might partially account for the higher mortality (13 more deaths) in this group.

Definitive conclusions for the use of MoAbs to endotoxin core are difficult to draw at present. Indeed, when the HA-1A MoAb was tested experimentally by two independent groups, it showed divergent efficacy that was possibly related to its degree of purification [26, 30]. The other antibody, the E5 MoAb, only once has been reported to be moderately efficacious in animals when tested as ascitic fluid. Moreover, the clinical results of the studies have been somewhat conflicting. For instance, in one study, the MoAbs protected predominantly patients in shock; in another study, only those patients who were not in shock were protected. In one study, only patients for whom blood cultures were positive were protected by the treatment, while in another study the protection occurred independently of the blood culture status. Thus, further studies are needed to define prospectively and specifically the types of patients who might benefit most from this therapeutic approach.

Conclusions

According to available study reports, the use of standard IVIG for the treatment of infection in critically ill patients seems ineffective. In contrast, two studies have shown a reduction of infections, mainly pneumonia, when standard IVIG preparations were administered prophylactically to chosen groups of postsurgical or trauma patients. However, no impact on mortality was demonstrated. Cost-effectiveness studies are therefore warranted.

At present, the treatment of the gram-negative septic syndrome with antibodies to lipid A or other epitopes of the core LPS should still be considered investigational. None of the preparations used in clinical studies has yet emerged as an established therapeutic modality that can be administered routinely to patients with septic shock. In the two studies investigating MoAbs, only subsets of patients with the gram-negative sepsis syndrome were protected, but both studies gave discrepant results concerning the specific characteristics of patients who were reported to benefit from the administration of these antibodies. In addition, the epitope specificity and the mode of action of the MoAbs investigated so far are still unknown. These concerns are not trivial. The indiscriminate use of such treatment might have considerable financial impact: the potential market for such antibodies has been estimated to be worth several billion dollars per year in the western countries.

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