Comparison of Early IgM-Enriched Immunoglobulin vs Polyvalent IgG Administration in Score-Identified Postcardiac Surgical Patients at High Risk for Sepsis*

Günther Pilz, MD; Roland Appel, MD; Eckart Kreuzer, MD; and Karl Werdan, MD

Study objective: To address the relevance of the IgM component in polyvalent immunoglobulins in sepsis treatment by comparison of the clinical course under polyvalent IgG vs IgGMA therapy in postcardiac surgical patients at high risk for sepsis and to reassess the prognostic validity of sequential changes in acute physiology and chronic health evaluation (APACHE II) scores during treatment.

Design: Prospective, randomized clinical trial.

Setting: Cardiac surgical ICU in a university hospital.

Patients: Among 870 consecutive patients after elective open-heart surgery, 29 (3.3%) met the previously validated high-risk criterion (APACHE II score ≥ 24 on the first postoperative day) with a mean APACHE II score-predicted mortality risk of 63%.

Interventions: In addition to standard therapy, 27 of these patients were randomized to receive commercially available IV IgG (Polyglobin N, n=14, total dosage: 18 mL/kg) or IgGMA (Pentaglobin, n=13, total dosage: 15 mL/kg).

Measurements and results: The two groups were comparable in baseline disease severity and concurrent therapy. The extent of score-quantified improvement in disease severity during treatment was similar in both groups (mean fall in APACHE II scores within 4 days: IgG, -6.9; IgGMA, -5.2), as were score-defined improvement rates (rate of patients with score decrease ≥ 7 within 4 days: IgG, 57%; IgGMA, 54%) and in-hospital mortality (IgG, 29%; IgGMA, 31%) (all p=NS). There was a strong association between the decrease over time in APACHE II scores during therapy and prognosis (mortality rates in patients with vs without score-assessed improvement: 0% vs 67%, p=0.0002).

Conclusions: IgG and IgGMA were associated with a comparable improvement in disease severity in score-identified postcardiac surgical patients at high risk for sepsis. Given the design as an efficacy rather than an equivalence study, this hypothesis derived from our results needs independent validation in larger trials. Sequential APACHE II score changes were reconfirmed as a prognostically valid quantitative measure of disease progress during sepsis therapy. (CHEST 1997; 111:419-26)

Key words: APACHE II score; cardiac surgery; immunoglobulin therapy; IgM; response to therapy; risk assessment; sepsis

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; Ig = immunoglobulin

In patients after cardiac surgery, the incidence of infections is high,1 owing to cardiac impairment and the intraoperative use of extracorporeal circulation and its sequelae.2-5 Accordingly, sepsis and septic multiple organ failure are among the major causes of death.1,6,7

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In a recent trial,8 we have shown that early supplemental IV immunoglobulin (Ig) treatment improves disease severity and may improve prognosis in prospectively Acute Physiology and Chronic Health Evaluation (APACHE II)9 score-identified high-risk postcardiac surgical patients, compared to a historical control population equivalent in patient characteristics and disease severity (Fig 1, left). This study had also confirmed an earlier concept10 for this particular population, that an improvement in APACHE II scores during sepsis therapy was significantly correlated with a reduction in mortality.

Regarding potential differences between various Ig
preparations, we are not aware of randomized clinical trials comparing the efficacy of commercially available polyvalent Ig preparations in adult patients with sepsis. Such comparisons seem of interest particularly in view of the conflicting experimental evidence regarding the role of the IgM component and the growing awareness for the aspect of cost-effectiveness of Ig administration in infections and sepsis. Therefore, on the basis of our previous Ig study’s concept of an early score identification of high-risk patients after cardiac surgery (Fig 1, left), we have carried out a randomized, prospective trial to compare the clinical course under a polyvalent IgG vs an IgM-enriched preparation (IgGMA) in these patients. The second study goal was to reassess the prognostic validity of the fall in APACHE II scores as a marker of improvement under Ig therapy in this independent postcardiac surgical patient population.

**Materials and Methods**

**Study Population and Treatment Regimen**

From July 1992 to July 1993, in all patients undergoing elective open-heart surgery (excluding transplantation) at the Department of Cardiac Surgery, Grosshadern Hospital, University of Munich, APACHE II scores were prospectively assessed on the first postoperative day (“day 1”) using a microcomputer-based scoring program. Patients fulfilling the previously validated high-risk criterion of an APACHE II score ≥24 on day 1 were randomized to receive one of the following supplemental Ig regimens in an open manner: IV IgG (Polyglobin N; Tropon Biologische Präparate; Cologne, Germany; dosage: day 1: 12 mL/kg; day 2: 6 mL/kg) or IV IgGMA (Pentaglobin; Biotest; Dreieich, Germany; dosage: 5 mL/kg on days 1, 2, and 3). The study preparations were commercially purchased. There was no restriction regarding standard therapy. All patients had given informed consent. The study was conducted in accordance with the principles established in Helsinki and was approved by the University of Munich Medical Faculty Ethics Committee.

**Data Collection and Analysis**

Parameters assessed to evaluate intergroup comparability are given in Table 1. The presence of shock was defined as mean...
arterial BP <60 mm Hg\(^{a}\) or need for vasopressor administration higher than 10 μg/kg/min dopamine. IgG levels were determined by nephelometric measurements in serum samples.

The main study end points were as follows: (1) the extent of APACHE II score-quantified improvement in disease severity; (2) the improvement rate under therapy (defined as rate of patients with a decrease in APACHE II score of ≥7 from day 1 to day 5 [Table 2]); and (3) in-hospital mortality.

Sample size considerations were based on the previously obtained improvement rates with IgGMA (55%) and standard therapy (controls) (19%) in a comparable population.\(^a\) With the null hypothesis of the ineffectiveness of the IgG preparation to be tested (defined as the previous control improvement rate of 19%), 36 high-risk patients were needed to detect differences with a power of 0.7 and significance of 0.05. This study was discontinued after inclusion of 27 high-risk patients (IgG, 14; IgGMA, 13), since interim analysis revealed the occurrence of similar results for the two Ig preparations (see "Results" section).

Differences between groups were analyzed statistically using the χ\(^2\) test for categorical variables; for continuous variables, the Mann-Whitney test was used. Changes of values within groups were analyzed using Scheffe’s multiple range test. In common with most clinical studies, a p value of <0.05 was considered statistically significant. All values are given as mean and 95% confidence interval (CI) for the mean.

### Results

#### Study Population

During the study period, 870 patients were eligible for postoperative score-based risk stratification. APACHE II scoring in this total population on the first postoperative day identified 29 (3.3%) high-risk patients (score: ≥24). Of these patients, 27 patients

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Table 1—Baseline Characteristics of Patients According to Treatment Group\(^a\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IgG Group (n=14)</th>
<th>IgGMA Group (n=13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr 63.9 (58.9-68.9)</td>
<td>66.8 (63.4-70.2)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F 9/5</td>
<td>9/4</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECC time, min 118 (92-144)</td>
<td>138 (98-178)</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Type, valve/hypoxia or combined 4/10</td>
<td>6/7</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>APACHE II score(^b)</td>
<td>26.9 (24.5-29.3)</td>
<td>27.7 (25.5-29.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Elevate sepsis score(^c)</td>
<td>11.9 (10.5-12.3)</td>
<td>13.0 (12.0-14.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Positive sepsis criteria(^d)</td>
<td>5.0 (4.1-5.9)</td>
<td>5.7 (4.9-6.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>7.4 (5.4-9.4)</td>
<td>6.8 (4.6-9.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>38.6 (37.8-39.4)</td>
<td>37.9 (37.0-38.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate, /min</td>
<td>115 (100-130)</td>
<td>127 (112-142)</td>
<td>0.15</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>68 (50-86)</td>
<td>78 (54-1029)</td>
<td>0.59</td>
</tr>
<tr>
<td>SVR, dynes · s · cm(^{-5})</td>
<td>750 (549-1029)</td>
<td>744 (521-967)</td>
<td>0.91</td>
</tr>
<tr>
<td>P(A-a)(^e)O(_2), mm Hg</td>
<td>230 (164-296)</td>
<td>280 (203-357)</td>
<td>0.31</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.5 (1.2-1.8)</td>
<td>1.6 (1.3-1.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>4.3 (3.8-4.8)</td>
<td>4.3 (3.9-4.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>53 (47-59)</td>
<td>46 (39-53)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>32 (30-34)</td>
<td>32 (29-35)</td>
<td>0.66</td>
</tr>
<tr>
<td>Thrombocytes, g/L</td>
<td>109 (102-116)</td>
<td>103 (81-125)</td>
<td>0.07</td>
</tr>
<tr>
<td>Leukocytes, g/L</td>
<td>10.8 (7.3-14.3)</td>
<td>11.8 (8.8-14.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>Documented infection, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (cultures from various sites(^f))</td>
<td>64</td>
<td>54</td>
<td>0.58</td>
</tr>
<tr>
<td>Proportion of Gram-negative cultures</td>
<td>53</td>
<td>47</td>
<td>0.88</td>
</tr>
<tr>
<td>Concurrent therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics/day (days 1-5, No.)</td>
<td>2.1 (1.7-2.5)</td>
<td>2.0 (1.6-2.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Vasopressor dosage/day (days 1-5)(^g)</td>
<td>3.4 (2.8-4.0)</td>
<td>4.0 (3.3-4.7)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

\(^a\)Mean values and 95% CIs. "Pretreatment"=first postoperative day. ECC=extracorporeal circulation; MAP=mean arterial pressure; SVR=systemic vascular resistance; P(A-a)\(^e\)O\(_2\)=alveolar-arterial oxygen pressure difference.

\(^b\)Respiratory tract, 60%; urinary tract, 20%; wound infection, 15%; bacteremia, 5%.

\(^c\)Dosage on an arbitrary scale from 1 to 8 ("1"=dopamine ≤10 μg/kg/min; "8"=adrenaline and noradrenaline and/or angiotensin, each >50 μg/min).

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Table 2—Prognostic Implication of the APACHE II Score Criterion for “Improvement Under Therapy” in Patients After Cardiac Surgery\(^*\)

<table>
<thead>
<tr>
<th>Mortality Rates for Score-Assessed Improvement</th>
<th>Therapy</th>
<th>p(^i) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>IgG</td>
<td>0/8 (0)</td>
<td>4/6 (67)</td>
</tr>
<tr>
<td>IgGMA</td>
<td>0/7 (0)</td>
<td>4/6 (67)</td>
</tr>
</tbody>
</table>

\(^*\)Score-assessed improvement"=patient with a decrease in APACHE II score of ≥7 on the fourth day after onset of therapy.

\(^i\)For the total study population, p=0.0002.
were treated within the study. Two patients (7%) had to be excluded, since Igs had been administered outside the randomization procedure on the basis of clinical judgment of the physician in charge. Of the 27 patients included, 13 had been randomized to receive IgGMA and 14 to receive IgG. No Ig treatment side effects were recorded.

At study entry, systemic inflammatory response syndrome (SIRS) was present in all but one patient (96%). Mean Elebute sepsis scores were 12.4 (11.6 to 13.2) and thus in the range indicative of a postoperative septic state. Shock was present in 26 of the 27 patients (96%). Mean pretreatment APACHE II scores were 27.3 (25.7 to 28.9) with a mean score-predicted mortality risk of 63%.

Patient Groups’ Comparability

The two treatment groups did not show significant differences in relevant baseline parameters and concurrent therapy (Table 1). In addition, logistic regression did not show an overall difference between the two groups regarding both the pretreatment single variables (Table 1) (χ²: 12.257 with 13 df, p=0.51) as well as the derived scores (χ²: 2.842 with 4 df; p=0.58). Furthermore, for the parameters displaying a trend toward imbalance, χ² statistics revealed no significant association with improvement or mortality rates.

Study End Points

The extent of APACHE II score-quantified improvement in disease severity was similar in both study groups (Fig 1, right). In particular, IgG administration was not associated with a lesser decrease in disease severity compared to IgGMA (mean fall in APACHE II score within 4 days: −6.9 for IgG (CI: −13.4 to −0.4) vs −5.2 (CI: −12.5 to 2.1) for IgGMA (p=0.51)). Accordingly, comparable results for the two groups were obtained for score-based improvement rates (see “Materials and Methods” section) (IgG: 57% [CI: 29 to 82%]; IgGMA: 54% [CI: 25 to 81%]; p=0.86) and in-hospital mortality (IgG: 29% [CI: 8 to 58%]; IgGMA: 31% [CI: 9 to 61%]; p=0.90).

Clinical data reflecting the severity of the patient’s course were comparable in the two groups: mechanical ventilation was required for a mean period of 8.4 days (CI: 2.9 to 13.9) in the IgG group and 8.0 days (CI: 1.8 to 14.2) in the IgGMA group (p=0.88). The mean duration of ICU treatment was 10.7 days (CI: 4.8 to 16.6) for the IgG group vs 9.8 days (CI: 3.1 to 16.5) for the IgGMA group (p=0.73).

In both Ig treatment groups, the separation into patients with as opposed to without improvement on the basis of a fall in APACHE II score (see “Materials and Methods” section) correlated significantly with mortality (Table 2). Since all patients survived until day 5, this finding was unaffected by a potential survival bias.

Serum Ig Levels

Postoperative pretreatment serum Ig levels (IgG, IgM) were borderline low to subnormal (Fig 2). Both IgG and IgGMA treatment led to higher IgG levels that persisted until day 5. This increase in IgG serum levels was significant on day 2 for the IgG preparation and on day 3 for the IgGMA therapy (Fig 2, left). IgM levels significantly rose after IgGMA therapy and were also significantly higher compared with the IgG group (days 2 and 3, Fig 2, right).

Discussion

Present Data on Ig Effectiveness in Sepsis

The available clinical trials do not yet allow definitive answers regarding the effectiveness of Ig treatment in human sepsis in general. Thus, its use remains controversial and will have to await the results of large placebo-controlled studies, one of which is currently underway.

In selected subsets of patients with sepsis, however, there is growing evidence that prophylactic or therapeutic Ig administration may reduce disease severity and even mortality. These potential Ig effects have been classically attributed to the antitoxic and opsonic activity of the antibodies administered or their synergism with β-lactam antibiotics. More recently, there is in vitro evidence for modulation of monokine production by Ig, such as down-regulation of interleukin 6 synthesis.

The present trial in a selected population of postcardiac surgery patients at high risk for sepsis is a follow-up study of a previous trial in a comparable population. It primarily aims to compare the course of the disease severity under two different Ig preparations in these patients with particular emphasis on the role of the IgM component.

Comparison of IgG vs IgGMA in Sepsis: Experimental Results

Previous trials have used either IgG or IgGMA and therefore cannot directly address the question of potential differences in efficacy between these polyclonal Ig preparations. Besides the aspect of cost-effectiveness, such comparisons seem of interest particularly in view of the conflicting experimental evidence regarding the role of the IgM component. Thus, in animal models and by in vitro...
neutralization tests of bacterial toxins, some authors have found a significantly improved protection rate and efficacy against both Gram-positive and Gram-negative bacteria of an IgM-containing preparation. These results have led to the hypothesis that such effects might be caused by specific IgM-type antibodies against endotoxin determinants. In contrast, other investigators found a polyvalent IgG compared with the IgM-containing preparation to be in most cases equally effective or even superior in several murine sepsis models using various pathogens. In addition, recent results regarding the detection of antibodies against bacterial lipopolysaccharides and lipid A by immunoblotting revealed a panel of antilipopolysaccharide and antilipid A antibodies of the IgG class in both IgG and IgGMA preparations but only few additional IgM class antibodies in the IgGMA Ig. In our view, these contradictory results do not yet allow a definite conclusion regarding the superiority of one specific Ig preparation in patients with sepsis. Therefore, the present trial primarily aimed to compare—to our knowledge, for the first time in a prospective, randomized manner in adults—the clinical course under polyvalent IgG vs IgGMA in selected patients at high risk for sepsis.

Comparison of IgG vs IgGMA Administration as Supplemental Sepsis Therapy After Cardiac Surgery

Concerning pharmacokinetics, our study confirms the ability of supplemental Ig administration to significantly increase serum IgG levels in patients with sepsis. As shown in Figure 2, left, both preparations were similar in obtaining this rise in IgG levels, despite a lower standard dosage of the IgGMA preparation. The earlier peak in the IgG group was most likely due to the higher dosage administered on day 1 (see "Materials and Methods" section). Regarding serum IgM, expectedly, only the IgGMA preparation led to significantly increased levels (Fig 2, right). With a comparable improvement in disease severity in the two study groups and with similar serum IgG levels achieved, though, an additional beneficial clinical effect of the IgM component was not demonstrated in our patients. In
contrast, the pattern of similar rises in serum IgG levels and improvement in disease severity favor the assumption of an association between higher post-treatment IgG levels and a beneficial outcome and thus the concept of an underlying deficient immunoprotein synthesis and/or abnormal IgG consumption in patients with severe infections.14

The study end points of our trial gave similar results for both Ig treatment regimens. Neither the APACHE II score-quantified improvement in disease severity and the score-based improvement rates nor the in-hospital mortality under IgG were significantly different from those encountered in the IgGMA group. In addition, the severity of the patients’ course as judged by the duration of mechanical ventilation and ICU stay were also comparable.

To ensure study groups comparability (thus, being at equal risk of having the outcome being assessed30), we have extensively evaluated a number of cofactors that might have affected the course and outcome of the two groups. We found no significant differences for demographic data, extracorporeal circulation time, pretreatment disease severity, occurrence of Gram-negative infection, and for concurrent antibiotic and vasopressor therapy (Table 1). The pretreatment scores are particularly considered to be useful tools to determine whether study groups were similar3,9,16,25 and thus reduce susceptibility bias.30 Although there was a slight tendency toward a lesser degree of baseline disease severity in the IgG group, which potentially could have led to an overestimation of IgG effectiveness, this imbalance can be regarded as counterbalanced by the more marked improvement in disease severity in this group (fall in APACHE II scores within 4 days: −6.9 for IgG vs −5.2 for IgGMA).

In summary, without a relevant patient selection bias responsible for the results obtained, our randomized trial shows that early polyvalent IgG and IgGMA therapy was associated with a comparable improvement in disease severity and a similar mortality in score-identified postcardiac surgical patients at high risk for sepsis. These results are in accordance with recent comparable findings in neonatal sepsis.31 For potential limitations of our study owing to the small treatment population size, see below.

Prospective Score-Based Risk Stratification With the Intention to Treat and the Prognostic Impact of Changes in APACHE II Scores

A major problem of postoperative care is the early identification of patients at risk of developing sepsis and multiple organ failure. The present trial confirmed the usefulness of an early APACHE II score-based identification of high-risk patients after cardiac surgery (Fig 1, left), with a nearly constant rate of this at-risk population out of the total consecutive patients in the present trial (29/870 [3.3%]) vs 60/2222 [2.7%] in our previous study8). As already described, such an approach yields several advantages: it allows the specific use of supplemental therapies in the small population at real risk (safety and cost-effectiveness considerations), avoids a delay in the onset of treatment, and provides a clear-cut prospective (a priori) identification of the target groups.8 In addition, our trial reconfirmed the very good practicability of such a daily prospective APACHE II score monitoring in the ICU over a study period of again more than 1 year (routine bedside availability within 5 to 10 min using a microcomputer-based program16).

A further important conceptual proposal of this study results from the repeatedly proved verification of the strong correlation between an improvement over time in APACHE II scores during sepsis therapy and a resulting reduction in mortality (Table 2).

Although it is conceivable that a change in the score may not be translates into a change in mortality, this trial represents our fourth independent population of patients with sepsis (for earlier studies, see reports of Pilz et al8,10,21), in which recording changes in APACHE II scores in close time relationship to treatment consistently displays a significant association with prognosis. These data are in agreement with the original findings of Bion et al32 in unselected ICU patients, that recording changes of score values under treatment improves the prognostic predictive power. They reconfirms the validity of score changes over time as a quantitative measure for improvement under therapy in reflecting the reversal of physiologic abnormalities, that have been shown to be the most important single predictor of outcome.33 Finally, our results support the use of such sequential score changes to compare improvement rates within clinical pilot studies and, potentially, even as surrogate study end points in controlled treatment trials in sepsis as an indicator of therapeutic efficacy.8,10,21,34,35

Limitations of Our Trial

The major limitation of this trial is the lack of a placebo group. Therefore, it cannot address the question of Ig effectiveness in sepsis as such and may only provide indirect suggestions for a potentially beneficial Ig effect. Thus, score-based expected mortality rates can be compared with actual death rates as a test of therapeutic efficacy.9 Using this approach, the mean observed mortality in our patients was lower (30%) than the APACHE II score-pre-
dicted mortality risk for the population studied (63%). Furthermore, both treatment groups displayed a marked improvement in disease severity in close time relationship to treatment (Fig 1, right), similar to that encountered in a preceding Ig treatment study (Fig 1, left) and superior to the previously described historical control population (Fig 1, left), equivalent in patient characteristics and disease severity.\(^5\)

A second limitation may arise from the limited population size. The limited number of patients intended for inclusion into this study was adequate to perform a comparison between IgG and IgGMA according to the trial’s null hypothesis (see “Materials and Methods” section). The numbers used in our assumptions for sample size calculations may be considered as overestimated, yet they were based on previously achieved results\(^3\) and within the range used in other Ig treatment trials.\(^36\) Given the wide CIs of our results, we are also aware that the nonsignificant differences do not statistically prove equivalence. Certainly, the study is underpowered to demonstrate small differences between the two treatment groups, which we therefore cannot rule out.

In summary, although we recognize that because of these limitations the present study may be regarded only as a primarily exploratory analysis that needs independent replication and validation in larger trials, our results nevertheless provide no initial suggestion for the presence of a clinically relevant additional benefit from an IgM-enriched polyvalent Ig compared with IgG within the population studied.

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CHEST / 111 / 2 / FEBRUARY, 1997 425
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