

Review: Intravenous polyclonal immunoglobulins reduce mortality in patients with bacterial sepsis and septic shock

Alejandria MM, Lansang MA, Dans LF, Mantaring JB. **Intravenous immunoglobulin for treating sepsis and septic shock.** *Cochrane Database Syst Rev.* 2001;(2):CD001090 (latest version 15 Jan 2001).

QUESTION

In patients with bacterial sepsis or septic shock, is intravenous immunoglobulin (IVIG) treatment more effective than placebo or no treatment in reducing mortality, bacteriologic failure rates, or duration of stay in the hospital?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to December 2000), EMBASE/Excerpta Medica (1988 to February 1999), and the Cochrane Controlled Trials Register. Content terms used in the search included immunoglobulins, septicemia, sepsis, shock, and septic. Bibliographies of relevant studies were reviewed and investigators or organizations working in this field were contacted for information on published and unpublished trials.

STUDY SELECTION

Studies in any language were selected if they were randomized controlled trials comparing IVIG (monoclonal or polyclonal) with placebo or no treatment in patients with bacterial sepsis or septic shock and if they

assessed all-cause mortality, bacteriologic failure rates, and duration of hospitalization.

DATA EXTRACTION

2 reviewers independently extracted data on time and geographical location of the study, patient characteristics, key components of the intervention, study quality, and outcomes.

MAIN RESULTS

27 trials (8856 patients) were included in the meta-analysis. 4949 patients received IVIG, and 3907 received placebo or no treatment (control group). Subgroup analysis showed a greater reduction in all-cause mortality in the polyclonal IVIG group than in the control group; it also showed a much smaller reduction in the monoclonal IVIG group (anti-

cytokines) than in the control group, but not in the monoclonal IVIG group (anti-endotoxins) (Table).

CONCLUSION

In patients with bacterial sepsis or septic shock, intravenous polyclonal immunoglobulin treatment is more effective than placebo or no treatment in reducing all-cause mortality.

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Intravenous immunoglobulins (IVIG) vs placebo or no treatment (control) for bacterial sepsis or septic shock*

| Outcome at 2 to 8 wk | Class of drugs | Weighted event rates | | RRR (95% CI) | NNT (CI) |
|----------------------|----------------------|----------------------|---------|----------------|-----------------|
| | | IVIG | Control | | |
| All-cause mortality | Polyclonal IVIG | 27% | 43% | 36% (20 to 49) | 7 (5 to 13) |
| | MIVIG anticytokines | 36% | 39% | 8% (1 to 14) | 35 (18 to 500) |
| | MIVIG antiendotoxins | 34% | 37% | 7% (-2 to 15) | Not significant |

*MIVIG = monoclonal intravenous immunoglobulins. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

In the last decade, the search for an adjunctive anti-inflammatory therapy for severe sepsis and septic shock has taken 3 avenues: high-dose steroids, antiendotoxin monoclonal antibodies, and specific inhibition of cytokines or other mediators of inflammation.

In this meta-analysis, Alejandria and colleagues found no clinically important benefit of antiendotoxins and anticytokines, whereas polyvalent IVIG may improve the survival of patients. The size of the trials included in the review varied markedly. The 8 antiendotoxin trials and 8 anticytokine trials involved 3084 and 5282 patients, respectively; however, 6 trials of polyvalent IVIG therapy in adults involved only 251 patients, and 5 trials of children involved only 241 patients. Therefore, the inferences that can be drawn from the analyses of polyvalent IVIG trials are weak. A previous review found a small but significant effect on mortality for anti-inflammatory monoclonal antibodies in patients with sepsis (1), which appeared to be more pronounced in patients with more severe conditions.

Although high-dose polyvalent IVIG may have some nonspecific immunomodulatory effects in sepsis, the use of IVIG during sepsis may also have a different rationale, such as use during the streptococcal toxic shock syndrome, in which IVIG is expected to enhance the clearance of superantigens produced by group A streptococci.

Because one clinical trial found that polyvalent IVIG reduced infectious morbidity in high-risk surgical patients (2) and because of its possible efficacy in the streptococcal toxic shock syndrome (3), further testing of polyvalent IVIG as adjunctive therapy during sepsis is justified. In my opinion, given the quality and size of trials, therapy with polyvalent IVIG should be considered experimental until further large randomized clinical trials are complete.

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