Review and critique of the use of immunoglobulins in prevention and treatment of infection in critically ill patients

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G ZANETTI, MP GLAUSER, J-D BAUMGARTNER. Review and critique of the use of immunoglobulins in prevention and treatment of infection in critically ill patients. Can J Infect Dis 1992;3(Suppl B):3B-10B. The study of standard intravenous immunoglobulin G (IVIG) preparations as adjunctive therapy in seriously ill patients is motivated by the possible need to: restore immunoglobulin G levels depleted after trauma or surgery; and/or to provide patients with specific antibodies directed against various microorganisms. Whereas no therapeutic efficacy has been shown in clinical studies with standard IVIG, some data suggest a benefit in prophylactic use. Antisera or IVIG hyperimmune against the biologically active, highly conserved core portion of the endotoxin of Gram-negative bacteria have demonstrated variable degrees of protection in animal models and clinical trials. Two clinical trials using monoclonal antibodies against core lipopolysaccharide have been completed. Only subsets of patients with the Gram-negative sepsis syndrome were protected, but both studies gave discrepant results concerning the type of patients that were reported to benefit from administration of these antibodies. Further studies will be necessary to establish whether application of this therapy can be recommended.

Key Words: *Critically ill patients, Clinical trial, Immunoglobulin G*

Revue critique du recours aux immunoglobulines dans la prévention et le traitement de l'infection chez les patients gravement malades

Le besoin de restaurer les niveaux d'immunoglobulines G diminuées suite à un traumatisme ou une chirurgie et/ou la nécessité d'offrir aux patients des anticorps spécifiques dirigés contre des microorganismes variés justifient amplement l'étude des préparations d'immunoglobulines intraveineuses standard (IVIG) comme thérapie adjuvante chez des patients très malades. Alors qu'aucune investigation clinique n'a démontré l'efficacité thérapeutique des IVIG, quelques études semblent suggérer qu'elles puissent être utiles comme agent prophylactique. Des antiserums ou des IVIG hyperimmunes dirigés contre le "core" de l'endotoxine, la portion biologiquement active et la mieux conservée de l'endotoxime des bactéries à Gram-négatif, ont démontré des degrés variables de protection dans des modèles animaux et lors d'essais cliniques. Deux essais cliniques portant sur des anticorps monoclonaux dirigés contre les "core" lipopolysaccharides ont été effectués. Seuls des sous-groupes de patients porteurs de syndromes infectieux à Gram-négatif ont été protégés, mais les deux études ont donné des résultats divergents relativement au type de patients qui auraient bénéficié de l'administration de ces anticorps. D'autres études devront être entrelprises pour établir si l'application de ce traitement est recommandable.

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CRITICALLY ILL PATIENTS ARE AT HIGH RISK FOR INFECTION as a result of several immunological dysfunctions. Decreased levels of immunoglobulin G have been described, especially after trauma and surgery (1). Moreover, neutrophils undergo a decline with respect to chemotaxis, opsonic activity and ability to kill bacteria. In addition, such patients are exposed to a wide variety of organisms in the hospital environment, which further increases the probability of infection. The administration of intravenous immunoglobulin (IVIG) to critically ill patients might enhance host defence by restoring immunoglobulin G levels, and/or by providing patients with specific antibodies directed against various microorganisms or against 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 attempted in critically ill patients: administration of standard IVIG (nonspecific use); and administration of whole plasma, immune globulin preparations or monoclonal antibodies directed against the endotoxin constituent of Gram-negative bacteria (specific use).

NONSPECIFIC USE OF IVIG

Treatment of infections: IVIG can be administered to patients therapeutically for infections. In a nonblinded, randomized, controlled clinical trial in 104 surgical intensive care patients, Just and colleagues (2) administered 4x100 mL of IVIG (Pentaglobin; Biotest Pharma, Frankfurt, Germany), in two 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 did not differ between IVIG and control groups. Efficacy was reported in patients preoperatively classified as 'high risk', but this result in one of several subgroups should be interpreted cautiously. Jesdinsky and co-workers (3) conducted a multicentre, unblinded, randomized, controlled clinical trial among 288 patients with fibrinopurulent peritonitis. Ten grams of an IVIG preparation (Immunoglobulin 7S human iv; Armour Pharmaceuticals, Eschwege, Germany) was administered to 145 patients; a nontreated control group consisted of 143 patients. This study failed to show efficacy of IVIG therapy. One possible explanation for the absence of benefit with IVIG therapy could be the amount of specific antibodies, which might have remained insufficient to confer protection against the large panel of pathogenic bacteria.

Prophylactic use of IVIG: IVIG can also be administered prophylactically and two studies of this approach have been published. Duswald and colleagues (4) administered 2.5 g of IVIG (Intraglobulin, Biotest Pharma, Frankfurt, Germany) to 150 critically ill patients. These investigators observed no protective effects with respect to wound infection, urinary tract infection or pneumonia. Glinz and associates (5) administered 36 g of IVIG (Sandoglobulin; Sandoz, Basel, Switzerland) (12 g on days 0, 5 and 12 after admission to intensive care unit) 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, while the microbiological documentation was questionable.

Recently, Cometta and co-workers (6) completed a blinded, placebo-controlled clinical trial using two IVIG preparations. The first was a standard preparation (Gammagard; Hyland Therapeutics Division, Glendale) administered to 109 patients at a dosage of 400 mg/kg when the patients entered the surgical intensive care unit, and subsequently once a week. The second preparation was IVIG enriched in antibodies against the core lipopolysaccharide (LPS) of *Salmonella minnesota* R595 (Re LPS) (see next section), and administered to 108 patients. The titre of the anticore LPS antibodies was eightfold higher than that in the standard IVIG. A control arm of 112 patients received albumin. The standard IVIG preparation reduced the number of patients who developed infections during the course of the study from 53% in the control group to 36% ($P<0.05$). The reduction was caused by a significant decline in the number of pneumonia cases ($P<0.05$). It appeared, therefore, that standard IVIG can have a protective effect when administered prophylactically to high risk surgical patients. Indeed, detailed analysis of the results showed that the stay in both the intensive care unit and the hospital was shorter for patients receiving standard IVIG than for control patients. Surprisingly, IVIG enriched in antibodies against the endotoxin core failed to give protection against Gram-negative sepsis, septic shock or focal infections. The reason for this is unclear.

Antibodies against endotoxin of Gram-negative bacteria: The toxicity of Gram-negative bacteria is caused by the toxic LPS (endotoxin) that constitutes the outer bacterial membrane. The endotoxin molecule consists of a lipoidal acylated glucosamine disaccharide designated as lipid A, which is the toxic moiety, linked to a polysaccharide side chain (called O antigen) through an intermediate oligosaccharide region, the core. Antibodies to the intact LPS are raised mainly against 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 (7), Ziegler (8) and McCabe (9) hypothesized that by raising antibodies against 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, lacking the enzyme uridine 5'-diphosphonate-galactose 4-epi-

merase; 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 J5, or with whole *E coli* J5 bacterial cells, results in high titres of antibody to epitopes of the LPS core (10). Another rough mutant which has been studied for its ability to raise antibodies to the core region is an Re mutant of *S minnesota*. It was reasoned that antibodies elicited by these two rough mutants should afford protection against a wide range of Gram-negative bacteria by a postulated mechanism requiring two steps: these antibodies should recognize epitopes of the core region shared by LPS from pathogenic Gram-negative bacteria; and the postulated binding should neutralize the endotoxic properties of LPS, ie, lead to suppression or attenuation of the release of mediators such as cytokines. Up to now, neither of these two hypothetical steps has been unequivocally demonstrated. The following sections review what has been learned from studies using the J5 mutant and other rough mutants.

Animal studies: Ziegler and colleagues (11) have shown that granulocytopenic rabbits challenged in the conjunctival sac with *Pseudomonas aeruginosa* develop a massive, lethal pseudomonas infection, and that these rabbits could be protected with J5 antiserum. Some of their results with purified immunoglobulins from human volunteers immunized with *E coli* J5 are reproduced in Table 1 (12). Braude (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 the rough mutant Re of *S minnesota*.

Some investigators, however, were unable to repeat these 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* 01111 were not protected by either of the two antisera to the J5 or to the Re mutants; the mortality was even greater than in mice receiving only saline. In that study, only antibody to the strain-specific LPS was protective (Table 2).

Thus, the animal studies described in this section show that some workers have been successful in demonstrating that antibodies to core glycolipid can be protective, whereas others have not. These discrepant results with various anticore LPS preparations have no simple explanation. First, the precise specificities as well as the mode of action of the antibodies tested have not been clarified. Second, the animal models that were used, the mode of challenge and the nature of LPS or of bacteria used for challenge were all parameters which could have an impact on the protective efficacy of these preparations (29).

These considerations, however, cannot explain all the discrepancies, as opposite results were sometimes

TABLE 1
Protection from lethal pseudomonas bacteremia in neutropenic rabbits treated with intravenous immunoglobulin from humans immunized with *Escherichia coli* J5

Type of immunoglobulin	Mortality (%)*
Preimmune	12 of 14 (86%)
Post immune	3 of 14 (21%)

$P=0.001$ (χ^2) (Reproduced with permission from reference 12)

TABLE 2
Lack of protection after pretreatment with various preparations and inoculations with LPS from *Salmonella typhimurium*

Pretreatment (0.5 mL)	Percentage mortality (number of mice inoculated)
Saline	52 (25)
Antiserum to J5*	75 (12)
Preimmune serum*	64 (11)
Antiserum to J5†	83 (12)
Preimmune serum†	83 (12)
Antiserum to *S typhimurium*	0 (25)‡

*Antisera prepared by the method of Braude et al (7). *Serum from rabbit 25; †Serum from rabbit 26; ‡P<0.005 compared with other trials. LPS Lipopolysaccharide; (Adapted with permission from reference 27)*

obtained using similar antibodies, similar animal models and similar bacterial or LPS challenges (8,9,26, 27,30). Therefore, it can be postulated that additional and as yet still undiscovered negative or positive factors might sometimes operate. For instance, a now well-recognized artefact can result from LPS contamination of the preparation to be tested. 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 protection experiments are almost uniformly administered before bacterial or LPS challenge, this artefact cannot be ruled out in many earlier published experiments. Moreover, the interpretation of protection experiments with rabbit antisera may heavily depend on whether preimmune and immune sera came from the same or different rabbits (27); it has been shown that some normal rabbit sera may have a natural protective power against Gram-negative bacterial or LPS challenge. Similarly, when testing monoclonal antibodies, the degree of purification is critical for protection experiments. Indeed, ascites and hybridoma fluids can contain various proteins and peptides, such as cytokines, some of which might be able to bind to LPS or to induce tolerance to LPS in experimental animals. Most protective experiments reported, including those by Teng et al (30) and Young et al (33), have involved ascites or hybridoma fluids. Finally, experimental variability might account for important differences in survival from one experiment to the other, so the reporting of only part of the experiment might contain some bias (34,35). In conclusion, the precise description of the control preparation and of the preparation

TABLE 3
Mortality of patients with Gram-negative bacteremia

Patients	Therapeutic serum: Nonimmune serum (mean titre 1/6)	Therapeutic serum: Immune (J5) serum (mean titre 1/32)	P value
All	38/100 (38%)	22/91 (24%)	0.04
Profound shock	26/34 (76%)	17/37 (46%)	0.009

Adapted with permission from reference 36

TABLE 4
Prophylaxis of Gram-negative (GN) shock with J5 plasma in surgical patients

	Nonimmune plasma	Immune (J5) plasma	P value
All patients	136	126	
Focal GN infections	55	45	
Development of GN shock	15	6	0.049
Death from GN shock	9	2	0.033
Abdominal surgery	83	71	
Development of GN shock	13	2	0.006
Death from GN shock	9	1	0.017

Adapted with permission from reference 37

containing antibody is critical for the interpretation of experimental data in animals.

Clinical studies: As in animal studies, some of the clinical data indicated that patients could be successfully treated or protected with antibodies, whereas some did not. In 1982, Ziegler and co-workers (36) reported a pioneering randomized, blinded, controlled study in patients with Gram-negative bacteremia who received either serum of 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 mean antibody titres to J5 LPS between control and immune serum. These sera were administered to 304 patients, among whom 191 had Gram-negative bacteremia (Table 3). The results led to the conclusion that human J5 antiserum substantially lowers mortality from Gram-negative bacteremia and septic shock. Regarding the mode of protection, it was hypothesized that J5 antibodies were present in the serum after immunization and 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, as favorable outcome was significantly correlated only with whether the patients had received control or immune serum, and not with the J5 antibody level contained in a given serum.

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 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 (5%) receiving J5 plasma and 15 of 136 patients (11%) in the control group developed Gram-negative shock, and related deaths occurred in two of 126 J5 recipients (1.6%) and in nine of 136 controls (6.6%) ($P<0.05$, one-tailed Fisher's exact test). The difference was observed mainly in patients undergoing abdominal surgery (Table 4). Although administration of J5 antibody failed to lower the incidence of Gram-negative infections, it seemed to reduce the most serious consequences of such infections. As in the previous study, protection was related to immune plasma, not to specific anticore antibody level in a given plasma (unpublished data).

Two other studies, however, have failed to demonstrate a beneficial effect of J5 antiserum. McCutchan and colleagues (38) studied neutropenic patients as well as patients receiving bone marrow transplants. These patients were given J5 serum as a prophylactic measure. The results did not suggest that J5 serum prevented Gram-negative bacteremia or the occurrence of fever which, in at least some of these patients, is considered to be caused by release of endotoxin from the gut. One possible explanation for this failure to demonstrate a beneficial effect of J5 serum could be the low power of the study, since the number of bacteremic Gram-negative infections was small. Recently, the present authors conducted a blinded study in which 73 children with purpura fulminans received either control plasma (33 patients) or J5 plasma (40 patients). There was no difference in mortality between the two groups, suggesting that J5 plasma was not effective in the treatment of meningococcal septicemia (unpublished data).

As already mentioned, in both successful clinical studies with J5 antiserum (36,37), the protection was of unclear origin because outcome could not be convincingly correlated with anti-J5 LPS antibodies (36, unpublished data). In addition, in 70 volunteers who donated their plasma for one of these studies (37), immunization with the *E coli* J5 vaccine (provided by E J Ziegler) induced a modest median threefold increase in anti-J5 LPS antibodies, but no increase in anti-Re LPS or antilipid A antibodies (39). Thus, the protection afforded by J5 antiserum could not be attributable to anti-J5, LPS, anti-Re LPS or antilipid A antibodies.

IVIG enriched with anti-LPS core antibodies have been purified from serum of immunized volunteers or from serum of donors with naturally acquired high levels of anti-LPS antibodies. Calandra and colleagues (40), in a randomized, double-blind trial, compared the

efficacy of IVIG collected from volunteers after *E coli* J5 immunization 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 antibody titres against J5 LPS in the hyperimmune preparation compared with standard IVIG. No difference in mortality was reported between the two groups. As previously noted, Cometta and co-workers (6) compared anticore LPS IVIG (collected from blood donors with naturally occurring high anti-Re antibodies) with standard IVIG or placebo in a prophylactic double-blind study. No protection was afforded by anticore LPS antibodies, in contrast to standard IVIG. One hypothesis to explain the ineffectiveness of core LPS IVIG is that IgM antibodies, which were absent from the IVIG preparations, might be necessary for protection (15). However, as the precise specificity and the mode of action of anticore antibodies is 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 have 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. This emphasizes the need for understanding which factors were responsible for protection in the successful studies using serum or plasma that were absent in the unsuccessful studies using plasma or immunoglobulin preparations.

Studies with monoclonal antibodies: In recent years, several monoclonal antibodies have been developed that recognize various epitopes of the core region of endotoxin (30,33,42-52). Two of these monoclonal antibodies, both of the IgM class, have been tested for treatment of patients with Gram-negative infections.

Young and associates (33) have developed murine monoclonal antibodies 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 raise monoclonal IgM antibodies against Re LPS or lipid A. The ability of the monoclonal antibodies to prevent or treat infection was tested in female mice. They found that the antibodies were not protective when administered alone (33), but one of them, an antilipid A IgM monoclonal antibody called E5, appeared to be synergistic with antibiotics in prophylactic or therapeutic experiments. For instance, mice were injected with a dose of live serum resistant bacteria (three challenge organisms were used) that would be expected to kill between 80 and 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 h, the monoclonal antibody E5 was injected intravenously. There were four treatment groups with 14 mice per group and per challenge organism. Group A received antibiotics alone with 45% survival (pooled results of the three challenge organisms); group B received antibiotics and monoclonal antibodies with 64% survival ($P<0.05$, one-tailed, compared with group A when the results with the three challenge bacteria were combined); group C received monoclonal antibodies and saline with 29% survival; and group D received saline alone with 24% survival.

In another experiment, E5 was used in the treatment of infections with two strains of *Ps 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 the treatment with antibiotics alone. These studies suggested that E5 might have a protective effect in some experimental conditions. However, definitive conclusions are difficult to draw because ascites fluid, not purified antibody, was used, and because individual experiments had to be pooled to obtain statistically significant differences.

In clinical study of E5 (53), patients with a suspected Gram-negative septic syndrome were randomly assigned to receive intravenously either the antibody (2mg/kg daily for two 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 of the mortality in the 137 patients without shock at entry ($P=0.03$), whereas the 179 patients who were in shock were not protected. Shock was defined as refractory hypotension, whereas patients with organ failure or disseminated intramuscular coagulation were not considered in shock if they had a systolic pressure higher than 90 mmHg. Among patients without shock, a comparable reduction in mortality occurred in both bacteremic and nonbacteremic patients. Administration of E5 was safe; less than 2% of patients developed allergic side effects. Because this study suggested that E5 was effective only in a subgroup of patients without shock, an unanticipated finding, a confirmatory multicentre study has been initiated.

The second monoclonal antibody, subsequently designated as HA-1A, was produced by Teng and coworkers (30) from a hybridoma obtained by fusing B lymphocytes from human spleen with heteromyeloma cells. Splenocytes from one patient with Hodgkin's disease who was undergoing splenectomy and who had previously been vaccinated with the J5 mutant of *E coli* were used. The monoclonal antibody reacted in vitro with many unrelated species of Gram-negative bacteria. Moreover, the monoclonal antibody in hybridoma fluid was shown to be protective against endotoxin in the dermal Shwartzman reaction in rabbits and against Gram-negative bacteremia in mice. Protection appeared to be specific for Gram-negative bacteria because the

anti-J5 monoclonal antibody failed to protect against pneumococcus, a Gram-positive organism that lacks endotoxin. Based on enzyme-linked immunosorbent assays and binding inhibition experiments, the monoclonal antibody was later considered to recognize specifically lipid A (54). These experimental observations, however, could not be reproduced. Indeed, using purified monoclonal antibody instead of crude hybridoma fluid, it could not be demonstrated that HA-1A could be protective (26) in models very similar to those used by Teng et al (30). In addition, HA-1A, in contrast to type specific anti-LPS antibodies, did not suppress LPS induced tumour necrosis factor secretion in mice, suggesting that it was not able to prevent LPS 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 to Gram-positive bacteria, fungi and to lipids unrelated to lipid A including cardiolipin and lipoproteins (such controls have not been previously reported [30,54]). This broad binding pattern suggested nonspecific interactions with hydrophobic constituents and may call into question the specificity of HA-1A for lipid A (unpublished data).

Ziegler and colleagues (54) administered a single dose of HA-1A (100 mg intravenously) or albumin as control to patients with a presumptive diagnosis of Gram-negative sepsis. Of the 543 patients, 317 had microbiologically documented Gram-negative infections, of which 200 had positive blood cultures at randomization. HA-1A did not reduce the mortality in the overall study population, nor in the 117 patients with nonbacteremic Gram-negative infections. However, there was a significant decrease in mortality in the subgroup of patients with Gram-negative bacteremia (P=0.014), the difference being most pronounced among the 101 patients who were in shock at study entry. When analyzing these data in detail, it appeared that, by chance, differences in risk factors between placebo and HA-1A recipients might have been present at randomization in the subgroup of 200 patients with Gram-negative bacteremia. Indeed, a total of 101 serious complications (disseminated intravascular coagulation, adult respiratory distress syndrome, acute hepatic failure and acute renal failure) were present at entry among the 95 placebo recipients (mean of 1.06 per patient) compared with 85 among the 105 HA-1A recipients (0.81 per patient) (P=0.07, comparison of Poisson rates). These 16 additional serious complications in the placebo group might account for some of the higher death rate in this group (13 deaths in excess).

Definitive conclusions for the use of monoclonal antibodies against endotoxin core are difficult to draw at the present time. Indeed, one antibody (the HA-1A) tested experimentally by two independent groups showed divergent efficacy possibly related to its degree of purification (26,30). The other antibody (E5) has been reported only once to be moderately efficacious in animals when tested as ascites fluid. Moreover, the clinical results of the two studies are somewhat conflicting. First, in one study, mostly patients in shock were protected, while in the other study only those patients not in shock were protected. Second, in one study, only patients with positive blood culture were protected by the treatment, while in the other group, protection occurred independently of blood culture status. Thus, further studies are needed to define prospectively and specifically the type of patients who might benefit from this therapeutic approach.

CONCLUSIONS

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

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

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