**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:●●●●●●)

**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 (ivlg) has been investigated as an adjunctive therapy for treating severe infections (4).

Three reports have summarized the clinical trials investigating the adjunctive use of ivlg in the treatment of sepsis and septic shock and overall have demonstrated a dramatic reduction in mortality associated with ivlg 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 ivlg preparations (5). In addition, two large trials have only recently been completed and published (8, 9). As a result, the overall effect of ivlg therapy on mortality of critically ill adults with severe sepsis and septic has not been well defined.

Given the uncertainty surrounding the effect of ivlg as an adjunctive treatment for severe infections in adults, we performed a systematic literature review and meta-analysis to investigate whether adjunctive therapy with ivlg 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 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 and the I² statistic, with I² > 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 DerSimonian and Laird (as reported in Ref. 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).

**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 ($I^2 = 53.8\%$). 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.

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

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

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

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

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 studies 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 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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td>0.059</td>
<td>0.027</td>
<td>.027</td>
</tr>
<tr>
<td>Dose of ivIg</td>
<td>-1.80</td>
<td>0.59</td>
<td>.003</td>
</tr>
<tr>
<td>Overall quality score</td>
<td>0.77</td>
<td>0.19</td>
<td>&lt;.0005</td>
</tr>
</tbody>
</table>

CI, confidence interval; ivIg, intravenous immunoglobulin; IgM, immunoglobulin M.
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 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 I² 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, is 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 nongrave 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 (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 (4, 39).

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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