Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis*

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Objectives: **To systematically review the literature to assess whether adjunctive therapy with polyclonal intravenous immunoglobulin (ivIg) reduces mortality among critically ill adults with severe sepsis and septic shock.**

Data Source: **MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases; the meta-register of controlled trials; and the Medical Editors Trial Amnesty register.**

Study Selection: **Prospective randomized clinical trials (RCTs) evaluating ivIg treatment in critically ill adults with severe sepsis or septic shock were included. Two reviewers conducted assessment of suitability for inclusion.**

Data Extraction: **Two authors independently determined the validity of included studies and extracted data.**

Data Synthesis: **The effect of ivIg on all-cause mortality was quantified using a fixed-effect meta-analysis.**

Results: **Fourteen RCTs published between 1988 and 2006 were included. Most were small, used relatively low doses of ivIg, and included predominantly surgical patients with Gram-negative infections. There was a significant reduction in mortality associated with use of ivIg treatment with a pooled odds ratio of 0.66 (95% confidence interval 0.53–0.83; $p < .0005$). In general, a greater treatment effect was seen among studies of lower methodological quality, studies using higher doses of ivIg, and studies that did not use albumin as a control. There was evidence of between-study heterogeneity (chi-square $p = .009$), and this was at least moderate as measured by the I^2 value ($I^2 = 53.8\%$). When only high-quality studies were pooled, the odds ratio for mortality was 0.96 (95% confidence interval 0.71–1.3; $p = .78$).**

Conclusions: **This meta-analysis demonstrates an overall reduction in mortality with the use of ivIg for the adjunctive treatment of severe sepsis and septic shock in adults, although significant heterogeneity exists among the included trials and this result was not confirmed when only high-quality studies were analyzed. These data warrant a well-designed, adequately powered, and transparently reported clinical trial. (Crit Care Med 2007; 35:2686–2692)**

KEY WORDS: critical care; sepsis; meta-analysis; intravenous immunoglobulins; human

Sepsis is a major cause of morbidity and mortality in critically ill adults (1, 2). Although numerous advances in the management of critically ill adults with severe infections have occurred in recent years, the mortality rate associated with severe sepsis and septic shock remains unacceptably high at 30% to 50% (1–3). Because of its broad and potent activity against both bacterial products and host cytokines, polyclonal intravenous immunoglobulin (ivIg) has been investigated as an adjunctive therapy for treating severe infections (4).

Three reports have summarized the clinical trials investigating the adjunctive use of ivIg in the treatment of sepsis and septic shock and overall have demonstrated a dramatic reduction in mortality associated with ivIg therapy (5–7). However, these reports either failed to include important studies (6), included neonates and children or patients with nonsevere disease (6, 7), or restricted inclusion to trials only evaluating specific enriched ivIg preparations (5). In addition, two large trials have only recently been completed and published (8, 9). As a result, the overall effect of ivIg therapy on mortality of critically ill adults with severe sepsis and septic has not been well defined.

Given the uncertainty surrounding the effect of ivIg as an adjunctive treatment for severe infections in adults, we performed a systematic literature review and meta-analysis to investigate whether adjunctive therapy with ivIg reduces mortality in critically ill adults with sepsis or septic shock.

MATERIALS AND METHODS

Search Strategy. A number of sources were used to identify potentially relevant studies. The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched using the OVID interface. Search terms included (*immunoglob** or *ivig* or *polyclonal* or *gamma globulin*) and (*sepsis* or *septic shock* or *infection*) and (*randomi** or *trial*) and (*ICU* or *severe* or *critical* or *intensive*). All databases were searched from inception until March 24, 2006. The search was limited to randomized controlled trials (RCTs) conducted in humans. No language restriction was placed on the search. The authors' personal files and the bibliographies of previously published reviews or meta-analyses were also

***See also pp. 2852 and 2855.**

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searched (4–7, 10, 11). In an effort to find any recent unpublished studies not identified by the electronic search, the meta-register of controlled trials and the Medical Editors Trial Amnesty register were also searched.

Study Selection. One author (KL) screened the titles and abstracts of all potentially eligible studies identified by the search strategy. Two authors (KL, AK) then independently reviewed the full reports of the potentially eligible studies to determine whether they met all of the inclusion criteria, with disputes resolved by discussion. All published and unpublished prospective clinical trials were considered eligible if the available data contained sufficient information to allow assessment of validity and mortality outcome. To be eligible the randomized clinical trial had to 1) principally involve adult patients admitted to ICUs; 2) identify severe infection, sepsis, or septic shock as the target disorder under investigation; 3) compare the intervention of a polyclonal ivIg preparation compared with either a placebo or no treatment; and 4) report all-cause mortality as an outcome.

Data Abstraction and Validity Assessment. For each of the included studies, two authors (KL, AK) independently abstracted data and assessed validity using predefined criteria. The main data recorded included the patient population under study, the intervention applied, and the mortality outcome as an intention-to-treat analysis wherever reported or if data were available. Each study was assessed in an unblinded fashion (12) and was evaluated for the adequacy of allocation concealment, the blinding of subjects and investigators to treatment assignment, and the availability of data for an intention-to-treat analysis. A study was classified as having adequate concealment if the available information did not allow an investigator to establish the treatment allocation for the next patient (e.g., numbered sequential opaque envelopes or a centralized phone-in system was used after enrollment). Blinding was considered adequate if a placebo that was not distinguishable was used. When it was unclear or not stated in the report that the study had addressed these validity issues, the criterion was recorded as absent/inadequate. The duration of follow-up for mortality outcome was the primary outcome that was reported in the individual studies. When the duration of follow-up was unclear, it was recorded as the survival outcome as of ICU discharge. Where data were not available in the original reports, had been updated in prior reviews or meta-analyses, or were published in a language other than English, summarized data from the most recent publications were incorporated as appropriate.

Data Synthesis. Agreement between the two study abstractors for study inclusion was assessed using the kappa statistic. The potential for publication bias was assessed using funnel plots and the statistical test described by Egger et al (13). Statistical heterogeneity was assessed using the chi-square statistic and the I^2 statistic, with $I^2 > 50\%$ indicating at least moderate heterogeneity (14). The mortality rates were pooled using the fixed-effect method of Mantel and Haenszel to produce a pooled odds ratio (OR) (15, 16). An estimate of the number needed to treat was obtained by applying the pooled estimate of the treatment effect to a baseline rate observed from recent published studies (17). Sensitivity analysis was performed using the random-effects model of DerSimmonian and Laird (as reported in reference 18). To assess the potential effect of trial quality on the outcomes, a component approach was used with the presence of adequate allocation concealment, adequate blinding, and availability of intention-to-treat analysis used to adjudicate the validity of the included RCTs (19). An overall trial quality score representing the sum of all three components was calculated, with studies that fulfilled all components denoted high-quality studies. Potential explanations for heterogeneity were explored by separately pooling those studies comparing immunoglobulin M (IgM)-enriched and standard ivIg preparations, those studies that used a total ivIg dose ≥1 g/kg (or total dose ≥70 g where dosing was not reported as weight based), and those studies that specified the use of albumin as the control arm compared with those that did not specify this and solely used standard therapy. Meta-regression was also used to examine potential sources of heterogeneity where continuous variables (overall quality score, year of publication, and dose of ivIg) were involved. All analyses were conducted using Stata 8.2 (Stata, College Station, TX).

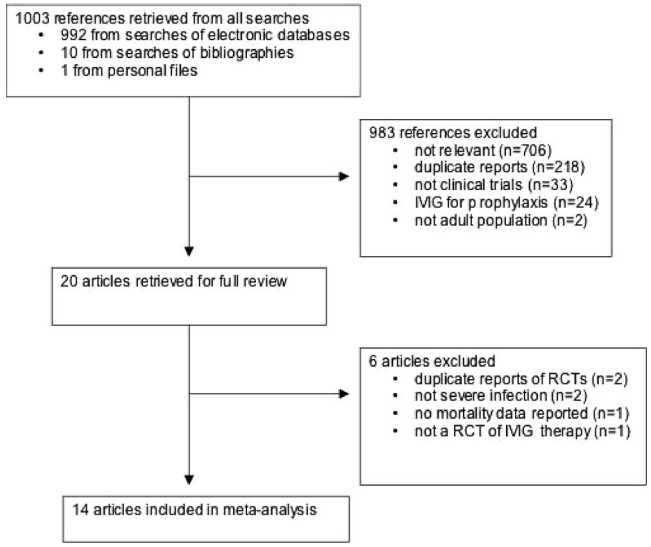

Figure 1. QUOROM (Quality of Reporting of Meta-analyses) profile showing flow of studies included in meta-analysis. *RCT,* randomized controlled trial; *IVIG,* intravenous immunoglobulin.

RESULTS

A total of 1,003 references were retrieved by the search, with 14 RCTs meeting all the inclusion criteria. The flow of studies and reasons for exclusion are shown in Figure 1. Initial agreement on the inclusion of studies occurred in 89% of cases, giving a kappa = 0.84.

The characteristics of the included studies are shown in Table 1. The majority of the studies were European, were predominantly conducted among critically ill surgical patients, had a small sample size, and used relatively low doses of ivIg. The median sample size was only 48 patients, and only two studies included >100 subjects. The median overall dose of ivIg used in the studies was relatively low (median 0.92, interquartile range 0.75–1.0 g/kg), and one half of the studies investigated enriched preparations of ivIg. The methodological validity assessments of the included trials are shown in Table 2. Of the 14 included studies, 13 had intention-to-treat data available, only nine had adequately concealed randomization, and in six the investigators and patients were blinded to treatment allocation. Only four studies (9, 11, 20, 21) met all of the *a priori* defined criteria for a high-quality study.

Overall Effect of ivIg on Mortality. There was evidence of significant funnel plot asymmetry both on visual inspection of the funnel plot (Fig. 2) and by assessment using Egger's statistic (bias = −2.1, $p < .0005$). Fourteen studies reported the effect of ivIg on mortality in adult patients with severe sepsis or septic shock. There was evidence of between-study heterogeneity (chi-square = 0.009), and this was at least moderate as measured by the I^2 value ($I^2 = 53.8\%$).

Table 1. Characteristics of included randomized trials of intravenous immunoglobulin (ivIg) for the treatment of severe sepsis and septic shock

Study	Setting	Population	Number of Participants	ivIg	ivIg Dose	Control
Vogel (5, 50)	University Hospital, Germany	Medical and surgical ICU patients with severe nosocomial infections	50	Pentaglobin (Biotest, Dreieich, Germany)	10 g total	No treatment
Grundmann (51)	Koln, Germany	Surgical ICU patients with clinical sepsis and endotoxemia	46	Intraglobin F (Biotest, Dreieich, Germany)	0.5 g/kg	No treatment
De Simone (52)	Rome, Italy	Septic medical and surgical ICU patients	24	Sandoglobulin (Sandoz Pharmaceutical, Holzkirchen, Germany)	1 g/kg	No treatment
Wesoly (5, 53)	Koln, Germany	Postoperative patients with sepsis	35	Pentaglobin	0.75 g/kg	No treatment
Schedel (54)	Hannover, Germany	Patients in a clinical immunology ward who had severe Gram-negative septic shock	69	Pentaglobin	60 g total	No treatment
Burns (20)	New York, USA	Medical and surgical patients with septic thrombocytopenia; majority in ICU	38	Sandoglobulin	1.2 g/kg	Albumin
Werdan (7, 11, 24)	Multiple centers, Germany	Medical and surgical ICU patients with severe sepsis and septic shock	653	Polyglobulin N (Bayer, Leverkusen, Germany)	0.9 g/kg	Albumin
Dominioni (33, 34)	Four universities in Italy	Surgical and trauma ICU patients with sepsis scores ≥17	117	Sandoglobulin	1 g/kg	Albumin
Yakut (7, 55)	Ankara, Turkey	Septic high-risk surgical patients in ICU	40	Gamumine N (Miles, Elkhart, Indiana)	1 g/kg	Albumin
Tugrul (56)	Instanbul, Turkey	Severe sepsis patients aged ≥10 yrs	42	Pentaglobin	0.75 g/kg	No treatment
Karatzas (7, 57)	Athens, Greece	Severe sepsis and septic shock	82	Pentaglobin	0.75 g/kg	No treatment
Darenburg (21)	17 centers in Norway, Sweden, Finland, and The Netherlands	Streptococcal toxic shock syndrome	21	Endoglobulin S/D (Baxter, Deerfield, IL)	2 g/kg	Albumin
Rodriguez (9)	Seven teaching hospitals in Argentina and Spain	Postabdominal surgical patients with severe sepsis or septic shock	56	Pentaglobin	1.75 g/kg	Albumin
Hentrich (8)	Six university hospitals, Germany	Neutropenic patients with hematologic disorders with severe sepsis or septic shock	211	Pentaglobin	65 g total	Albumin

ICU, intensive care unit.

Table 2. Summary of validity assessments of included clinical trials assessing intravenous immunoglobulin for the treatment of severe sepsis and septic shock

Study	Adequate Allocation Concealment	Adequate Blinding	Intention-to-Treat Analysis	Overall Quality Score	Mortality Outcome
Vogel (5, 50)	No	No	No	0	12 days
Grundmann (51)	Yes	No	Yes	2	ICU
De Simone (52)	Yes	No	Yes	2	ICU
Wesoly (5, 53)	No	No	Yes	1	ICU
Schedel (54)	Yes	No	Yes	2	6 wks
Burns (7, 20)	Yes	Yes	Yes	3	9 days
Werdan (7, 11, 24)	Yes	Yes	Yes	3	28 days
Dominioni (33, 34)	No	Yes	Yes	2	ICU
Yakut (7, 55)	No	Yes	Yes	2	ICU
Tugrul (56)	No	No	Yes	1	28 days
Karatzas (7, 57)	Yes	No	Yes	2	28 days
Darenburg (21)	Yes	Yes	Yes	3	28 days
Rodriguez (9)	Yes	Yes	Yes	3	ICU
Hentrich (8)	Yes	No	Yes	2	28 days

ICU, intensive care unit.

The Mantel and Haenszel fixed-effect pooled OR (Fig. 3) for the effect of ivIg on mortality in adult patients with severe sepsis or septic shock was 0.66 (95% confidence interval [CI] 0.53–0.83; $p < .0005$), indicating a significant reduction in mortality for patients treated with ivIg. With a conservative estimated baseline mortality rate of 30% (1, 2), there would be 78 (95% CI 39–114) deaths avoided per 1,000 patients with severe sepsis treated with ivIg, giving a number needed to treat of 12.7.

Sensitivity Analysis and Potential Sources of Heterogeneity. An overall pooled analysis using a random-effects model demonstrated a significant benefit favoring treatment with ivIg, with a pooled OR of 0.45 (95% CI 0.30–0.69; $p < .0005$). That the estimate of treatment effect still demonstrated a significant benefit in favor of the use of ivIg in critically ill adults with severe sepsis and septic shock shows that the result is robust to the model used to pool the data.

The results of the prespecified subgroup analyses are shown in Table 3. There is evidence that studies without adequate allocation concealment tended to show larger treatment effects; however, there was no significant difference between the estimate of the OR for stud-

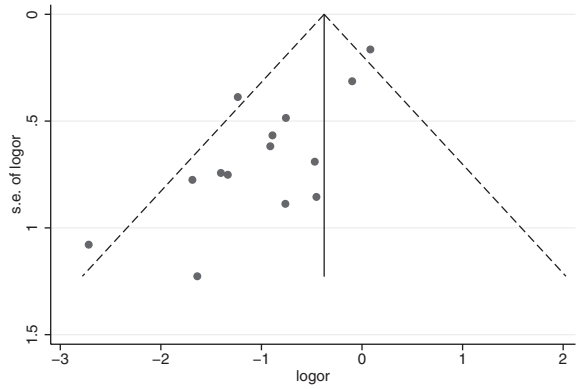

Figure 2. Funnel plot with pseudo 95% confidence limits.

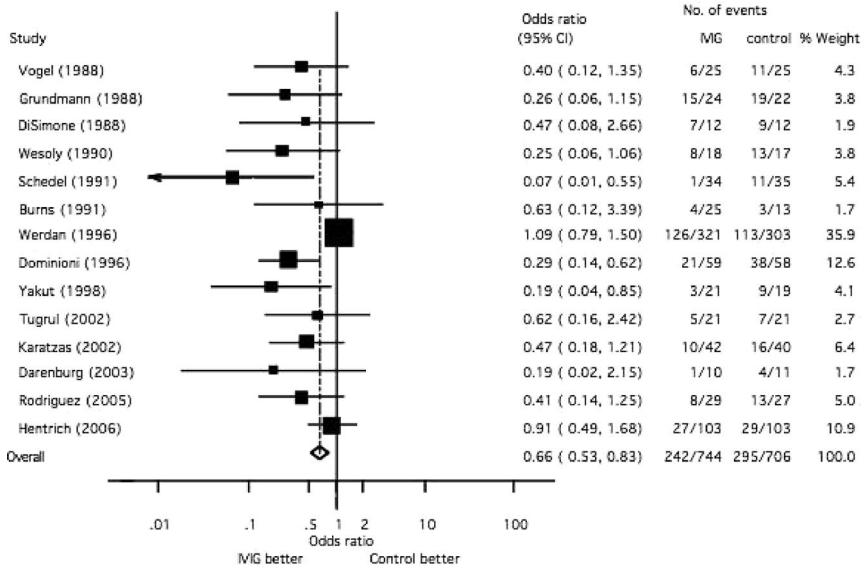

Figure 3. Forrest plot showing the overall effect of intravenous immunoglobulin (*IVIG*) on mortality in adults with sepsis. *CI*, confidence interval.

Table 3. Summary of the estimated odds ratios (OR) for mortality for the prespecified trial quality and trial-level covariates

Subgroup	No. of Studies	Estimate of OR	95% CI	Test for Between-Group Heterogeneity, *p*
High-quality studies	4	0.96	0.71–1.3	
Allocation concealment				.001
Yes	9	0.57	0.35–0.92	
No	5	0.32	0.19–0.53	
Blinding				.12
Yes	6	0.77	0.59–1.01	
No	8	0.50	0.34–0.73	
IgM enriched				.15
Yes	7	0.51	0.35–0.75	
No	7	0.76	0.58–0.99	
ivIg dose				.002
Low dose	8	0.79	0.62–1.01	
High dose	6	0.32	0.20–0.59	
Control group				.007
Standard therapy	7	0.34	0.21–0.56	
Albumin	7	0.79	0.62–1.01	

CI, confidence interval; ivIg, intravenous immunoglobulin; IgM, immunoglobulin M.

Table 4. Results of multiple meta-regression analysis of trials investigating intravenous immunoglobulin (ivIg) for treatment of severe sepsis and septic shock

Variable	Coefficient	SE	*p*
Year of publication	0.059	0.027	.027
Dose of ivIg	−1.80	0.59	.003
Overall quality score	0.77	0.19	<.0005

ies with and without adequate blinding. As only one study did not present an intention to treat analysis, this covariate was not analyzed. When the four studies (9, 11, 20, 21) that fulfilled all of the validity criteria were pooled, the fixed effects estimate of the OR for mortality was 0.96 (95% CI 0.71–1.3; $p = .78$). There appears to be a stronger effect of ivIg in studies in which larger doses of ivIg were used and in studies that did not specify the use of albumin as the control therapy.

The potential sources of heterogeneity in the overall pooled analysis were explored in a number of ways. An influence analysis was conducted to determine whether any single study significantly altered the overall pooled result (22). The study by Werdan (11) is the only study that dramatically altered the estimate of the OR. Sensitivity analysis was conducted, omitting the Werdan study. When the remaining studies were pooled using a fixed-effect model, the tests for heterogeneity revealed a chi-square $p = .39$ and $I^2 = 6.8\%$. The fixed-effect estimate of the OR was 0.43 (95% CI 0.31–0.58; $p < .005$) when the Werdan study was omitted. Meta-regression analysis was also performed on three study-level covariates: year of publication, overall quality score, and dose of ivIg. The results of this analysis are shown in Table 4. This could be interpreted to infer that later studies and higher quality studies tended to show a smaller effect and studies that used larger doses of ivIg showed a larger effect. This analysis also needs to be interpreted cautiously given the small number of studies included in the analysis.

DISCUSSION

This systematic review demonstrated a significant reduction in mortality in critically ill adult patients with severe sepsis and septic shock treated with polyclonal ivIg. This finding is based on the results from 14 published and unpublished

RCTs, albeit studies not uniformly of a high methodological quality. There is a suggestion that ivIg is more effective in higher doses, although the apparent effect of ivIg was less pronounced in studies that specified the use of albumin in the control group compared with those that did not specify this. Significant heterogeneity was evident, which may be accounted for by the fact that a single, apparently high-quality, unpublished study exerted significant influence over the pooled results. There was also evidence from meta-regression analysis that the year of publication, overall study quality, and total dose of ivIg given accounted for some of the observed heterogeneity. The overall results are robust to the model used to pool the data; however, no significant effect of ivIg treatment was seen when only the high-quality studies were pooled.

There are a number of strengths to this review. Following currently accepted methodological standards for the conduct and reporting of meta-analyses (23) should have minimized systematic biases in this meta-analysis. The inclusion of both published and unpublished studies as well as studies published in languages other than English also adds credence to the results. One of the particular strengths of this review is that it addressed a single focused clinical question that allows the results of the study to be more easily applied in clinical practice.

There are also a number of concerns raised by the results of this review. The most pressing concern is the influence of one unpublished study on the results. While it is recommended to include both published and unpublished studies in systematic reviews, when a single study exerts significant influence on the pooled results, as the Werdan (7, 11, 24) study does in this case, it is important to examine the particular characteristics of the study that set it apart from the others. In this case, it is not possible to do so, because although a protocol for the study was published (24) and the results were made available in a subsequent review (7), a full report of this study has never been subjected to peer review and published. Even at this late stage, a full peer-reviewed report of this important trial would add significantly to the state of knowledge in this field. The nonpublication of negative trials, or publication bias, raises significant ethical issues (25, 26), and some have gone as far as to suggest that this practice may be scientific misconduct (27). The Medical Editors Trial Amnesty was designed to address this issue, and although there have been successes (28), there is obviously still a long way to go.

The evidence of funnel plot asymmetry found in this study also raises questions. While publication bias is one cause of this asymmetry, it is not the only cause (29). True heterogeneity is likely to be the cause for at least some of the observed asymmetry, and small study bias may also play a role. It should be recognized, however, that there will always be some heterogeneity between studies included in a meta-analysis (14). In this analysis there was at least moderate heterogeneity as measured by the I^2 statistic. This raises the possibility that the true effect of ivIg on mortality may be different in different populations of patients with differing sources of infection or causative organisms or with differing immune status. The differing definitions of severe sepsis used in the individual studies may contribute to the observed heterogeneity. The underlying risk of mortality also may be an important effect modifier in this relationship, although this relationship can be very difficult to assess (30).

Another problem, commonly found in studies of this type, was the poor methodological quality of the included RCTs. While commonly accepted principles for adjudicating the quality of the included trials were used in this study (19), these features do not necessarily capture all aspects of the conduct and reporting of an RCT that ensure the validity of the results. The fact that the studies adjudicated to be high quality by the criteria used in this review included an unpublished study (11) and another that only completed a 9-day follow-up (20) highlights the difficulties in arriving at firm conclusions from this type of evidence. That being said, the high-quality studies, when pooled, showed no overall effect of the treatment, which casts some doubt on the strength of the observed reduction in mortality associated with ivIg treatment in this population.

While our analysis is novel based on the specific population studied and the trials included, our overall results are consistent with previous reviews (5–7). While the first reported study (6) looked at both monoclonal and polyclonal immunoglobulin in a population that included neonates as well as adults, the subgroup of adults showed a relative risk (RR) for mortality of 0.62 with the use of ivIg. This study also showed that the IgM-enriched preparations showed a greater effect with an RR for mortality 0.48. Another study was a cost-effectiveness analysis that focused solely on the use of IgM-enriched immunoglobulin (5). The pooled estimate of the RR in this study was 0.57 with an estimated number needed to treat of 5. This study concluded that IgM-enriched ivIg was a promising adjuvant therapy for sepsis, in both clinical and economic terms. It is interesting to note, however, that only one of the RCTs included in this analysis that examined the effect of IgM-enriched ivIg was adjudicated to have adequate blinding. This lack of methodological rigor of the primary studies may lead to an exaggerated estimate of treatment effect and makes it difficult to draw firm conclusions regarding the true effect of IgM-enriched ivIg. The use of albumin in the control group as a potential modifier of treatment effect, potentially to ensure that the blinding in the RCTs was maintained, was not examined in the previous analyses either. Neither of these analyses included the largest, as yet unpublished study. When this unpublished study was first included in a systematic review (7), an overall pooled RR showed a significant reduction in the risk of mortality (RR 0.77; 95% CI 0.68–0.88) that was not confirmed in subgroup analysis including only high-quality RCTs (RR 1.02; 95% CI 0.84–1.24). However, as this study included neonates as well as adults, did not solely look at patients with severe sepsis and septic shock, and did not have the benefit of including two large trials that have only recently been published (8, 9), the effect of ivIg in adult patients with severe sepsis and septic shock remained uncertain.

Another meta-analysis has recently been published that had similar conclusions to our review (31). That paper included 20 references in comparison to 14 studies in our report. In two of these cases interim study results were reported (32, 33); only the later completed studies (8, 34) were included in our meta-analysis to avoid the problem of double counting patients. Three papers included in the Turgeon et al. (31) meta-analysis were excluded from our meta-analysis based on the use of a chemically modified ivIg product (35) and inclusion of patients with nonsevere infections (36, 37). One study included in the Turgeon et al. study that investigated ivIg vs. no specific

therapy in patients with peritonitis was missed by our search strategy (38). This study, which suffered major methodological limitations, found no difference in 20-day mortality outcome with 95 g of ivIg compared with control (66 of 145 [46%] vs. 58 of 143 [41%]). Inclusion of this study in our meta-analysis gives an estimate of the pooled OR of 0.74 (95% CI 0.61–0.90, $p = .003$). The magnitude and significance of the results remain essentially unaltered.

Following the publication of evidence-based guidelines for the management of patients with severe sepsis and septic shock, there has been a burgeoning interest in this area (39–41). Widely accepted guidelines have included recommendations to use treatments like corticosteroids (42), intensive insulin therapy (43), and early goal-directed therapy (44) based on the results of single-center studies and recommendations to use activated protein C based on the results of a single controversial RCT (45). On the other hand, ivIg offers the potential to have a similar if not more profound effect on the outcome of patients with severe sepsis and septic shock, and decades of use in a wide range of illnesses have demonstrated its safety (4). It is somewhat anomalous that widely accepted guidelines have not considered its use and that it is rarely used in many countries for the treatment of most patients with severe sepsis and septic shock (4, 39).

Meta-analysis cannot provide reliable evidence when the available RCTs are of a poor quality. When faced with these difficulties, researchers have resorted to large simple clinical trials, such as SAFE (46) and CRASH (47), to address important questions in critical care when meta-analyses have failed to provide robust answers (48, 49). An adequately powered, well-designed, and transparently reported clinical trial of ivIg in adult patients with severe sepsis and septic shock is warranted.

CONCLUSION

This meta-analysis demonstrates an overall reduction in mortality with the use of ivIg for the adjunctive treatment of severe sepsis and septic shock in adults, although significant heterogeneity exists among the included trials and this result was not confirmed when only high-quality studies were analyzed. The effect of ivIg appeared more pronounced when larger doses (>1 g/kg) of ivIg were used and when ivIg was compared with placebo. An adequately powered, well-designed, and transparently reported clinical trial is urgently needed to define the potential of this promising therapy.

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REFERENCES

1. Harrison DA, Welch CA, Eddleston JM: The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: Secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006; 10:R42
2. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
3. Finfer S, Bellomo R, Lipman J, et al: Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med* 2004; 30:589–596
4. Laupland K: Polyclonal intravenous immunoglobulin for the prophylaxis and treatment of infection in critically ill adults. *Can J Infect Dis* 2002; 13:100–106
5. Neilson AR, Burchardi H, Schneider H: Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (Pentaglobin) in the treatment of severe sepsis and septic shock. *J Crit Care* 2005; 20:239–249
6. Alejandria MM, Lansang MA, Dans LF, et al: Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002; CD001090
7. Pildal J, Gotzsche PC: Polyclonal immunoglobulin for treatment of bacterial sepsis: A systematic review. *Clin Infect Dis* 2004; 39: 38–46
8. Hentrich M, Fehnle K, Ostermann H, et al: IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: A randomized, controlled, multiple-center trial. *Crit Care Med* 2006; 34: 1319–1325
9. Rodriguez A, Rello J, Neira J, et al: Effects of high-dose of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. *Shock* 2005; 23: 298–304
10. Werdan K: Intravenous immunoglobulin for prophylaxis and therapy of sepsis. *Curr Opin Crit Care* 2001; 7:354–361
11. Werdan K: Supplemental immune globulins in sepsis. *Clin Chem Lab Med* 1999; 37: 341–349
12. Berlin JA: University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet* 1997; 350:185–186
13. Egger M, Davey Smith G, Schneider M, et al: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634
14. Higgins JP, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557–560
15. Villar J, Mackey ME, Carroli G, et al: Meta-analyses in systematic reviews of randomized controlled trials in perinatal medicine: Comparison of fixed and random effects models. *Stat Med* 2001; 20:3635–3647
16. Deeks JJ: Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002; 21:1575–1600
17. Altman DG, Deeks JJ: Meta-analysis, Simpson's paradox, and the number needed to treat. *BMC Med Res Methodol* 2002; 2:3
18. Petitti DB: Approaches to heterogeneity in meta-analysis. *Stat Med* 2001; 20:3625–3633
19. Juni P, Altman DG, Egger M: Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001; 323: 42–46
20. Burns ER, Lee V, Rubinstein A: Treatment of septic thrombocytopenia with immune globulin. *J Clin Immunol* 1991; 11:363–368
21. Darenberg J, Ihendyane N, Sjolin J, et al: Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: A European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003; 37: 333–340
22. Sterne JA, Bradburn MJ, Egger M: Meta-analysis in Stata. *In:* Systematic Reviews in Healthcare: Meta-Analysis in Context. Second Edition. Egger M, Davey Smith G, Altman D (Eds). London, BMJ Publishing, 2001, pp 347–369
23. Moher D, Cook DJ, Eastwood S, et al: Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement: Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896–1900
24. Pilz G, Fateh-Moghadam S, Viell B, et al: Supplemental immunoglobulin therapy in sepsis and septic shock-comparison of mortality under treatment with polyvalent i.v. immunoglobulin versus placebo: Protocol of a multicenter, randomized, prospective, double-blind trial. *Theor Surg* 1993; 8:61–83
25. Dickersin K, Rennie D: Registering clinical trials. *JAMA* 2003; 290:516–523
26. Shields PG: Publication bias is a scientific problem with adverse ethical outcomes: The case for a section for null results. *Cancer Epidemiol Biomarkers Prev* 2000; 9:771–772
27. Chalmers I: Underreporting research is scientific misconduct. *JAMA* 1990; 263: 1405–1408
28. Roberts I: An amnesty for unpublished trials: One year on, many trials are unregistered

and the amnesty remains open. *BMJ* 1998; 317:763–764
29. Sterne JA, Egger M, Smith GD: Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; 323:101–105
30. Sharp SJ, Thompson SG: Analysing the relationship between treatment effect and underlying risk in meta-analysis: Comparison and development of approaches. *Stat Med* 2000; 19:3251–3274
31. Turgeon AF, Hutton B, Fergusson DA, et al: Meta-analysis: Intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; 146:193–203
32. Behre G, Ostermann H, Schedel I, et al: Endotoxin concentrations and therapy with polyclonal IgM-enriched immunoglobulins in neutropenic cancer patients with sepsis syndrome: Pilot study and interim analysis of a randomized trial. *Anti-infect Drugs Chemother* 1995; 13:129–134
33. Dominioni L, Dionigi R, Zanello M, et al: Effects of high-dose IgG on survival of surgical patients with sepsis scores of 20 or greater. *Arch Surg* 1991; 126:236–240
34. Dominioni L, Bianchi V, Imperitori A, et al: High-dose intravenous IgG for treatment of severe surgical infections. *Dig Surg* 1996; 13:430–434
35. Lindquist L, Lundbergh P, Maasing R: Pepsin-treated human gamma globulin in bacterial infections: A randomized study in patients with septicaemia and pneumonia. *Vox Sang* 1981; 40:329–337
36. Just HM, Metzger M, Vogel W, et al: Effect of adjuvant immunoglobulin therapy on infections in patients in an surgical intensive care unit: Results of a randomized controlled study. *Klin Wochenschr* 1986; 64:245–256
37. Masaoka T, Hasegawa H, Takaku F, et al: The efficacy of intravenous immunoglobulin in combination therapy with antibiotics for severe infections. *Jpn J Chemother* 2000; 48: 199–217
38. Jesdinsky HJ, Tempel G, Castrup HJ, et al: Cooperative Group of Additional Immunoglobulin Therapy in Severe Bacterial Infections: Results of a multicenter randomized controlled trial in cases of diffuse fibrinopurulent peritonitis. *Klin Wochenschr* 1987; 65:1132–1138
39. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
40. Kortgen A, Niederprum P, Bauer M: Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Crit Care Med* 2006; 34:943–949
41. Shapiro NI, Howell MD, Talmor D, et al: Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 2006; 34:1025–1032
42. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862–871
43. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359–1367
44. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
45. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
46. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
47. Edwards P, Arango M, Balica L, et al: Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet* 2005; 365:1957–1959
48. Roberts I, Schierhout G, Alderson P: Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: A systematic review. *J Neurol Neurosurg Psychiatry* 1998; 65:729–733
49. Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. *BMJ* 1998; 317:235–240
50. Vogel F: Bewertung der intravenosen IgM-therapie bei schweren nosokomialen infektionen (ergebnis einer kontrollierten randomisierten studie). *In:* Klinische angewandte Immunologie. Deichner HH, Schoeppe W (Eds). Berlin, Springer, 1988, pp 30–41
51. Grundmann R, Hornung M: Immunoglobulin therapy in patients with endotoxemia and postoperative sepsis—A prospective randomized study. *Prog Clin Biol Res* 1988; 272: 339–349
52. De Simone C, Delogu G, Corbetta G: Intravenous immunoglobulins in association with antibiotics: A therapeutic trial in septic intensive care unit patients. *Crit Care Med* 1988; 16:23–26
53. Wesoly C, Kipping N, Grundmann R: Immunoglobulin therapy of postoperative sepsis. *Z Exp Chir Transplant Kunstliche Organe* 1990; 23:213–216
54. Schedel I, Dreikhausen U, Nentwig B, et al: Treatment of Gram-negative septic shock with an immunoglobulin preparation: A prospective, randomized clinical trial. *Crit Care Med* 1991; 19:1104–1113
55. Yakut M, Cetiner S, Akin A, et al: Effects of immunoglobulin G on surgical sepsis and septic shock. *Bulletin of Gulhane Military Medical Academy* 1998; 40:76–81
56. Tugrul S, Ozcan PE, Akinci O, et al: The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis [ISRCTN28863830]. *Crit Care* 2002; 6:357–362
57. Karatzas S, Boutzouka E, Venetsanou K, et al: The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis: Another point of view. *Crit Care* 2002; 6:543–544

Mirror, mirror on the wall, which is the fairest meta-analysis of all?*

Although the results of initial studies with activated protein C, hydrocortisone, and intensified insulin therapy in severe sepsis and septic shock were encouraging and seemingly convincing, we have had to accept that recent consecutive trials have failed to reproduce these same positive results. After >20 yrs of randomized, controlled sepsis trials, there is not one single drug or treatment concept that has proven its mortality-reducing effect by the highest evidence-based standard: two controlled trials with a high statistical power. What shall we do? Shall we tell the families of our sepsis patients they have to wait until we have achieved the highest level of evidence for all our therapies? Or, would it be better to gather all the information we have (high- and low-quality trials, retrospective analyses, case control studies, expert opinions), judge it as best we can, and then recommend to our colleagues what they could do. . .even with all the uncertainty we are used to in intensive care medicine?

In cases of adjunctive sepsis therapy with intravenous immunoglobulins (ivIg), the story goes back to the 1980s when the first placebo-controlled trials had been performed. Small sepsis trials with polyvalent immunoglobulins competed at that time with much larger monovalent approaches with monoclonal anti-endotoxin and anti-cytokine antibodies. However, the latter all failed, whereas the small ivIg trials displayed at least some positive aspects. The complexity was and is further advanced by the existence of several polyvalent ivIgG preparations, but only a single ivIgGMA preparation might act differently in those patients.

The Cochrane Institution, which started the ivIg meta-analysis business (1) in 2002, analyzed adjunctive sepsis therapy with monoclonal and polyclonal ivIg in adults and neonates. In a subgroup analysis of 11 trials (n = 492) using polyclonal ivIg, a significant reduction in all-cause mortality was demonstrated for the treatment group (relative risk [RR], 0.64; 95% confidence interval [CI], 0.51, 0.80). It was especially interesting that *post hoc* subanalysis, according to type of polyclonal ivIg, demonstrated a greater reduction in mortality among patients given immunoglobulin M (IgM)-enriched ivIg (n = 194; RR, 0.48; 95% CI, 0.30, 0.76) compared with standard polyclonal ivIg (n = 219; RR, 0.68; 95% CI, 0.51, 0.89). Subgroup analysis according to age group showed a significant decrease in mortality among adults (n = 222; RR, 0.62; 95% CI, 0.49, 0.79) and a similar but not statistically significant result among neonates with sepsis (n = 241; RR, 0.70; 95% CI, 0.42, 1.18). Often, in meta-analyses dealing with small trials of low quality, the authors come to the conclusion that "polyclonal ivIg has a very promising role as an adjuvant therapy in sepsis," but they also state that "large, multicenter studies are needed to confirm the effectiveness of polyclonal ivIgs in reducing mortality in patients with sepsis" (1).

So far, correct, but how helpful?

Shall we rely on grade C recommendations (the third of five grades) based on small, randomized trials with uncertain results and a moderate to high risk of false-positive (alpha) or false-negative (beta) error (the second of five grades of evidence [2]) and treat our patients with ivIg, or shall we not?

Is it more helpful for the intensivists to get more and more meta-analyses of the same trials? We have ivIg meta-analyses by Pildal and Gotzsche (3), Norrby-Teglund et al. (4), and in this issue of *Critical Care Medicine*, Laupland et al. (5) and Kreymann et al (6).

What makes the difference between these recent meta-analyses and the Cochrane statement from 2002? In a quantitative sense, they have included more trials and study patients, including the large SBITS study with ivIgG (see Pildal and Gotzsche [3]: 21 randomized, controlled trials [RCTs] with a total of 1,711 patients; Norrby-Teglund et al. [4]: nine trials with a total of 645 patients treated exclusively with ivIgGMA; Laupland et al. [5]: 14 RCTs with a total of 1,987 adults patients; and Kreymann et al. [6]: 15 RCTs with a total of 1,492 adult patients [932 patients treated with ivIgG and 560 patients treated with ivIgGMA). Summarizing all trials, a reduction in mortality by ivIg treatment was consistently found, with an odds ratio (OR) of 0.77 for ivIgG + ivIgGMA (3), 0.35 for ivIgGMA (4), 0.66 for ivIgG + ivIgMA (5), as well as 0.78 for ivIgG + ivIgGMA, 0.85 for ivIgG, and 0.66 for ivIgGMA (6). These risk reductions are very similar to those found by the Cochrane meta-analysis (see previously). So, nothing new?

There are some new aspects, no doubt. First, as already found by the Cochrane meta-analysis (1), ivIgGMA preparations (per 100 mL: 3.8 g of IgG, 0.6 g of IgM, and 0.6 g of IgA) indeed seem to give better results than ivIgG preparations (6). When we look at the results of the SBITS study (7) and the ESSICS study (8) performed with ivIgG, then we do not find a reduction in mortality at all with ivIgG, neither in patients with sepsis (SBITS study) nor in cardiac surgery patients with postoperative severe systemic inflammatory response syndrome (the ESSICS study). However, why should an ivIgGMA preparation work better than an ivIgG preparation (9)? When we compare both types of preparations, then indeed several quantitative and qualitative differences in properties and functions have been described (Fig. 1): a superior antibody content (10) and a more intense complement inactivation (11) of ivIgGMA make more differences in the initial stage of sepsis; the experimental improvement of microvascular perfusion failure in an experimental sepsis model was seen only

***See also pp. 2677, 2686, and 2693.**

The author is engaged in clinical and experimental work on immunoglobulins in sepsis. In this respect, the following categories of financial interest existed/do exist with Bayer, Germany (Polyglobin, SBITS study, ESSICS study) and Biotest, Germany (Pentaglobin): consultancies, honoraria/speaking fees, and grants.

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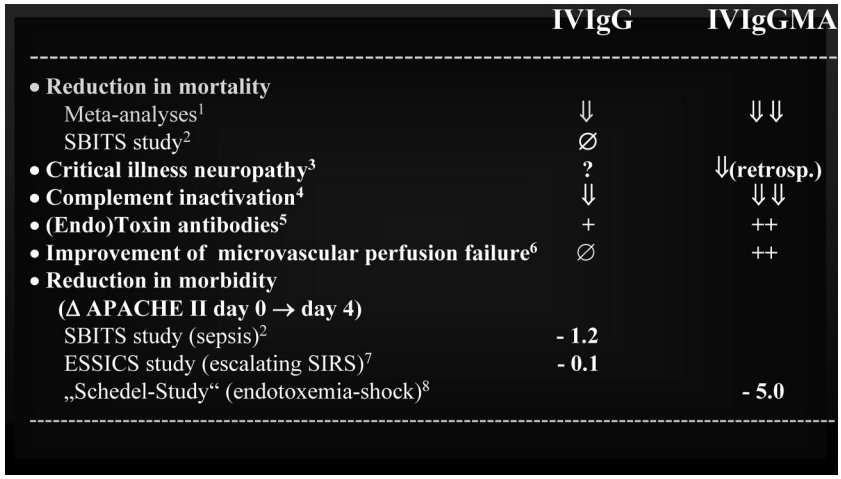

Figure 1. Sepsis treatment with intravenous immunoglobulins (*IVIg*): ivIgG vs. ivIgGMA—what could make the difference? [1]References 1 and 6; [2]reference 7; [3]reference 14; [4]reference 11; [5]reference 10; [6]reference 12; [7]reference 8; [8]reference 15; *APACHE*, Acute Physiology and Chronic Health Evaluation; *SIRS*, systemic inflammatory response syndrome.

with ivIgGMA, but not with ivIgG (12). In neither the SBITS study (7) nor the ESSICS study (8) was a lowering of proinflammatory cytokine plasma levels observed with ivIgG, despite impressive *in vitro* findings (13). No data are available yet as to whether ivIgGMA might suppress cytokine plasma levels and thereby act as an anti-inflammatory agent. An interesting finding also is the beneficial effect of early treatment with ivIgGMA in Gram-negative severe sepsis and septic shock in critical illness polyneuropathy (14), which has not yet been described for adjunctive ivIgG treatment. Finally, a reduction in mortality and morbidity in septic patients seems to be more effective by ivIgGMA than by ivIgG. In the case of ivIgG, the initial fall in the Acute Physiology and Chronic Health Evaluation (APACHE) II score (a marker of multiple organ dysfunction syndrome improvement) is only moderate in septic patients (the SBITS study) (7) and even absent in patients with severe systemic inflammatory response syndrome after cardiac surgery (the ESSICS study) (8), whereas in the case of ivIgGMA, a relevant fall of the APACHE II score by five points has been observed in endotoxemic septic shock (15). These findings show that there might indeed be a more beneficial effect with ivIgGMA in sepsis than with ivIgG. An immunoglobulin preparation with a higher IgM fraction than presently available could give a more convincing but less speculative answer.

Second, methodologic progress in meta-analysis shines on the horizon. *High-quality RCT* are the magic words. Focusing on high-quality RCTs and neglecting low-quality RCTs should make meta-analyses more precise. This idea is not new and can readily be found in the Cochrane analysis (1), but the authors of recent meta-analyses focus intensively on this point, defining high-quality RCTs by way of randomization, analysis, blinding, patient selection, etc. To the surprise of the reader, however, the results obtained in the respective meta-analyses, although based on the same trials, could not be more discrepant. By being restricted to high-quality trials (on one hand, the beneficial ivIg effect vanes in the meta-analyses reported by Pildal and Gotzsche [3] and by Laupland et al. [5], and on the other hand, in the meta-analysis of Kreymann et al. [6]), the beneficial ivIg effect is relatively stable and persists even in high-quality trials (ivIgG, all trials: OR, 0.85; ivIgG, high-quality trials: OR, 0.86; ivIgGMA, all trials: OR, 0.66; ivIgGMA, high-quality trials: OR, 0.40). Consequently, opposing conclusions are drawn. Pildal and Gotzsche (3) state: “Because high-quality trials failed to demonstrate a reduction in mortality, polyclonal immunoglobulin should not be used for treatment of sepsis except in randomized clinical trials.” In this volume, we read in the article by Laupland et al. (5): “This meta-analysis demonstrates an overall reduction in mortality with the use of ivIg for the adjunctive treatment of severe sepsis and septic shock in adults although significant heterogeneity exists among the included trials and this result was not confirmed when only high-quality studies were analyzed. These data warrant a well-designed, adequately powered, and transparently reported clinical trial.” On the other hand, Kreymann et al. (6) tell us the opposite: “Polyvalent immunoglobulins exert a significant effect on mortality in sepsis and septic shock with a trend in favor of IgGAM.”

Does this somewhat new generation of meta-analyses help intensivists in treating septic patients? My first impression is “no” when I read such discrepant recommendations drawn from the very same clinical trials. The reader of such meta-analyses may ask whether it is really the right way that every author team chooses its own criteria for high-quality RCTs, with the very same RCT being a high-quality trial in one meta-analysis and a lower quality RCT in the other. It is also difficult to understand why a RCT with a total of 21 patients included (ten in the ivIgG group with one death and 11 in the control group with four deaths) is classified as high-quality RCT. There is a need for consensus definitions of high-quality RCTs and also a transparent registration not only of clinical trials but also of meta-analyses. Our international grading system of evidence (2) classifies grade I as “large randomized trials with clear-cut results,” grade II as “small randomized trials with uncertain results,” class III as “nonrandomized, contemporaneous controls,” grade IV as “nonrandomized, historical controls and expert opinion,” and grade V as “case series, uncontrolled studies, and expert opinion.” Grades II to V are useless when we do not draw consequences from these studies but state only that “well-designed, adequately powered and transparently reported clinical trials” are necessary (5). This is not very helpful for me. As an intensivist, I would like to know whether the data available fulfil the criteria of evidence grades I, II, III, IV, or V, resulting in a recommendation grade A (supported by at least two level I investigations), grade B (supported by one level I investigation), grade C (supported by level II investigations only), grade D (supported by at least one level III investigation), or grade E (supported by level IV or V evidence). Therefore, the meta-analysis of Kreymann et al. (6) is an “intensivist-oriented” meta-analysis. This meta-analysis tells me that all ivIg trials available are grade II trials, with the exception of the SBITS trial (grade I), and therefore the positive recommendation for an adjunctive therapy with polyvalent immunoglobulins for sepsis or septic shock deserve a grade C

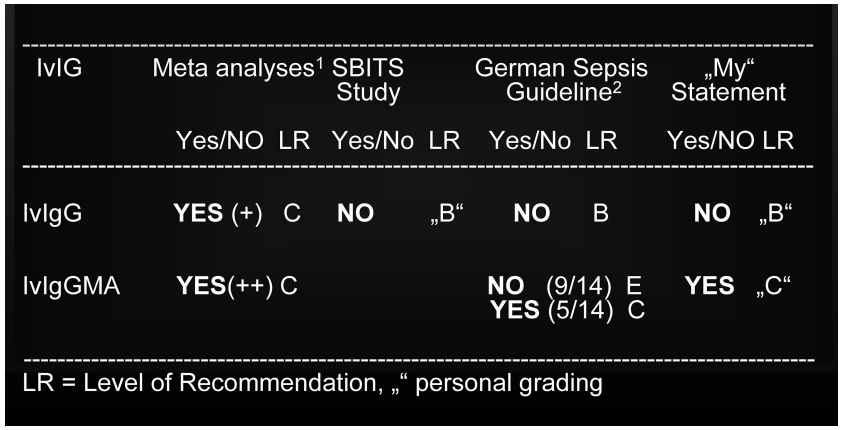

Figure 2. Immunoglobulin treatment in sepsis—how strong is the evidence? *IvIG*, intravenous immunoglobulins; *LR*, level of recommendation; " ", personal grading; [1]references 1 and 6; [2]reference 16.

recommendation. This is a higher level of evidence than expert opinion (level IV or V)! Also, this meta-analysis is consequent in stating "Our data showed that the IgGAM preparation can reduce mortality in adults by 34% . . . as long as there is no better evidence, the results demonstrated should be sufficient reason to use such a preparation for adjunctive therapy of sepsis or septic shock." This is exactly what I do (Fig. 2).

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REFERENCES

1. Alejandria MM, Lansang MA, Dans LF, et al: Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002; CD001090
2. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
3. Pildal J, Gotzsche PC: Polyclonal immunoglobulin for treatment of bacterial sepsis: A systematic review. *Clin Infect Dis* 2004; 39: 38–46
4. Norrby-Teglund A, Haque KN, Hammarström L: Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: A review of clinical efficacy in relation to microbiological aetiology and severity of sepsis. *J Intern Med* 2006; 260:509–516
5. Laupland K, Kirkpatrick AW, Delaney A: Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis. *Crit Care Med* 2007; 35:2686–2692
6. Kreymann KG, de Heer G, Nierhaus A, et al: Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; 35:2677–2685
7. Werdan K, Pilz G, Bujdoso O, et al: Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study. *Crit Care Med* 2007; 35:2693–2701
8. Werdan K, Pilz G, Mueller-Werdan U, et al: Immune globulin G treatment of post cardiac surgery patients with score-identified severe SIRS—The ESSICS study. *Crit Care Med* 2008; 36:In Press
9. Kazatchkine MD, Kaveri SV: Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001; 345:747–755
10. Trautmann M, Held TK, Susa M, et al: Bacterial lipopolysaccharide (LPS)specific antibodies in commercial human immunoglobulin preparations: Superior antibody content of an IgM-enriched product. *Clin Exp Immunol* 1998; 111:81–90
11. Rieben R, Roos A, Muizert Y, et al: Immunoglobulin M enriched human intravenous immunoglobulin prevents complement activation in vitro and in vivo in a rat model of acute inflammation. *Blood* 1999; 93: 942–951
12. Hoffmann JN, Fertmann JM, Vollmar B, et al: Immunoglobulin M-enriched human intravenous immunoglobulins reduce leukocyte-endothelial cell interactions and attenuate microvascular perfusion failure in normotensive endotoxemia. *Shock* 2007 [Online ahead of print]
13. Andersson JP, Andersson UG: Human intravenous immunoglobulin modulates monokine production in vitro. *Immunology* 1990; 71:372–376
14. Mohr M, Englisch L, Roth A, et al: Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. *Intensive Care Med* 1997; 23: 1144–1149
15. Schedel I, Dreickhausen U, Nentwig B, et al: Treatment of Gram-negative septic shock with an immunoglobulin preparation: A prospective, randomized clinical trial. *Crit Care Med* 1991; 19:1104–1113
16. Reinhart K, Brunkhorst FM, Bone H-G, et al: Diagnosis and treatment of sepsis: S-2 guidelines of DSG and DIVI. *Intensivmed* 2006; 43:369–384; 464–475

To use or not to use? Polyclonal intravenous immunoglobulins for the treatment of sepsis and septic shock*

This issue of *Critical Care Medicine* publishes one long-expected original, randomized, controlled clinical trial (1) and two meta-analyses (2, 3) on the effect of adjuvant intravenous immunoglobulins (ivIg) on mortality in sepsis and septic shock. Both meta-analyses followed previously published meta-analyses on the same topic (4–6). The Cochrane review by Alejandria et al. (4) published in 2002 calculated a significant effect of ivIg on overall mortality but was criticized because it did not include the results of the large Score-Based Immunoglobulin G Treatment in Sepsis (SBITS) study (1), which had been published in preliminary parts. The second previous meta-analysis (5) did include the data but concluded that polyclonal immunoglobulins should not be used because a subgroup of four high-quality trials failed to demonstrate a reduction in mortality. In the third meta-analysis, published in 2007, Turgeon et al. (6) included 20 studies in their examination using different inclusion/exclusion criteria. They included the SBITS study (1) based on an abstract and published protocol information, and they suggested that a further large randomized controlled trial be conducted because of methodological limitations of the current literature.

After >25 yrs of studies examining ivIg in the treatment of sepsis and septic shock (the first study was published in 1981), with millions of dollars spent, we are left with questions. To use or not to use? For which patients? At what time? With which drug and dose regimen? Do the two further meta-analyses published here (2, 3) and the long-awaited trial by Dr. Werdan and colleagues (1) contribute to a more definitive answer? *I think yes!*

The multicenter SBITS study by Dr. Werdan and colleagues (1) using intravenous immunoglobulin G (ivIgG) as verum (n = 321 patients) compared with human serum albumin (n = 303 patients) as placebo control did not show a reduction in the 28-day mortality rate (39.3% vs. 37.3%, respectively) as the primary end point. This study overrules all smaller trials of ivIgG in power and study quality and can be considered a landmark trial. At least in adults, ivIgG should not be used as adjuvant in sepsis and septic shock. The study protocol was published before the start of the trial and was the basis for a discussion forum titled Methodology of Clinical Trials in Sepsis (8). As mentioned by the authors (1), this contributed significantly to the improvement of the study design and performance.

The two recent meta-analyses (2, 3) published in this issue of *Critical Care Medicine* also help answer our question: to use or not to use.

Dr. Laupland and colleagues (2) focused on adult patients (n = 14 studies) admitted to intensive care units with all-cause mortality reported as an outcome, with predefined subgroup analyses on study quality criteria, type of immunoglobulin (ivIgG vs. IgM-enriched ivIgG), ivIg dose, and control group differences (standard vs. albumin).

Dr. Kreymann and colleagues (3) extended the previous meta-analysis by including randomized controlled trials in adults, children, and neonates (n = 27 studies). The data were summarized separately for adults or older children and neonates. According to prior design, results for adult patients were aggregated for two subgroups: studies using IgM-enriched ivIgG vs. studies using various preparations that contained only ivIgG. The meta-analysis by Dr. Kreymann and colleagues included all studies in the report by Dr. Laupland and colleagues (2) but one: Burns et al (9). Dr. Laupland and colleagues also missed one study included by Dr. Kreymann and colleagues: Just et al (10). There are few other discrepancies, especially in the references used.

The immunoglobulin preparation enriched by IgM and IgA molecules (IgGAM) was studied in eight smaller trials involving 560 adult patients (3). The estimate of the pooled effect on mortality was a relative risk (RR) of 0.66, which translates to a 34% relative reduction in mortality ($p < .0009$) with no substantial heterogeneities. A similar or even better result was obtained in neonate trials with 352 patients in five smaller studies (relative risk, 0.50) equivalent to a 50% relative reduction in mortality. Also, ivIgG preparations (seven trials) with 358 neonates in total showed positive effects (relative risk, 0.63) equivalent to 37% reduction in mortality.

Because possible biases in smaller trials may lead to an overestimation of the treatment effect of IgGAM preparations, as discussed by Dr. Laupland and colleagues (2), the separation between immunoglobulin preparations and patient groups at least lends credit to further larger trials with increased concentrations of IgM solutions. The well-performed analysis by Dr. Kreymann and colleagues (3), however, should lead to an upgrade of the current German sepsis guideline recommendation on ivIgGAM use (11): A grade B recommendation for its use based on the new data presented is appropriate.

To use or not to use? Considering the available results, the answers must be ivIgG no and ivIgGAM yes, as long as larger high-quality clinical trials are not available.

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REFERENCES

1. Werdan K, Pilz G, Bujdoso O, et al: Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study. *Crit Care Med* 2007; 35:2693–2701

*See also pp. 2677, 2686, and 2693.

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2. Laupland K, Kirkpatrick AW, Delaney A, et al: Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis. *Crit Care Med* 2007; 35:2686–2692
3. Kreymann KG, de Heer G, Nierhaus A, et al: Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; 35:2677–2685
4. Alejandria MM, Lansang MA, Dans LF, et al: Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002; CD001090
5. Pildal J, Gotzsche PC: Polyclonal immunoglobulin for treatment of bacterial sepsis: A systematic review. *Clin Infect Dis* 2004; 39:38–46
6. Turgeon AF, Hutton B, Fergusson DA, et al: Meta-analysis: Intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; 146:193–203
7. *Deleted in proof*
8. Lorenz W, Neugebauer E, Pilz G, et al: Discussion forum—Methodology of clinical trials in sepsis. *Theor Surg* 1994; 9:10–67
9. Burns ER, Lee V, Rubenstein A: Treatment of septic thrombocytopenia with immune globulin. *J Clin Immunol* 1991; 11:363–368
10. Just HM, Metzger M, Vogel W, et al: Effects of an adjuvant therapy with immunoglobins in patients of a surgical intensive care unit. *Klin Wochenschr* 1986; 64:245–256
11. Reinhardt K, Brunkhorst F, Bone H, et al: Diagnosis and therapy of sepsis. Guidelines of the German Sepsis Society Inc. and the German Interdisciplinary Society for Intensive and Emergency Medicine. *Internist (Berl)* 2006; 47: 356, 358–360, 362–368, passim

Suppression of monocyte metabolism by septic plasma: Revisiting the concept of "blood poisoning"*

Recent evidence links sepsis-induced organ failures to changes in cell metabolism, including altered mitochondrial oxygen consumption. Mechanistically, various reactive oxygen species, particularly NO and superoxide, are of particular interest (1). In this context, circulating mediators released into the bloodstream during the systemic inflammatory response of sepsis, including tumor necrosis factor-α and interleukin-1β, promote the expression and activation of inducible NO synthase, which leads to dramatic increases in NO production, particularly by monocytes and macrophages localized to the site of infection (2). NO diffuses rapidly and is highly reactive with other reactive oxygen species (e.g., with superoxide to form peroxynitrite), which leads to the modification of proteins and lipids. With respect to cellular oxygen metabolism, NO and its byproducts (e.g., peroxynitrite) inhibit mitochondrial electron transport, such that the formation of high energy phosphates (i.e., adenosine triphosphate) is compromised, and renders mitochondria susceptible to high amplitude swelling caused by the opening of high conductance pores spanning the inner mitochondrial membrane, which is referred to as the *mitochondrial permeability transition* (3). The mitochondrial permeability transition, in turn, is a signal for the removal of damaged mitochondria (autophagy) and cells (apoptosis) (1). The importance of this mechanism is emphasized by a recent study by Dr. Larche and colleagues (4), who demonstrated that inhibition of the mitochondrial permeability transition preserves organ function and improves survival in an animal model of sepsis. Thus, mitochondrial damage likely contributes to organ failures during sepsis, and may participate in altered metabolism and function of other cell types.

In addition to vital organ failures, sepsis is associated with impaired cell-mediated immunity, which has been referred to as "immune paralysis" (5); however, it is unknown if altered mitochondrial function contributes to this phenomenon. Monocytes derived from septic patients exhibit impaired immune functions and reduced expression of human lymphocyte antigen-DR, and the latter is predictive of increased mortality (6). In this issue of *Critical Care Medicine*, Dr. Belikova and colleagues (7) sought to determine whether sepsis leads to altered mitochondrial respiration in human peripheral blood monocytes (PBMCs), and if a factor present in septic plasma was responsible. To this end, they measured adenosine diphosphate–independent (state 4) respiration, adenosine diphosphate–dependent (state 3) respiration, and fully uncoupled mitochondrial oxygen consumption rates (Vo_2 max) in PBMCs from septic patients and nonseptic controls. They did not measure high energy phosphate levels, which would have been necessary to confirm "energetic failure," such as was observed in skeletal muscle of sepsis nonsurvivors (8). Nonetheless, the results of these investigations are provocative in that they show for the first time that PBMCs derived from septic humans have impaired mitochondrial respiratory function, which is caused by an unidentified substance in septic plasma.

The present study provides some important insights relating to the potential mechanisms by which septic plasma promotes PBMC mitochondrial dysfunction. Paradoxically, baseline mitochondrial respiration was elevated in monocytes derived from septic patients, whereas state 3 respiration and Vo_2 max were depressed. To the extent that baseline mitochondrial respiration approximates state 4 respiration, which implies that adenosine diphosphate is depleted in the cells (an unmeasured parameter in these investigations), the results suggest that oxygen consumption is partially uncoupled from adenosine 5'-triphosphate formation. Uncoupling of oxygen consumption from adenosine 5'-triphosphate formation was confirmed by experiments wherein PBMCs incubated in septic plasma were shown to consume oxygen at high rates despite the presence of oligomycin, a potent inhibitor of mitochondrial adenosine 5'-triphosphatase. The observed reduction in state 3 respiration and Vo_2 max in septic PBMCs and nonseptic PBMCs exposed to septic plasma imply inhibition of mitochondrial electron transport, but provide no mechanistic insight. In this context, similar results were observed when mitochondrial function was assessed in vital organs of septic animals, wherein it

***See also p. 2702.**

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