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EFFECTS OF HIGH-DOSE OF INTRAVENOUS IMMUNOGLOBULIN AND ANTIBIOTICS ON SURVIVAL FOR SEVERE SEPSIS UNDERGOING SURGERY

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ABSTRACT—The objective of this study was to assess the impact on outcome of adjuvant therapy (high-dose of immunoglobulin [Ig] M-enriched intravenous Ig, IVIG) in intensive care unit (ICU) patients who underwent surgery by abdominal sepsis. This was a prospective, randomized, double-blind, controlled study set in the medical/surgical ICUs of seven teaching hospitals. Patients with severe sepsis and septic shock of intra-abdominal origin admitted to the ICU within 24 h after the onset of symptoms were included in the study. Polyvalent IgM-enriched Ig (Pentaglobin®; IVIG group) at a dosage of 7 mL/kg/day for 5 days or an equal amount of 5% human albumin (control group) was randomized. Fifty-six patients were enrolled. The overall mortality rate was 37.5.%. Twenty patients had shock and 36 had severe sepsis (the mortality rate was 55.0% and 25.0%, respectively). In the intent-to-treat analysis, the mortality rate was reduced from 48.1% in patients treated with antibiotic (ATB) plus albumin to 27.5% ($P = 0.06$) for patients with ATB plus IVIG. The organ failure score (1.0 ± 0.6 vs. 1.2 ± 0.9), organ dysfunction score (1.7 ± 1.1 vs. 1.8 ± 1.0), and reoperation rate (17.2% vs. 29.6%) were not different between IVIG and control groups, respectively. Eight patients (14.3%) received inappropriate ATB initial therapy (IAT), and seven died (87.5%). IAT was the only variable independently associated with death (odds ratio, 19.4) in a logistic regression model. We conclude that IVIG administration, when used in combination with adequate antibiotics, improved the survival of surgical ICU patients with intra-abdominal sepsis. The initial choice of antibiotic has a dramatic impact on outcome.

KEYWORDS—Intra-abdominal sepsis, intravenous immunoglobulins, IgM-enriched IVIG, ICU mortality, septic shock, severe sepsis, antibiotic therapy

INTRODUCTION

Sepsis in surgical patients continues to have high morbidity and mortality despite the development of new and powerful antibiotics. Insufficient antibody response in critically ill patients, particularly those undergoing surgical procedures, may be due to failure of T cell-mediated help, resulting in insufficient secretion or activity of cytokines required for adequate B cell activation, proliferation, or differentiation into immunoglobulin (Ig)-secreting cells (1). Diminished levels of IgG, IgA, and IgM have been reported after trauma and after major surgical procedures (2, 3). In patients with sepsis, favorable outcome seems to be closely associated with antibody levels against the causative pathogen (4).

Different strategies in sepsis are concerned with modulating a dysregulated host response (5). Therefore, passive immunotherapy with intravenous Igs (IVIGs) may represent a logical attempt to restore normal levels of antibodies directed against common pathogens and to enhance the function of polymorphonuclear and Kupffer cells (6). Moreover, the IVIGs can neutralize endotoxins and exotoxins by scavenging active complement components and lipopolysaccharides, by stimulating opsonizing and bactericidal activity in serum, by reducing proinflammatory mediators, and by increasing anti-inflammatory mediators (7).

However, results of clinical studies on the prophylactic and therapeutic effect of IVIG in patients with sepsis have been conflicting. It has been reported that administration of IVIG improves the survival of septic surgical patients (8) and that, when used in combination with antibiotics, this effect seems superior to that of antibiotics on their own in patients at high risk of postsurgical infection (9). However, it has been reported that IVIGs have no effect on the mortality and septic shock complications of pediatric head trauma patients (10), but that they can prevent the development of nosocomial pneumonia in adult multitrauma patients (11). Furthermore, IgG was applied to 653 sepsis patients having an APACHE II score >20 points (12); an improvement was obtained in the clinical picture, but the mortality rate could not be reduced. Nevertheless, the heterogeneity of participants, small patient numbers, and a lack of standardization in measuring outcome may account for the reported variation in benefits obtained in sepsis-related and trauma-related studies.

Therefore, this prospective, randomized, double-blind, controlled, multicenter study was conducted to assess the impact of IgM-enriched IVIG (Pentaglobin®) and antibiotic (ATB) therapy in an homogeneous group of critically ill patients with proven intra-abdominal sepsis. Pentaglobin is a commercially available IVIG specifically enriched in IgM and IgA (content of 38 g/L IgG, 6 g/L IgM, and 6 g/L IgA) and also

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contains toxic-binding and neutralizing antibodies to various gram-positive and gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas* sp., and *Klebsiella* sp (13, 14).

The primary objective of the study was to compare the outcome of ICU patients with abdominal sepsis treated with Pentaglobin in addition to antibiotics versus ATB therapy plus 5% albumin. Secondary aims were to assess the impact of inappropriate initial ATB therapy on mortality rate, the severity of multiorgan dysfunction syndrome, and the incidence of reoperation in each group.

PATIENTS AND METHODS

From January 1996 through January 2001, all potentially eligible patients with severe sepsis or septic shock (according to the 1992 ACCP/SCCM sepsis criteria) (15) of intra-abdominal origin admitted to intensive care units (ICUs) of the participating hospitals within 24 h after the onset of symptoms were eligible to participate in a prospective, randomized, double-blind, controlled study. The study was interrupted from 1997 through 1999 because of administrative issues relating to the study medication supply. The exclusion criteria were as follows: severe immunosuppression, irreversible end-stage organ damage, Glasgow coma score of 3/15, very late heart failure with grade IV dyspnea, and pregnancy. The study protocol was approved by the Ethics Committee of the Argentine Society of Intensive Care Medicine, and in every case, informed consent was obtained from the patients or their relatives.

Abdominal sepsis was defined by the presence of systemic inflammatory response syndrome (SIRS) (16) and a surgically confirmed abdominal focus. To include etiologies such as suppurative cholangitis and pancreatic infection, it was mandatory to obtain purulent material or to detect potential pathogens using gram staining. Appropriateness of the surgical procedure (successful eradication of focus) according to criteria of the attending surgical team and the intensivist was required for inclusion in the study. The surgical technique and ATB management were not standardized and were left at the discretion of each center. Appropriate microbial samples were obtained before prescribing ATB therapy. All isolated bacteria were identified and antimicrobial susceptibilities of isolates were determined by the disk diffusion method. Inappropriate ATB therapy (IAT) was considered if the isolates were not sensitive to the empiric ATB therapy administered (17–19).

The enrolled patients received standard care and treatment in the ICU, in addition to empirical ATB therapy. Patients were randomized into two groups (the IVIG group and the control group) according to a computer-generated randomization list stratified by center. The delivering randomized assignment was done using contact (by telephone) with a central office (central randomization process). The allocation was unknown to the investigators and they remained blind to therapy the next patient might receive. A polyvalent IgM-enriched immunoglobulin preparation (Pentaglobin; Biotest, Frankfurt, Germany; IVIG group) or an equivalent amount of 5% human albumin (control group) was administered at a dosage of 7 mL/kg/day for 5 days. The information on the vials was totally obscured (by covering with labels) before being issued. Each group of patients received routine therapy for abdominal sepsis according to the criteria of the attending ICU team.

Demographic data (age and sex), diagnosis at ICU admission, days of stay in the ICU, and outcome at discharge were recorded for each patient. Severity of illness at admission was assessed by the APACHE II score, and the value recorded for each variable was the worst value during the first 24 h of ICU stay, as this was the procedure reported by Knaus et al. (20). Procedures carried out for each patient were assessed daily using the therapeutic intervention scoring system (TISS) (21). The TISS value are shown as the overall average per patients (the TISS value was computed at first as the mean value for each patient and was then averaged). Multiple organ dysfunction and organ failure were assessed using a scoring system previously used by our group (22) (Table 1).

Patients with early death (<5 days postsurgery) were considered nonevaluable. Patients for whom ATB susceptibility testing showed pathogens resistant to empirically administered antibiotics were also excluded in a per-protocol analysis. All patients were included in the intent-to-treat analysis.

Statistical analysis

An intent-to-treat analysis was carried with all randomized patients. A secondary analysis was planned with evaluable patients who received appropriate empiric therapy. Patients with protocol violation or who did not receive a full course of therapy (5 days) were considered not evaluable. The number of patients required to be included in the study to achieve a statistical power of 80% and an alpha error of 5% was a minimum of 45 in each arm. The expected mortality rate in the control group was 50% and the magnitude of the expected treatment effect was 30%.

The coordinators of the study (A.R. and F.P.) were scheduled to carry out a blind interim analysis of data after reaching 60% (n = 24) of the expected numbers of patients in each group to decide whether to continue or to terminate the study.

Differences between IVIG and control groups were analyzed by means of the χ^2 test or Fisher's exact test (for comparison of rate), Student's *t* test, and the Mann-Whitney *U* test. Differences in the 30-day survival rates between the IVIG group

TABLE 1. **Criteria used to define organ dysfunction and organ failure**

Organ	Organ dysfunction	Organ failure
Cardiovascular	• Expansion requirement to maintain mean arterial pressure (MAP) in absence of acute volemic losses • Vasoactive drug requirement and/or acute indication of digital or antiarrhythmic agents	At least two of: • Heart rate > 130/min • MAP < 80 mmHg • Severe arrhythmias or of difficult control • Acute myocardial infarction with <72 h
Respiratory	• Oxygen requirement	• Arterial oxygen pressure < 50 mmHg with inspired O_2 ≤0.21% • Arterial oxygen pressure < 70 mmHg with inspired O_2 >0.21% and <0.50% • Delta(A-a) O_2 >200 with inspired O_2 >50%
Renal	• Expansion requirement with volume or diuretics to maintain diuresis	• Creatinine > 2 mg% in absence of chronic renal failure • Doubling of creatinine levels within 24 h • Emergency dialysis
Digestive	• Change in bilirubin or hepatic enzyme levels • Ileus or diarrhea within 72 h postoperatively	• Nonvaricose bleeding • Bilirubin > 10mg% • Amylasemia > 1000 U • Alkaline phosphatase > 200 U • Acalculous cholecystitis • Ileus >72 h postoperatively • Diarrhea (in absence of chronic diarrhea)
Hematology	• Transfusion requirement in absence of active bleeding • Disturbed clotting parameters • Vitamin K and/or plasma requirement	• Hematocrit < 30% in absence of chronic anemia • Leukocytes > 30,000 or < 3,000 mm^3 • Platelets < 80,000 mm^3
Central nervous system	• Confusion, agitation, or delirium	• Glasgow Coma Score < 10 in absence of depressive drugs

and the control group were assessed using the Kaplan-Meier method. Differences between the groups were analyzed by log-rank test. The estimated probability of death was calculated based on the APACHE II score (13). A stepwise logistic regression model was realized to identify the independent factors associated with mortality (SPSS 11.0). Independent variables were Apache II score, inadequate ATB, age, Ig administration, and multiorgan dysfunction and organ failure. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 56 patients was randomized. Thirty-six patients had severe sepsis, and 20 developed septic shock (mortality rate of 25.0% and 55.0%, respectively). Twenty-nine patients integrated into the IVIG group and 27 into the control group. Figure 1 shows the flow chart of the study. There were no differences between the two groups at ICU admission (Table 2). The postoperative diagnoses were fecal peritonitis (n = 27), appendicular peritonitis (n = 4), purulent peritonitis (n = 6), perforated peptic ulcer (n = 8), suppurative cholangitis (n = 3), bile peritonitis (n = 2), suppurative pelvic peritonitis (n = 1), pancreatic abscess (n = 2), intra-abdominal abscess (n = 2), and penetrating abdominal trauma (n = 1). After blind interim analysis of the data from 56 patients, enrollment was suspended because a significant difference in the mortality rate in a subgroup analysis of evaluable patients with appropriate ATB therapy was documented.

Twenty-one patients died, representing an overall mortality rate of 37.5% in the intent-to-treat analysis. The mortality rate was lower in the IVIG group (27.5%; n = 8) than in the control group (48.1%; n = 13), although this difference was not statistically significant ($P = 0.06$). The estimated odds ratio (OR) for survival was 2.43 (95% confidence interval [CI] = 0.80–7.39). The survival analysis by the Kaplan-Meier method showed differences that were not statistically significant ($P = 0.06$), although a positive trend was observed (data not shown). A nonsignificant trend of less reoperations in the IVIG group compared with the control group (17.2% vs. 29.6%, P = NS) was observed. The multiorgan dysfunction score and organ failure score did not demonstrate significant differences between the groups over the ICU stay (Table 2). Stepwise logistic regression analysis adjusting for severity-of-illness at admission identified only inappropriate ATB as an independent variable associated with mortality (OR, 19.4; 95% CI, 1.17-324.1).

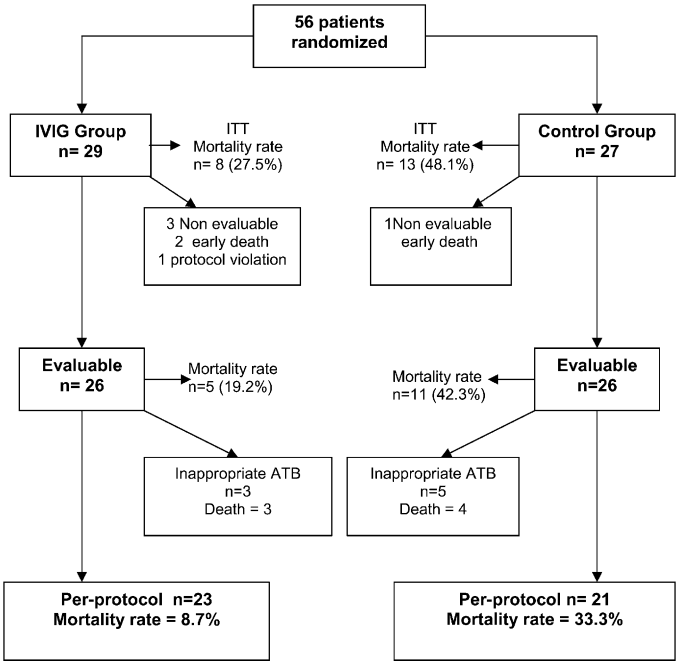

FIG. 1. **Flow chart of patients of study.** ITT, intent-to-treat analysis.

TABLE 2. **Characteristics in the intention-to-treat population**

Data	IVIG Group, n = 29	Controls, n = 27
Age in years*	61.3 (19.9)	65.9 (18.2)
APACHE II score*	16.11 (5.9)	15.22 (6.1)
TISS score*		
First day	19.0 (6.5)	21.3 (9.3)
Overall	16.6 (5.2)	18.9 (1.0)
Multiorgan dysfunction score*		
First day	2.6 (1.2)	2.3 (1.3)
Overall	1.73 (1.1)	1.88 (1.0)
Organ failure score*		
First day	1.6 (1.1)	1.5 (0.9)
Overall	1.0 (0.6)	1.2 (0.9)
ICU stay, days*	14.2 (14.1)	10.8 (10)
Male (n,%)	15 (51.7)	12 (44)
Adequate antibiotic therapy (n,%)	26 (89.7)	22 (81.4)
Shock (n,%)	12 (41.4%)	8 (29.6%)

*Data reported as means (SD). All comparisons had $P > 0.05$. IVIG, active group. APACHE and TISS scores at admission.

Four patients enclosed in the intent-to-treat analysis were not evaluable per protocol: three patients failed to receive the 5-day course of therapy due to early death (two in the IVIG group and one in the control group), and one patient in the IVIG group failed to meet the inclusion criteria. Thirty-four evaluable patients (n = 52) had severe sepsis and 18 developed shock (the mortality rate was 23.5% and 50.0%, respectively; P = NS). The mortality rate in evaluable patients with shock and severe sepsis according to administration of IVIG or appropriate initial ATB therapy is shown in Table 3. Among the 26 patients who received IVIG, five died. Three patients who received IAT died, whereas the mortality rate was significantly lower (8.7%, $P < 0.01$) in the remaining 23 patients with an adequate ATB prescription. In the control group, five patients received IAT and four died, whereas 21 patients received adequate initial ATB and only seven died (a mortality rate of 80% vs. 33.3%, $P = 0.10$).

Inadequate ATB was considered as a confounding factor, and eight patients (seven of which died) were excluded (three in the IVIG group and five in the control group). Details of patients with IAT are shown in Table 4. The characteristics

TABLE 3. **Mortality rate in 52 evaluable patients according to immunoglobulin administration (IVIG) or adequate antibiotic (ATB) therapy.**

	Overall		Patients with shock		Patients with severe sepsis	
	n	Death	n	Death	n	Death
IVIG	26	5 (19.2%)	11	4 (36.4%)	15	1 (6.7%)
5% Alb	26	11 (42.3%)	7	5 (71.4%)	19	6 (31.6%)
ATB	44	9 (20.4%)	12	3 (25.0%)	32	6 (18.8%)
IAT	8	7 (87.5%)	6	6 (100%)	2	1 (50%)

TABLE 4. **Features and microbiological spectrum of eight patients with inadequate ATB**

Group	Diagnosis	APACHE II	TISS	Length of stay (days)	Age	ICU death	ATB	Abdominal microorganisms isolated
IVIG	Fecal peritonitis	22	21	7	65	Yes	Ampicillin (Amp), Gentamicin (G), and Metronidazole (M)	*Klebsiella* sp.
	Intestinal necrosis	21	26	30	72	Yes	Ceftriaxone (Cro) and M	*Candida* sp.
	Apendicular peritonitis	18	8	7	73	Yes	Amp, G, and M	*E. coli* and *P. aeruginosa*
	Mean values	20.3	18.3	14.6	70			
Control	Bile peritonitis	17	31	6	41	Yes	Ceftazidime (Caz) and M	MRSA
	Fecal peritonitis	8	19	10	76	Yes	Amp, G, and M	MRSA
	Postoperative peritonitis	13	10	5	22	No	Cro and Clindamycin	*P. aeruginosa*
	Fecal peritonitis	13	21	21	63	Yes	Cro and M	*P. aeruginosa*
	Fecal peritonitis	25	20	12	90	Yes	Amp, G, and M	*Klebsiella* sp. and MRSA
	Mean values	15.2	20.2	10.8	58.4			

IVIG, Intravenous immunoglobulins

(such as sex, age, APACHE II score, TISS, and ICU length of stay) of the excluded patients did not differ significantly from those of the patients included in the per-protocol analysis. However, the mortality rate was significantly higher ($P = 0.02$) in these patients (seven of eight = 87.5%) than in the per-protocol population (9/44 = 20.4%).

The per-protocol analysis was based on 44 patients, resulting in a satisfactory inclusion of 79% of the total intention-to-treat population. Twenty-three were assigned to the IVIG subgroup and 21 received 5% albumin. Diagnoses in these patients were as follows: fecal peritonitis in 23 (52.4%), purulent peritonitis in 10 (22.4%), perforated peptic ulcer in 4 (9.1%), suppurative cholangitis in 3 (6.9%), intra-abdominal abscess in 2 (4.6%), hemorrhagic necrotic pancreatitis in 1 (2.3%), and suppurative pelvic peritonitis in 1 (2.3%). The isolated microbes were *E. coli* (41.7%), *Peptostreptococcus* sp. (13.7%), anaerobic flora (9.2%), methicillin-resistant *S. aureus* (6.6%), *Enterococcus* sp. (6.6%), *Pseudomonas* sp. (6.6%), *Enterobacter* sp., *Acinetobacter baumannii*, *Klebsiella* sp., and *Proteus* sp. (each 2.3%), and polymicrobial flora (4.6%). No isolated microorganisms were documented in 13 patients (29.5%), despite a purulent abdominal specimen being taken from these patients. There were no differences between the two subgroups with regard to demographic data or to mean values of APACHE II score, TISS, multiorgan dysfunction syndrome and organ failure, and length of ICU stay (Table 5).

In the subset of patients with appropriate ATB therapy, the mortality rate was significantly lower ($P = 0.04$) in patients treated with Igs than in controls (8.7% vs. 33.3%). The estimated probability of death according to the APACHE II score was 37.0% for the IVIG group and 38.0% for controls (P = NS). However, a significant reduction in mortality for IVIG group patients ($P < 0.01$) was observed, with reductions in the relative and absolute risks of death of 74.0% and 25.0%, respectively. Finally, the survival analysis by the Kaplan-Meier method (Fig. 2) showed that survival in the IVIG group was significantly higher than in the control group (log-rank test, 5.07; $P = 0.02$). The estimated increase in survival associated with prescribing initial appropriate ATB therapy was 64.7% (95% CI, 30%–90%), whereas it was estimated to be 26.9% (95% CI, 2%–50%) for IVIG.

DISCUSSION

This is the first prospective, randomized, controlled trial designed to evaluate the impact of high-dose intravenous Ig (as coadjuvant therapy) in an homogeneous group of patients with abdominal sepsis. An important finding was that the administration of IgM-enriched Igs (Pentaglobin) in addition to ATB did produce a 20% of mortality reduction in the intent-to-treat analysis. The lack of significant difference in the mortality rate between both groups may be attributable to the small sample size (beta-error). Only in the subgroup of patients with appropriate initial ATB was a significant reduction in the mortality rate seen, associated with Pentaglobin administration. It represented 25% reduction in the absolute risk of death. These findings suggest that in this subgroup of patients with abdominal sepsis, one additional life would have been saved for every four patients treated. These results agree with a recent meta-analysis (23). Others authors (24) reported that the analysis of the patients with adequate ATB therapy is more important to the clinical care of patients than the "clinically evaluable" group analysis of the entire cohort.

An outstanding finding was that the appropriate initial

TABLE 5. **Characteristics of evaluable patients with appropriate initial ATB therapy**

Data	IVIG subgroup, n = 23	Control subgroup, n = 21
Men (%)	11 (47.8)	9 (42.8)
Age, years	59.7 (21.8)	67.6 (15.0)
ICU stay, days	15.6 (14.6)	11.1 (11.0)
APACHE II score	14.9 (5.5)	15.6 (5.8)
TISS score		
Overall	15.3 (4.7)	18.3 (9.1)
First day	18.2 (5.9)	20.4 (9.6)
Multiorgan dysfunction score		
Overall	1.5 (1.0)	1.7 (1.0)
First day	2.7 (1.4)	2.2 (1.1)
Organ failure		
Overall	0.9 (0.6)	1.1 (0.9)
First day	1.5 (1.2)	1.4 (0.9)

Data as mean (SD). P = not significant in the all comparison between IVIG subgroup and Control subgroup. IVIG, active subgroup. APACHE II and TISS scores at admission.

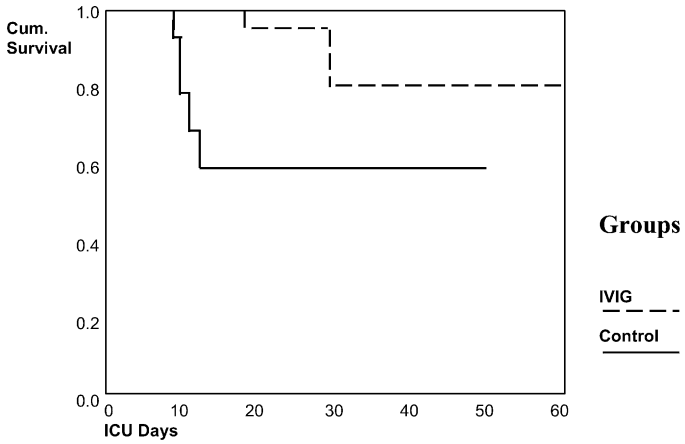

FIG. 2. **Actuarial Kaplan-Meier analysis in the evaluable patients with appropriate ATB therapy demonstrated that IVIG group survival was significantly greater than that of the control group.** $P = 0.02$, log-rank = 5.07.

prescription of ATB is the major determinant of survival in surgical patients with abdominal sepsis. The importance of appropriate initial ATB therapy has been previously emphasized (25–27). Crude mortality rates in critically ill patients are 8.5% to 39.9% lower if initial empiric antimicrobial therapy is appropriate than if modification is required (26, 27). In addition, the adequate empirical ATB treatment of the gram-negative sepsis reduces the probability of shock and mortality by 50% (28). In a recent study, Garnacho-Montero et al. (29) observed that the appropriate ATB use reduces mortality rate by >43% in patients with septic shock and by 23% in those with severe sepsis. In our study, the estimated increased in survival associated with adequate initial ATB therapy was 75% in patients with septic shock and 31.2% in patients with severe sepsis.

The selection of patients with sepsis who actually benefit from new sepsis treatment strategies is difficult and remains the main restrictive factor when designing a clinical study. The main reasons why the results of multicenter trials on sepsis are often inconclusive are the differences in types of participants, interventions, and method of measuring outcome (30–35). It has been reported that a more uniform population may be enrolled by using explicit, reproducible, and minimally manipulable inclusion criteria (36). A re-evaluation of the approach to clinical trial design for assessing new treatment options that significantly reduce the mortality and morbidity rates associated with sepsis (35) has proposed three pre-enrollment criteria. First, there should be evidence of infection using standard clinical and microbiological criteria, thus avoiding terms such as "clinical signs and symptoms of infection." Our patients met this criteria. Second, it should be demonstrated that the patient indeed falls into a group that may reasonably be expected to respond to the particular therapeutic intervention being studied (patients with appropriate initial ATB therapy). Finally, patients should fall into an appropriate category of severity. This requires determining the levels of severity above and below which patients should be excluded because their prognosis will significantly affect the event rate.

Given that the treatment of sepsis is complex, it is impossible to compare new treatments against a standard basal therapy. Therefore, studies on sepsis examine new strategies in addition to standard treatments. These "standard" procedures include the "appropriate administration of antibiotics" and adequate restoration of intravascular volume, with or without a contribution from inotropic/vasopressor agents. Our results differ from other studies on sepsis (31–34). One reason for this may be that our target population was homogeneous because criteria for site of infection (intra-abdominal), type of patient (surgical), acute pathological condition (abdominal sepsis), and time from the onset of symptoms (within 24 h) had to be met before patient enrollment. This is in agreement with recommendations regarding conditions to be met by clinical trials to evaluate new therapeutic strategies for sepsis (36–40).

It should be noted that the dosage of polyvalent IgM-enriched preparation used in the study was double than that which was approved. This dosage was chosen because it was considered possible that higher concentrations of IgM could have immunomodulatory effects (30). Recent studies (41, 42) support the use of the dosage chosen in this trial.

The patients in our control group received albumin and showed higher mortality than the interventional group. Two meta-analysis (43, 44) reported that albumin may increase the risk of death in critically ill patients. By contrast, a recent meta-analysis (45) (including only studies using purified albumin) detected no difference in mortality in critically ill patients treated with albumin. Moreover, these authors considered that the use of albumin might be beneficial. These results were confirmed by the SAFE study (46). Our patients received albumin at a lower concentration (5% instead of 20%). It is unlikely that a 5% albumin infusion would be responsible for a potential increase in mortality in the control group because the estimated and observed mortalities in the control group were similar.

Our study has several limitations. First, it had a small sample size, and therefore, the results may not be able to be extrapolated and underpowered to detect a clinically important mortality differences in overall analysis. However, Foster and Doig (38) consider that although the heterogeneity of a study (less strict inclusion criteria) improves the general applicability of results (external validation), it also makes it more difficult to demonstrate the true effect of the treatment drug being studies. Furthermore, matching of large and smaller studies were highly positively correlated ($r = 0.75$) and is in agreement with 82% to 90% of the meta-analyses. The principal discrepancy between the two types of studies were that larger trials identified smaller treatment benefits than did smaller trials (39). Second, our secondary outcomes are based on a subgroup analysis. The use of subgroup analyses to draw conclusions is associated with several difficulties (47, 48) and care should be taken to avoid subgroup analyses based on events that occurs after randomization. However, a variety of appropriate subgroups may exist within a study population. They are classified in two categories: those that impact mortality rate independent of the study drug and those that additionally affect the activity of the study drug under investigation (37). The first possibility is applicable to our subgroup analysis. Further, although not ideal, subgroup analysis is used routinely for important decisions, including the approval of investigational agents in which optimal data are not available (24). It may be that colonization with ATB-resistant organisms would be

surrogate for a patients at higher risk of death. To compare effects of coadjuvant therapy of sepsis in patients with inappropriate ATB therapy has little bearing on clinical medicine. Third, this study evaluated patients with abdominal sepsis with successful surgical eradication of sepsis and adequate empirical ATB. Therefore, our results may be not generalizable to other infectious sites. Finally, a small proportion of patients with abdominal sepsis were randomized because of the strict inclusion criteria of the study protocol and we did not record a screening log for the excluded patients. Douzinas et al. (49) reported that it is extremely difficult to obtain a large population of homogeneous patients. Indeed, the implementation of strict inclusion criteria makes enrollment troublesome and invariably restricts the number of patients under study.

In summary, our findings suggest that there is no simple therapy for sepsis, just as there are no simple therapys for cancer. Survival increased 20% in the arm receiving IVIG at the intent-to-treat analysis. Interestingly, for evaluable patients, survival was lowered to 20% when IAT was prescribed, independent of the administration of IVIG. Adequate initial ATB prescription was associated with survival of 76.7% of patients and improved to >90% when coadjuvant therapy with high-doses of Ig was added.

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APPENDIX 1: ABDOMINAL SEPSIS STUDY GROUP

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REFERENCES

1. McRitchie DI, Girotti MJ, Rotstein OD, Teodorczk-Injeyan JA: Impaired antibody production in blunt trauma. Possible role for T cell dysfunction. *Arch Surg* 125:91–96, 1990.
2. Cheadle WG, Mercer-Jones M, Heinzelman M, Polk HC: Sepsis and septic complications in the surgical patients: Who is at risk? *Shock* 6(suppl 1):S6–S9, 1996.
3. Moran K, Munster AM: Alterations of host defense mechanisms in burned patients. *Surg Clin North Am* 67:47–56, 1987.
4. McGowan JEJ, Barnes WN, Finland MB: Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972) with special reference to hospital-acquired cases. *J Infect Dis* 132:326–341, 1975.
5. Zanetti G, Calandra T: Intravenous immunoglobulins and granulocyte colony-stimulating factor for the management of infection in intensive care units. *Curr Opin Crit Care* 3:342–347, 1997.
6. Ito Y, Lukita-Atmadja W, Machen NW, Baker GL, McCluskey RS: High doses of intravenous immunoglobulin G enhance Kupffer cell phagocytic function during the late phase of sepsis and endotoxemia in rats. *Shock* 13:485–491, 2000.
7. McCuskey RS, Nishida J, McDonnell D, Baker GL, Urbaschek R, Urbaschek B: Effects of immunoglobilin G on the hepatic microvascular inflammatory response during sepsis. *Shock* 1:28–33, 1996.
8. Dominioni L, Dionigi R, Zanello M, Chiaranda M, Dionigi R, Acquarolo A, Ballabio A, Sguotti C: Effects of high-dose IgG on survival of surgical patients with sepsis scores of 20 or greater. *Arch Surg* 126:236–240, 1991.
9. Cafiero F, Gipponi M, Bonalumi U, Piccardo A, Sguotti C, Corbetta G: Prophylaxis of infection with intravenous immunoglobulins plus antibiotics for patients at risk for sepsis undergoing surgery for colorectal cancer: results of a randomized, multicentre clinical trial. *Surgery* 112:24–31, 1992.
10. Gooding A, Bastian J, Peterson B, Wilson NW: Safety and efficacy of intravenous immunoglobulin prophylaxis in pediatric head trauma patients. A double-blind controlled trial. *J Crit Care* 8:212–216, 1993.
11. Glinz W, Grob PJ, Nydegger UE, Ricklin T, Stamm F, Stoffel D, Lasance A: Polyvalent immunoglobulins for prophylaxis of bacterial infection in patients following multiple trauma. *Intensive Care Med* 11:288–294, 1985.
12. Werdan K, Pilz G, and the SBITS Study Group: Polyvalent immune globulins. *Shock* 7(suppl A5):1918, 1997.
13. Stephan W, Dichtemüller H, Schedel I: Properties and efficacy of a human immunoglobulin M preparation for intravenous administration. *Arzneimittelforschung* 35:933–936, 1985.
14. Dichtemüller H, Stephan W: Studies on the efficacy of immunoglobulin M-enriched intravenous immunoglobulins against bacterial infections and neutralization of bacterial toxins. *Drug Res* 27:1273–1275, 1987.
15. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 101:1644–1655, 1992.
16. Bone R: Systemic inflammatory response syndrome. A unifying concept of systemic inflammation. In Fein AM, Abraham EM, Balk RA, Bernard GR, Bone RC, Danztker DR, Fink MP (eds.): *Sepsis and Multiorgan Failure*. Baltimore, MD: Williams & Wilkins, 1997, pp 3–10.
17. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA: Community-acquired bloodstream infection in critically ill patients. Impact of shock and inappropriate antibiotic therapy on survival. *Chest* 123:1615–1624, 2003.
18. Leone M, Bourgoin B, Cambon S, Dubuc M, Albanese J, Martin C: Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. *Crit Care Med* 31:462–467, 2003.
19. Sandiumenge A, Díaz E, Bodi M, Rello J: Treatment of ventilator-associated pneumonia: a patient-base approach based in the ten rules of the "the Tarragona Strategy." *Intensive Care Med* 29:876–883, 2003.
20. Knaus WA, Drader EA, Douglas PW, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med* 13:818–829, 1985.
21. Cullen DJ, Civetta JM, Briggs BA, Ferrara LC: Therapeutic interventions scoring system: a method of quantitative comparison of patient care. *Crit Care Med* 2:57–60, 1974.
22. Rodriguez A, Palizas F, Neira J, Maskin B, Raimondi N, Alvarez J, Vasta L: Inmunoglobulina polivalente en el tratamiento de la sepsis abdominal. *Medicina Intensiva (Argentina)* 18:11–15, 2001.

23. Alejandria MM, Lansang MA, Dans LF, Mantaring JBV: Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). *The Cochrane Library* 2:1–19, 2001.
24. Wunderink RG, Kollef M, Rello J: Linezolid and vancomycin for methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest* 126:315–316, 2004.
25. Rello J, Rodríguez A: Improving survival for sepsis: on the cutting edge. *Crit Care Med* 31:2807, 2003.
26. Rello J, Gallego M, Mariscal D, Sonora R, Valles J: The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med* 156:196–200, 1997.
27. Kollef MH, Sherman G, Ward S, Fraser VJ: Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 115:462–474, 1999.
28. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. *Am J Med* 68:344–355, 1980.
29. Garnacho-Montero J, García Garmendia JL, Barrero-Almodóvar AE, Jiménez-Jiménez FJ, Pérez-Paredes C, Ortiz-Leyva C: Impact on the outcome of adequate empirical antibiotic therapy in patients admitted to the ICU by sepsis. *Crit Care Med* 31:2742–2751, 2003.
30. Nachbaur D, Herold M, Gachter A, Niederwieser D: Modulation of alloimmune response *in vitro* by an IgM-enriched immunoglobulin preparation (Pentaglobin). *Immunology* 94:279–283, 1998.
31. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M: The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. *N Engl J Med* 311:1137–1143, 1984.
32. Dhainaut JF, Tenaillon A, Le Tulzo Y, Schelemmer B, Solet JP, Wolff M, Holzapfel L, Zeni F, Dreyfuss D, Mira SP, Guinot P, De Vathaire F: The BN 52021 Sepsis Study Group. Platelet activating factor receptor antagonist BN 52021 in the treatment of severe sepsis: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Crit Care Med* 22:1720–1728, 1994.
33. Fisher CJ, Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ, Iberti TJ, Rackow EC, Shapiro MJ, Greenman RL, H Reines D, Shelly M, Thompson BW, La Brecque JF, Catalano MA, Knaus WA, Sadoff JC, for the Phase III rhIL-1ra Sepsis Syndrome Study Group.: Recombinant human interleukin-1 receptor antagonist in the treatment of patients with sepsis syndrome: results from randomized, double-blind, placebo-controlled trial. *J Am Med Assoc* 271:1836–1843, 1994.
34. Abraham E, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, Bone RC, Wenzel RP, Balk R, Pennington JE, Wherry JC, for the TNF Mab Sepsis Study Group.: Efficacy and safety of monoclonal antibody to human tumor necrosis factor in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. *J Am Med Assoc* 273:934–941, 1995.
35. Pilz G, Fateh-Moghadam S, Viell B, Bujdoso O, Döring G, Marget W, Neumann R, Werdan K: Supplemental immunoglobulin therapy in sepsis and septic shock: comparison of mortality under treatment with polyvalent i.v. immunoglobulin versus placebo: protocol of multicenter, randomized, prospective, double-blind trial. *Theor Surg* 8:61–68, 1993.
36. Fisher CJI Jr., Cook D: Critical evaluation of design and conduct of previous clinical trial in sepsis. In Sibbald WJ, Vincent JL (eds.): *Clinical Trial for the Treatment of Sepsis*. Berlin: Springer-Verlag, 1995, pp 317–328.
37. Cohen J, Guyatt G, Bernard GR, Calandra T, Cook D, Elbourne D, Marshall J, Nunn A, Opal S on behalf of a UK Medical Research Council International Working Party. New strategies for clinical trials in patients with sepsis and septic shock. *Crit Care Med* 29:880–886, 2001.
38. Foster DM, Doig GS: Clinical trials for the evaluation of sepsis therapies. In Vincent JL (ed.): *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer-Verlag, 1997, pp 149–157.
39. Cappelleri JC, Loannidis JP, Schmidb CH, Ferranti SD, Aubert M, Charmers TC, Lau J: Large trials versus meta-analysis of smaller trials. How do their results compare? *J Am Med Assoc* 276:1332–1338, 1996.
40. Sibbald WJ, Vincent JL: Round table conference on clinical trials for the treatment of sepsis. *Crit Care Med* 23:394–399, 1995.
41. Reith HB, Mittelkotter U: Markers of inflammation for prognosis and control of therapeutic success in patients with abdominal sepsis: option for using adjuvant intravenous immunoglobulins. In Eugen F (ed.): *Immunological Screening and Immunotherapy in Critically Ill Patients with Abdominal Infections*. Berlin: Springer-Verlag, 2001, pp 15–28.
42. Tugrul S, Ozcan PE, Akinci O, Seyhun Y, Cagatay A, Cakar N, Esen F: The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis (ISRCTN28863830). *Crit Care* 6:357–362, 2002.
43. Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients. A systematic review of randomized controlled trials. *Br Med J* 317:235–240, 1998.
44. Alderson P, Bunn F, Lefebure C, Li WP, Roberts I, Schierhout G: Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev (1) CD001208, 2002.
45. Wilkes MM, Navickis RJ: Patients survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 135:149–164, 2001.
46. The SAFE study: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 350:2247–2256, 2004.
47. Freemantle N: Interpreting the results of the secondary end points and subgroups analysis in clinical trials: should we lock the crazy aunt in the attic? *Br Med J* 322:898–992, 2001.
48. Assmann SF, Pocock SJ, Enos LE, Kasten LE: Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 355:1064–1069, 2000.
49. Douzinas EE, Pitaridis MT, Louris G, Andrianakis I, Katsouyanni K, Kampaliotis D, Economidou J, Dimitrios S, Charis R: Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins. *Crit Care Med* 28:8–15, 2000.