Continuous plasmafiltration in sepsis syndrome

John H. Reeves, MBBS; Warwick W. Butt, MBBS; Frank Shann, MD; Judith E. Layton, PhD; Alistair Stewart, PhD; Paul M. Waring, MBBS, PhD; Jeffrey J. Presneill, MBBS

From the Intensive Care Unit, Royal Children's Hospital, Parkville, Victoria, Australia (Drs. Reeves, Butt, and Shann); the Melbourne Tumour Biology Branch, Ludwig Institute for Cancer Research, Parkville, Victoria, Australia (Dr. Layton); the Bernard O'Brien Institute of Microsurgery, Fitzroy, Victoria, Australia (Dr. Stewart); the Cancer Research Unit, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia (Dr. Waring); and the Intensive Care Unit, The Royal Melbourne Hospital, Parkville, Victoria, Australia (Dr. Presneill).

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Objective: To assess the effect of plasmafiltration (PF) on biochemical markers of inflammation, cytokines, organ dysfunction, and 14-day mortality in human sepsis.

Design: Multicenter, prospective, randomized, controlled clinical trial.

Setting: Seven university-affiliated intensive care units.

Patients: Thirty patients (22 adults, eight children) with new (<24 hrs) clinical evidence of infection and sepsis syndrome were enrolled. Fourteen of 30 (nine adults, five children) were randomized to PF.

Interventions: All patients received protocol-driven supportive intensive care, and those randomized to PF received continuous plasma exchange for 34 hrs using a hollow-fiber plasma filter.

Measurements and Main Results: Illness severity and risk of death were calculated with the Pediatric Risk of Mortality (children) and the Acute Physiology and Chronic Health Evaluation II (adults) scales. Plasma samples (0, 6, 24, and 48 hrs) were assayed for acute-phase proteins (albumin, globulin, C-reactive protein, α1-antitrypsin, haptoglobin), inflammatory mediators (complement fragment C3, thromboxane B2), and cytokines (interleukin-6, granulocyte colony-stimulating factor, leukemia inhibitory factor). Sieving coefficients were estimated from filtrate concentrations at 3 hrs. The two groups were matched for incidence of septic shock (13 of 14 vs. 11 of 16), refractory shock (three of 14 vs. six of 16), bacteremia (six of 14 vs. five of 16), severity of illness, and calculated risk of death (0.68 vs. 0.64). There was no difference in mortality. Eight of 14 PF patients (57%) and eight of 16 controls (50%) survived for 14 days (p = .73, Fisher's exact test). Multiple logistic regression revealed age (odds ratio, 16.4:1; 95% confidence interval, 2.12-∞) and shock (10.6:1; 1.32-∞) as significant predictors of death; plasmafiltration was associated with a nonsignificant reduction in the risk of death (odds ratio, 1.78:1; 95% confidence interval, 0.20-18.1). The mean (SD) number of organs failing in the first 7 days in the PF group was 2.57 (0.94) vs. 2.94 (0.85) in controls (p = .37, Mann-Whitney U test). Both groups had similarly elevated plasma concentrations of all inflammatory mediators except complement fragment C3 at study entry. Leukemia inhibitory factor was detectable in four patients only. PF did not influence mean concentrations of interleukin-6, granulocyte colony-stimulating factor, thromboxane B2, total white cell count, neutrophil count, or platelet count, but it was associated with significant reductions of α1-antitrypsin, haptoglobin, C-reactive protein, and complement fragment C3 in the first 6 hrs (p < .05). The sieving coefficients for all inflammatory mediators approached unity.
Conclusions: PF caused a significant attenuation of the acute-phase response in sepsis. There was no significant difference in mortality, but there was a trend toward fewer organs failing in the PF group that suggests that this procedure might be beneficial.

Key Words: sepsis; randomized, controlled trial; mortality; cytokines; plasmapheresis; multiple organ failure; acute phase proteins; albumins; eicosanoids; inflammation.

The incidence of severe infection is increasing (1), but the approach to supportive therapy and the resulting mortality has remained unchanged for almost 20 yrs (2). Most of the clinical manifestations of severe infections are caused by an intense, generalized inflammatory response in the host mediated by a multitude of interrelated cellular and humoral factors (3). Judicious modulation of this response may hold the key to improved survival (4).

Because of the high mortality of sepsis (5) and the potentially large number of patients at risk (6), considerable money and effort has been invested in the development and testing of novel therapies. Systemic immunomodulation with corticosteroids (7, 8), monoclonal antibodies to endotoxin (9, 10), and tumor necrosis factor-α (11, 12), a recombinant human interleukin (IL)-1 receptor antagonist (13), and pharmacologic inhibition of platelet-activating factor (14) have all failed to show any increase in survival in large prospective, randomized, controlled trials.

Plasma exchange has been used as salvage therapy in severe infection, especially meningococcemia (15-20). In 1992, van Deuren et al. (21) reported improved survival in a cohort of 15 patients with fulminant meningococcal sepsis treated with plasma exchange compared with 10 historical controls, but they were unable to demonstrate any change in endotoxin clearance during the procedure. Controlled animal studies of plasma exchange in sepsis have yielded conflicting results. Muraji and colleagues (22) observed improved survival in endotoxemic puppies treated with plasma exchange, and Cohen et al. (23) observed improved survival in endotoxemic rats treated with plasma exchange. In contrast, Natanson and colleagues (24) observed increased mortality in dogs with experimental peritonitis treated with plasma exchange.

To the best of our knowledge, there has been no prospective, controlled study of plasma exchange in humans with sepsis. The aim of this randomized trial was to investigate the effect of 34 hrs of continuous plasmapheresis (plasma exchange using a large-pore hemofilter) on the humoral inflammatory response, the number of organ failures in the first 7 days, and 14-day survival in sepsis.

MATERIALS AND METHODS

Ethical Approval. Separate ethical approval for the trial was obtained at each participating hospital, and written informed consent was obtained for each patient.

Entry Criteria. The criterion for entry to the trial was sepsis syndrome (25). In adults, this definition required all of the following: 1) clinical evidence of infection; 2) respiratory rate > 20 breaths/min or minute ventilation > 10 L/min; 3) heart rate > 90 beats/min; 4) temperature > 38°C (100.4°F) or < 35.5°C (95.9°F); and 5) one or more of the following: a) altered mental state; b) PaO2/FIO2 < 280; c) lactic
In children, certain aspects of this definition were modified. The critical value for heart rate (90 beats/min in adults) was adjusted to 2 SD above the mean for the age group (1-2 yrs, 155 beats/min; 2-3 yrs, 140 beats/min; 3-7 yrs, 120 beats/min; 7-10 yrs, 110 beats/min; 10-12 yrs, 100 beats/min; >12 yrs, 90 beats/min), and the adult criterion for respiratory rate or minute ventilation was replaced with "clinical requirement for mechanical ventilation."

**Exclusion Criteria.** The exclusion criteria were failure to obtain informed consent, positive human immunodeficiency virus serology, uncomplicated meningococcal meningitis without shock in children, or recent (<48 hrs) cardiac surgery. Children with uncomplicated meningococcal meningitis and no circulatory shock have a good prognosis with conventional therapy (26), and cardiopulmonary bypass can cause an inflammatory process resembling sepsis syndrome (27). The presence of immunocompromise other than human immunodeficiency virus was not an exclusion criterion.

**Randomization.** Before randomization, patients were stratified first by hospital and then by the presence or absence of immunocompromise as defined by Acute Physiology and Chronic Health Evaluation (APACHE) II score (28). When a patient with sepsis was admitted to the intensive care unit, the attending physician contacted the trial coordinator to discuss eligibility. If all entry criteria were met, the attending physician sought written consent from the next of kin. Patients were then randomized by the coordinator to conventional treatment only or conventional treatment plus plasmafiltration using computer-generated randomization lists consisting of randomly varying block lengths. Two separate lists were produced for each hospital, one for immunocompromised patients and one for immunocompetent patients. Immediately after enrollment, a randomization number from the appropriate list was matched with a corresponding number on a master "key" and the treatment assignation was read. The master key itself consisted of hundreds of randomly ordered numbers to prevent inadvertent identification of future patient assignations. All lists and the master key were locked in the trial coordinator's office.

**Conventional Treatment.** A consensus was struck on guidelines for supportive treatment between participating hospitals (Appendix 1). These guidelines described agreed goals for cardiovascular, respiratory, and renal support. They also included protocols for antibiotics and an agreement to use early enteral feeding whenever possible. Goals for mean arterial pressure were age adjusted in children.

**Plasmafiltration.** We aimed to perform a rapid exchange of twice the estimated plasma volume (100 mL/kg) during the first 4-6 hrs and then a lower maintenance rate of exchange for another 28-30 hrs during which another 3 plasma volumes (150 mL/kg) would be exchanged. If the filter clotted in <24 hrs, it was replaced, and any filters still functioning at 34 hrs were electively discontinued. A new polypropylene hollow-fiber plasma filter (PF1000, Gambro, Lund, Sweden) was used for each patient. This filter has 1,000 fibers, a total surface area of 0.14 m², and a maximum pore size of 0.5-0.6 μm. The sieving coefficient (concentration of solute in filtrate divided by its concentration in plasma) in vitro for large molecules such as immunoglobulin M and apo-lipoprotein is approximately 1.00 (package insert, PF1000). Each hospital developed its own catheters to connect the filter to the patient. Vascular access was obtained with a double-lumen catheter placed percutaneously in a central vein. Blood was pumped by a calibrated roller pump incorporating alarms for air entrainment, catheter occlusion, and overpressure. The rate of filtrate production and fluid replacement was controlled with volumetric infusion pumps. Filtrate was replaced isovolumetrically with a mixture of fresh frozen plasma and protein-electrolyte solution at a ratio of 1:4. The protein-electrolyte solution was made up fresh from a...
custom electrolyte mixture to which 20% human albumin was added to produce a final albumin concentration of 40 g/L and final electrolyte concentrations similar to those in plasma (Appendix 2). No \( \gamma \)-globulin infusions were used. Anticoagulation was achieved with heparin. A bolus of 2000-5000 units was injected into the plasma filter circuit at the commencement of filtration, and an infusion of heparin was titrated to achieve a systemic activated partial thromboplastin time of 1.5 times control.

Severity of Illness. The severity of illness was classified using the APACHE II scale (28) in adults and the Pediatric Risk of Mortality (PRISM) scale (29) in children. Severity scores were calculated using the most abnormal values in the first 24 hrs after randomization. Patients were identified retrospectively as bacteremic if blood cultures taken on the day of randomization grew pathogenic organisms within 7 days. Patients were classed as immunocompromised if they satisfied the APACHE II definition. Septic shock was identified in adults when systolic blood pressure decreased to <90 mm Hg or mean blood pressure decreased >40 mm Hg from baseline (25). In children, septic shock was identified when mean arterial pressure decreased >2 SD values below the mean for that age group. Refractory shock was identified when this level of hypotension persisted for more than 1 hr despite adequate fluid challenge and vasopressor therapy (25).

Outcome. The outcome at 14 days and survival at the time of last review were recorded. The number of organs failing was assessed daily for the first 7 days after randomization using accepted dichotomous definitions (30).

Formed Elements of the Blood. Routine daily automated full blood examinations were performed by each hospital.

Mediator Assays. Four samples of arterial blood were collected for factor assays at trial entry and then at 6, 24, and 48 hrs. In addition, a sample of filtrate was collected at the halfway point of the fast phase of plasmapheresis (approximately 3 hrs) for the estimation of sieving coefficients. Samples were taken into sterile, heparinized, endotoxin-free polyvinyl chloride tubes and refrigerated at 4°C (39.2°F) until processed. Plasma was separated by centrifugation at 300 \( \times \) g for 10 mins and then frozen at -30°C (-22°F). Filtrate samples were frozen without centrifugation. Interleukin (IL)-6 and granulocyte colony-stimulating factor (G-CSF) concentrations were assayed using ELISA using previously described techniques (31). The IL-6 assay used a commercial kit with a detection limit of 0.005 ng/mL (Immunotech International, Marseille, France). The G-CSF assay (Ludwig Institute for Cancer Research, Melbourne, Australia) had a detection limit of 0.1 ng/mL. Leukemia inhibitory factor (LIF) was measured by radioreceptor assay with a detection limit of 1 ng/mL using a previously described technique (32). Thromboxane B\(_2\) was measured by radio-immunoassay as described previously (33), with a detection limit of 0.32 ng/mL. Albumin and globulin were measured using automated dry chemistry (Kodak [Rochester, NY] Ektachem 700XR), and acute-phase proteins, \( \alpha_1 \)-antitrypsin, haptoglobin, C-reactive protein, and complement fragment C\(_3\) were assayed using rate immunonephelometry (automated immunochemistry system, Beckmann Instruments, Fullerton, CA). The detection limit was 0.17 g/L for \( \alpha_1 \)-antitrypsin, 5 mg/dL for haptoglobin, 1.3 mg/L for C-reactive protein, and 0.08 g/L for complement fragment C\(_3\).

Statistics. All analyses were carried out on an intention-to-treat basis. An Australia-wide shortage of blood products necessitated a reduction in sample size from an original calculated number of 73 in each group (expected mortality in controls, 40%; in plasmapheresis patients, 20%; one-sided \( \alpha \) = 0.05,
Univariate comparisons of baseline demographic characteristics were made with Fisher's exact test, the Mann-Whitney U test, and unpaired $t$-tests as appropriate. The individual risk of death in intensive care was calculated for each patient using PRISM or APACHE II scores and their respective regression equations. The arithmetic mean of the logit of the individual risks was back transformed to quantify expected group mortality. The total number of organs failing per patient in the 7 days after randomization was compared between groups with the Mann-Whitney U test. Crude 14-day survival rates in the two groups were compared with Fisher's exact test. Multiple logistic regression was used to assess the effects on survival of age, presence of septic shock or refractory shock, bacteremia, immunodeficiency, multiple organ failure, and plasmafiltration.

The results of daily platelet and white cell counts were analyzed with two-way analysis of variance. To quantify the effect of intense plasmafiltration on inflammatory mediator concentrations, a summary statistic was devised: the change in plasma concentration of the mediator from baseline to 6 hrs. For all mediators except G-CSF and IL-6, the mean change in plasma concentration from 0 to 6 hrs was calculated for plasmafiltration patients and controls and then compared between groups with unpaired $t$-tests. For G-CSF and IL-6, data were first log transformed and the mean difference in log-transformed concentration was compared with unpaired $t$-tests.

To compare the overall plasma concentration of each mediator in survivors and nonsurvivors throughout the study period, a time-weighted mean concentration was derived for each patient and each mediator using the area under the concentration time curve, calculated with the trapezoidal rule. The weighted means were compared between survivors and nonsurvivors using an unpaired Student's $t$-test. An approximate sieving coefficient (filtrate concentration of mediator/plasma concentration of mediator) was calculated for each mediator using the concentration measured in filtrate divided by the interpolated plasma concentration.

Statistical analysis was performed with Systat version 7.0.1 for Windows (SPSS, Chicago, IL), Statview for Windows (Abacus Concepts, Berkeley, CA), and LogXact (Cytel Software, Cambridge, MA).

**RESULTS**

The intensive care units of six tertiary adult teaching hospitals and one tertiary pediatric teaching hospital participated in the study. Thirty patients were randomized between March 1992 and March 1994. Their individual clinical details are presented in Table 1 and Table 2 and summarized in Table 3. The plasmafiltration patients were plasmafiltered for a mean duration of 33.1 hrs (SD, 3.55), and a mean of 213 mL/kg (SD, 42.2) plasma was exchanged per patient. No bleeding, mechanical failure, or other complication attributable to plasmafiltration itself occurred during a total of more than 460 hrs of continuous therapy.
Outcome. There was no statistically significantly difference in baseline characteristics between the two groups when assessed by univariate analysis. There was no significant difference in crude 14-day mortality between the two groups. Eight of 16 of the control patients (50%) and eight of 14 of the plasmafiltration patients (57%) survived for 14 days \((p = .73, \text{Fisher's exact test; 95\% confidence limits for odds ratio, 0.172-3.90})\). The Kaplan-Meier cumulative survival curve is shown in Figure 1. The Kaplan-Meier derived survival estimate for 28 days was 40\% in the control group and 42\% in the plasmafiltration group.

Figure 1. Kaplan-Meier cumulative survival curve in control and plasmafiltration patients with sepsis. \(p\) is for log rank test on survival.

Multiple logistic regression generated a best-fit model with age <16 or >60 yrs (odds ratio, 16.4; 95\% confidence interval, 2.12-\infty; two-sided \(p = .005\)) and shock (odds ratio, 10.6; 95\% confidence interval, 1.32-\infty, two-sided \(p = .024\)) as the only statistically significant predictors of death. When plasmafiltration was included in the model, it was associated with a nonsignificant reduction in the risk of death (odds ratio, 1.7812; 95\% confidence interval, 0.20-18.1, one-sided \(p = .432\)).
There was no difference between groups in the total number of organ failures per patient in the first 7 days after randomization. The mean (SD) number of organs failed was 2.94 (0.55) in controls and 2.57 (0.94) in plasmafiltration patients ($p = .37$, Mann-Whitney U test).

**Formed Elements of the Blood.** There was no significant difference in total white cell count, neutrophil count, or platelet count between the two groups during the first 3 days after randomization ($p > .2$ for all tests, two-way analysis of variance), but there was a statistically significant decrease in platelet count in both groups with time ($p < .001$, two-way analysis of variance.) Mean (SE) platelet counts ($\times 10^9$/mm$^3$) were 223 (44) in controls vs. 178 (37) in plasmafiltration patients on day 1, 164 (40) vs. 108 (22.6) on day 2, and 135 (38) vs. 79 (16) on day 3.

**Inflammatory Mediators.** The exact times of blood sampling were 0, 5.86 (SD, 3.04), 24.2 (SD, 3.22), and 48.5 hrs (SD, 5.47) after randomization. The exact time of filtrate sampling was 2.61 hrs (SD, 0.81) after randomization. Whole blood and filtrate samples were refrigerated at 4°C for a mean time of 9.27 hrs (SD, 11.2) (because of practical considerations) before centrifugation and freezing.

Box and whisker plots (Systat version 7.0.1 for Windows graphics manual) of plasma concentrations for inflammatory mediators and formed elements of the blood are shown in Figure 2, Figure 3, Figure 4 and Figure 5. The $p$ for each between-group comparison of change in mediator concentration between plasmafiltration and control patients from baseline to 6 hrs is included. Although all patient samples were analyzed for LIF, it was detectable only in the plasma of two control and two plasmafiltration patients at entry to the study (patients 1, 2, 7, and 15 in Table 1 and Table 2); it was still detectable at 24 hrs in two of these patients (patients 1 and 2) and persisted in detectable amounts in patient 1 until 48 hrs after randomization. LIF was also detectable in the plasmafiltrate of this patient.
Figure 4. Plasma complement C₃ (C₃) and thromboxane B₂ (TxB₂) concentrations in control and plasmafiltration patients with sepsis. Summary data are presented in boxes, and whisker plots and actual values are superimposed as solid dots. The boxes enclose the interquartile range and median (middle line in each box); the whiskers enclose 1.5 times the interquartile range. Individual outlying values are represented by asterisks and far outliers by open circles. p is for between-group unpaired Student's t-test comparing the change in mediator concentration from 0-6 hrs in plasmafiltration vs. control patients.

Figure 5. Plasma interleukin-6 (IL-6) and granulocyte colony-stimulating factor (G-CSF) concentrations in control and plasmafiltration patients with sepsis. Summary data are presented in boxes, and whisker plots and actual values are superimposed as solid dots. The boxes enclose the interquartile range and median (middle line in each box); the whiskers enclose 1.5 times the interquartile range. Individual outlying values are represented by asterisks and far outliers by open circles. p is for between-group unpaired Student's t-test comparing the change in log₁₀ mediator concentration from 0-6 hrs in plasmafiltration vs. control patients.

There was no significant difference in the time-weighted mean concentration of any inflammatory mediator between survivors and nonsurvivors. All noncellular inflammatory mediators were detectable in the plasmafiltrate at 3 hrs after randomization in concentrations close to those of plasma, so the resulting sieving coefficients approached unity (Table 4).

Table 4. Estimated plasmafilter sieving coefficient by inflammatory mediator

DISCUSSION

There is continued interest in extracorporeal therapies for severe sepsis, such as hemofiltration (34) and plasma exchange (35), because they have the potential to remove bacterial products and to modulate the host inflammatory response. To the best of our knowledge, this study represents the first time that the effect of plasma exchange has been examined in a prospective, controlled trial in human sepsis. We observed a slightly lower mortality (50 vs. 57%) and slightly fewer organs failing (2.57 vs. 2.94) in the plasmafiltration patients, but the differences were not statistically significant.

We measured the plasma concentration of several different classes of humoral inflammatory mediators and found that most were elevated at entry and decreased with time, consistent with previous reports of...
sepsis (36-42). Plasma concentrations of complement fragment C3 were not increased at study entry, perhaps because sample handling was not ideal for assays of complement (43). LIF was detected only in a minority of patients. Although LIF is a good indicator of severity of illness in meningococcal infection (44), it may be an insensitive inflammatory marker in this more diverse group of patients.

We did not find a difference between survivors and nonsurvivors in the plasma concentration of any individual inflammatory mediator. We quantified the clearance of inflammatory mediators through the plasma filter and found that all classes of humoral mediator passed freely into the filtrate. The most striking effect of plasmafiltration in sepsis observed in this study was an attenuation of the acute-phase response and reversal of the normal changes in albumin and globulin in response to inflammation (42). Instead of decreasing, serum albumin concentration increased and, instead of increasing, serum globulin concentration decreased. Plasma concentrations of C-reactive protein, α1-antitrypsin, haptoglobin, and complement fragment C3 all decreased substantially more in plasmafiltration patients than in controls. The changes in albumin and globulin may be explained by dilution of plasma with albumin-rich replacement solutions, but the effects on the acute-phase response may represent a real immunomodulatory action.

We observed no effect of continuous plasmafiltration on the plasma concentrations of the cytokines IL-6 and G-CSF or the eicosanoid thromboxane B2, in spite of their appearance in plasmafiltrate. This is in contrast to a case report of plasmapheresis in fulminant meningococcemia (17) that documented a decrease in the plasma concentration of tumor necrosis factor and IL-1. However, tumor necrosis factor and IL-1 concentrations decreased rapidly after a septic challenge unrelated to therapy (45, 46). The differential effect of continuous plasmafiltration on different classes of inflammatory mediators may be attributable to their volume of distribution. Substances with a large volume of distribution exist predominantly outside the circulation, where they are unavailable for removal by extracorporeal techniques. Alternatively, there may be a proinflammatory feedback mechanism for some mediators that increases their production in the face of increased clearance through the plasma filter.

Systemic cytokines may represent "spillover" of intense local inflammatory processes (47, 48), and their removal from the systemic circulation could reduce distant organ damage. Extracorporeal techniques can only remove substances present in the circulation and, for freely filtered mediators, the mass removed is proportional to their concentration in plasma. Therefore, extracorporeal blood purification may have a "smoothing" effect on the plasma profile of inflammatory mediators in sepsis, without completely neutralizing any particular factor in the way that a monoclonal antibody might. No bacterial mediators were studied, but it is reasonable to expect that molecules such as lipopolysaccharide and Gram-positive toxins would also be removed by plasmafiltration, and this hypothesis is supported by animal experiments (23).

Hemofiltration and plasma exchange have different effects on the inflammatory response in sepsis. Hemofiltration removes unbound mediators up to approximately 10,000 daltons by ultrafiltration (49), and larger molecules, including cytokines, are removed by adsorption onto the hemofilter membrane (50). This is associated with the reversal of shock in animal models of sepsis (51-53) and improvement in respiratory and cardiac function in human multiple organ failure (54, 55), but the effect on survival is unknown. In contrast, plasma exchange has the potential to remove much larger molecules than hemofiltration, but this is not without risk (56). It is likely that beneficial factors are cleared along with
deleterious mediators. The numerous favorable case reports of plasma exchange in human sepsis (15-21) are uncontrolled, and the apparently beneficial effects of plasmapheresis may be attributable as much to the infusion of fresh frozen plasma as to the removal of deleterious factors (57).

This study was limited by its small sample size. Although we observed a small difference in mortality between the two groups, there was insufficient power to allow any conclusions about the effect of plasma exchange on outcome. Given the observed 50% mortality in the control group and our nominal sample size of 15 patients per group, the chance of this study detecting a halving of mortality was only 17%. Moreover, to reliably test the observed 7% difference in mortality would require a study with more than 800 patients in each group. The practical considerations of mounting such a large-scale trial of a novel therapy for severe sepsis are daunting, and the uniformly disappointing results for very large multicenter trials of novel therapies in sepsis using mortality as the primary outcome are discouraging (7-9, 11, 12, 58). Other outcome variables, such as organ failure scores, may provide more sensitive detection of potentially beneficial treatments with more practical sample sizes (59, 60). In this study, there was a nonsignificant trend toward a reduced number of organs failing in the plasmapheresis group. A significant difference may have emerged if a more sophisticated measure of organ failure, such as that recently described by Marshall et al. (61), had been used prospectively.

Both the plasmapheresis and control patients were very comparable with respect to the risk of death as measured by APACHE II and PRISM scores, but the range of diagnoses was wide, and there were more children and more immunocompromised patients in the plasmapheresis group. In spite of this, univariate analysis of baseline characteristics did not detect any statistically significant difference between the two groups, perhaps because of the small numbers. Multivariate analysis was more informative. In the model of best fit, extremes of age and the presence of shock were significant predictors of death. The advantage of multiple logistic regression is that it allows estimation of the risk (or benefit) associated with a particular intervention, taking into account the influence of other important baseline characteristics.

The entry criterion for this trial was sepsis syndrome, as described originally by Bone et al. (8, 62), with a previously reported 14-day mortality of 25%-30%. The observed mortality in this trial was 14 of 30 (47%), which is consistent with the original definition because several patients had "shock" or "refractory shock" at entry. Although "sepsis syndrome" has been superseded in the literature by the "systemic inflammatory response syndrome" (SIRS) (63), acceptance of the new term is not unanimous (64). The mortality of SIRS with only two criteria is 7% (5); clinical trials of interventions with existing mortality *as low as this would need to be very large to reliably detect or rule out treatment benefits. The addition of positive microbial cultures to SIRS increases the mortality to 16% (5), and the condition is termed "sepsis." Mortality further increases to 20% with evidence of organ dysfunction (5), and the condition is then termed "severe sepsis." This mortality (and this severity of illness) lends itself to practicable clinical trials of novel therapies. However, the definition is almost the same as that of the original sepsis syndrome, except that now it requires positive cultures-a relatively uncommon early finding in clinical practice-and a significant constraint to patient recruitment. Finally, large clinical trials continue to use sepsis syndrome rather than SIRS as their entry criteria (11, 12).

Recent sepsis trials quote 28- or 30-day mortality as the primary outcome (9, 13), but we prospectively chose 14-day mortality in line with earlier, landmark sepsis trials (7, 8). The most informative time to compare mortality after a therapeutic intervention is the subject of ongoing discussion (65). An early
comparison (after several hours or days) may relate more discriminatingly to the specific intervention than a later comparison (after days or weeks), which may be confounded by multiple other treatments.

Continuous plasmafiltration is a practicable undertaking in the critically ill patient. The equipment cost and risks are similar to those of continuous hemofiltration. Using critical care nurses experienced with continuous renal replacement therapies, we continuously plasmafiltered 14 critically ill patients for a total of 460 hrs and experienced no bleeding or equipment-related complications related specifically to the technique. We observed no destabilization of patients during the treatment, but prospective data on vasopressor requirements and respiratory function were not obtained. The most significant demand caused by continuous plasmafiltration, and the limiting factor for this study, was the need for fresh frozen plasma and human albumin.

In conclusion, the predominant immunomodulatory effect of continuous plasmafiltration in sepsis was an attenuation of the acute-phase response without any effect on the cytokine response; whether this translates into a survival benefit remains unknown. Fewer organ systems failed in plasmafiltration patients than in control patients, but the difference was not statistically significant. Until it can be demonstrated that plasmafiltration confers significant survival benefit in a larger prospective, controlled trial, its use in sepsis should be considered experimental.

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REFERENCES  
[Click here for reference links. (53 references linked.)]


42. Dowton SB, Colten HR: Acute phase reactants in inflammation and infection. Semin Hematol 1988; 25:84-90


49. Hazards of apheresis. Lancet 1982; ii:1025-1026


52. Petros AJ, Marshall JC, van Saene HKF: Should morbidity replace mortality as an endpoint for clinical trials in...
APPENDIX 1: CONVENTIONAL MANAGEMENT PROTOCOL

Cardiovascular Support

Aim to keep mean arterial pressure:
>60 mm Hg in adults;
>50 mm Hg for children 1-3 yr, >55 mm Hg for children 3-7 yr, >60 mm Hg for children >7 yrs.

Use fluids to achieve central venous pressure > 10 mm Hg.

Add dopamine to a maximum of 5 μg/kg/min.

Measure cardiac output:
If systemic vascular resistance index < 450, use noradrenaline;
If systemic vascular resistance index > 450, use adrenaline.

Respiratory Support

Minimum FIO₂ to maintain oxygen saturation > 90% (positive end-expiratory pressure as needed).

Ventilate to keep pH > 7.30.

Minimum PCO₂ of 25 torr.

If pH < 7.20 and base deficit > 10 mmol/L, consider NaHCO₃.

Antibiotics

Known organism, use specific antibiotic.

Unknown organism, immunocompetent host, cefotaxime, flucloxacillin, and metronidazole.

Unknown organism, immunocompromised host, vancomycin, gentamicin, ticarcillin, and metronidazole.

Feeding

Enteral feeding as soon as possible.

If total parenteral nutrition is necessary,

day 1, dextrose;
day 2, amino acids;
day 3, lipid.
Renal Replacement Therapy

Indications:
- serum creatinine > 0.4 mmol/L or increasing by >0.1 mmol/L/day;
- serum urea > 40 mmol/L.

Technique:
continuous venovenous hemofiltration or hemodialysis with filtration.

(APPENDIX 2)

APPENDIX 2: ELECTROLYTE CONTENT OF PROTEIN-ELECTROLYTE REPLACEMENT SOLUTION

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The Plasmaphiltration in Sepsis Study Group: Dr. J. D. Santamaria, St Vincent's Hospital, Fitzroy, Victoria, Australia; Dr. G. K. Hart, Austin Hospital, Heidelberg, Victoria, Australia; Dr. C. Corke, Geelong Hospital, Geelong, Victoria, Australia; Dr. C. Scheinkestel, Alfred Hospital, Prahran, Victoria, Australia; Dr. P. J. Cranswick, Box Hill Hospital, Box Hill, Victoria, Australia; and Dr. B. Ihle, Royal Melbourne Hospital, Parkville, Victoria, Australia.

Address requests for reprints to: John H. Reeves, M.D., Director, Critical Care, Maroondah Hospital, Ringwood East, VIC, 3135, Australia.