A randomised controlled trial of plasma filtration in severe paediatric sepsis

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Severe sepsis is a leading cause of morbidity and mortality in intensive care, with mortality reported from 20% to 60%.[1] In severe sepsis there is abnormal regulation of the immune response, with activation of both pro- and anti-inflammatory pathways;[2] profound immunosuppression and active inflammation can co-exist in the same host. This dysregulated system is thought to contribute significantly to cell injury and the progression from systemic inflammatory response syndrome to multiorgan dysfunction syndrome.[3] The soluble mediators of both pro- and anti-inflammatory pathways include medium-sized (5–55 kD) peptides known as cytokines.[4] Individual cytokines, such as interleukin-6, interleukin-1β, platelet-activating factor, and tumour necrosis factor, have been the target of specific therapeutic interventions, with no demonstrable improvement in survival.[5] Non-specific immunomodulating agents, such as steroids, have not resulted in survival benefit when studied in large, randomised controlled trials.[6-8] Recombinant human activated protein C was initially associated with a reduction in absolute risk of death in adults with severe sepsis,[9] but has subsequently been withdrawn from the market due to association with an increased risk of serious adverse events in children[10] and failure to show a survival benefit in adults.[11]

Extracorporeal blood filtration removes pro- and anti-inflammatory cytokines, and may be beneficial in the treatment of severe sepsis.[12] Plasma filtration involves separation of plasma from whole blood, and replacement with donor plasma. It has been shown in animal and human studies to remove pro- and anti-inflammatory cytokines.[13-15] However, it remains unclear whether non-specific removal of cytokines through plasma filtration is associated with improved survival in septic shock. As with all extracorporeal circulation procedures, plasma filtration can cause bleeding, haemodilution, and emboli.[16] It has also been associated with hypotension requiring vasopressor support, citrate toxicity, arrhythmias secondary to electrolyte imbalance, coagulopathy and hypogammaglobulinaemia.[17]

The aim of this study was to determine whether plasma filtration improved 28-day survival in children with septic shock.

Methods

A multicentre randomised controlled trial of plasma filtration in sepsis was designed. A clinical protocol was devel-

ABSTRACT

Objective: To determine whether plasma filtration improves 28-day survival in infants and children with severe sepsis.

Design: A multicentre randomised controlled trial.

Setting: Paediatric intensive care units in teaching hospitals.

Patients: Forty-eight infants and children with severe sepsis.

Interventions: Patients were randomly assigned to receive plasma filtration ($n = 25$) or standard therapy ($n = 23$) for the treatment of septic shock. The primary outcome measure was 28-day survival. Secondary outcome measures included the number of failed organ systems on Day 7, a requirement for extracorporeal membrane oxygenation (ECMO), and the modified Glasgow outcome score (MGOS) at 6 months (where 1 is normal and 6 is dead).

Results: The trial was stopped early due to poor recruitment. Patients in the plasma filtration group had higher initial disease severity as measured by serum lactate level, inotrope score and MGOS. Ten (40%) children died in the plasma filtration group and 4 (17%) died in the control group. With intention-to-treat analysis and adjustment for lactate level, ventilation index, inotrope score and MGOS at admission using logistic regression, the odds ratio for death with plasma filtration was 1.20 (95% CI, 0.23–6.20; $P = 0.82$). The median number of failing organ systems at 7 days was 2 (interquartile range [IQR], 1–4) in the plasma filtration group versus 2 (IQR, 1–3) in the control group. Two children in the plasma filtration group required ECMO for 2.5 and 123 hours, and one child in the control group required ECMO for 45 hours. The median MGOS at 6 months was 4 (IQR, 2–6) in the plasma filtration group and 2 (IQR, 1–4) in the control group.

Conclusions: Our study did not recruit enough patients to test the hypothesis that addition of plasma filtration to our standard care protocol reduces 28-day mortality in children with severe sepsis. However, mortality in the treatment and control groups was not significantly different after adjustment for severity of illness at the time of randomisation.

Box 1. Inclusion criteria

- Genuine uncertainty regarding patient survival (not mildly ill, and not moribund)
- Age > 28 days and < 16 years
- No extracorporeal membrane oxygenation or cardiopulmonary bypass in the preceding 72 hours
- Not known (or likely to be) HIV positive
- Clinical diagnosis of probable bacterial infection
- Clinical requirement for mechanical ventilation (non-invasive ventilation was not included)
- At least one of: altered mental state, $PaO_2/FiO_2 < 280$, serum lactate level > 1.8 mmol/L, oliguria (urine output, < 0.5 mL/kg/h for at least 4 hours)
- Requirement for inotropic support: despite fluid administration to achieve central venous pressure > 10 mmHg, a mean arterial pressure < 40 mmHg (1–4 months), < 45 mmHg (5 months – 5 years), < 50 mmHg (6–7 years), < 55 mmHg (≥ 8 years)
- An inotropic requirement for < 12 hours (or an increased dose needed for < 12 hours in a patient already on inotropes for non-sepsis reasons).

oped to standardise treatment in both filtered and non-filtered patients (Appendix). The modified Glasgow outcome score (MGOS) at the time of randomisation was used as a surrogate for the presence of comorbidities. Inclusion criteria are listed in Box 1. Patients were excluded if they were moribund or only mildly ill, had received extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass in the previous 72 hours, or were known or likely to have HIV infection.

Plasma filtration was performed using PF1000 or PF2000 filters (Gambro) with a pore size of 0.5–0.6 μm. We aimed to exchange twice the estimated plasma volume (100 mL/kg) over the first 6 hours, and an additional six plasma volumes (300 mL/kg) over the following 30 hours. Any filters that clotted before 24 hours were replaced, and any filters still functioning at 36 hours were electively discontinued. Anticoagulation was achieved with heparin and citrate. Immunoglobulin 0.5 g/kg was administered to all patients at the time of entry into the trial, and after 36 hours. One bag of fresh frozen plasma (about 230 mL) was administered in the plasma filtration group after every 800 mL of replacement fluid. Cryoprecipitate 5 mL/kg was administered in the plasma filtration group if the blood fibrinogen level was < 2.0 g/L.

The primary end point was 28-day survival. Secondary end points were the number of organ systems that failed at 7 days, requirement for ECMO, and 6-month MGOS (1, normal; 2, functionally normal but requiring medication; 3, mild handicap but likely to lead an independent existence; 4, handicapped and dependent on care; 5, totally dependent on care or vegetative; 6, dead).[18,19] Assessment for the

number of failing organ systems and the 6-month MGOS was performed in a blinded fashion. Immunosuppression was defined as disease or therapy suppressing resistance to infection.

A sample size of 262 in each group was required to demonstrate a 25% reduction in mortality from 50% in the control group to 37.5% in the plasma filtration group with a power of 0.8 and a two-sided alpha error of 0.05. Written consent was obtained for all patients before randomisation. Randomisation was concealed and performed centrally in blocks, stratified by study centre, immunosuppression, and an inotrope score of above or below 15. Inotrope score was calculated as: (1 × dopamine dose [μg/kg/min]) + (1 × dobutamine dose [μg/kg/min]) + (20 × adrenaline dose [μg/kg/min]) + (20 × noradrenaline dose [μg/kg/min]) + (25 × 10% calcium gluconate dose [mL/kg/h]) + (150 × vasopressin dose [units/kg/h]).[20-23] Logistic regression was used to calculate the odds of 28-day mortality adjusted for markers of disease severity that were unequally distributed between the treatment and control groups. *P* values were calculated using the Mann–Whitney *U* test for ordinal data, and the student *t* test for continuous data with logarithmic transformation if required.

The study was approved by the Human Research Ethics Committees at participating hospitals. Antibiotic choice for the treatment of sepsis was not specified due to local variation in sensitivity patterns.

Results

Forty-eight patients were enrolled from three tertiary-level paediatric intensive care units between September 2000 and November 2005; 23 in the control group and 25 in the plasma filtration group (Figure 1). Nine patients were recruited from Starship Children's Health in Auckland, New Zealand, nine were recruited from Birmingham Children's Hospital in the United Kingdom, and the remainder were recruited from the Royal Children's Hospital in Melbourne, Australia. One patient who was randomly assigned to the plasma filtration group was withdrawn from the study before commencing filtration; results for this patient were included in the plasma filtration group in the intention-to-treat analysis. Protocol adherence in the two treatment groups was not recorded, but it is highly unlikely that there were systematic differences between treatment groups as the protocol reflected routine practice in the three ICUs. The study was terminated early due to poor patient recruitment.

The treatment groups were well matched for age, number of organ systems failing before intervention, and initial ventilation index ($pCO_2 \times RR \times PIP \div 1000$ if pCO_2 is in mmHg, $pCO_2 \times RR \times PIP \div 131.7$ if pCO_2 is in kPa [RR = respiratory rate, PIP = peak inspiratory pressure]), but were

Figure 1. Consort diagram outlining flow of patients through the plasma filtration study
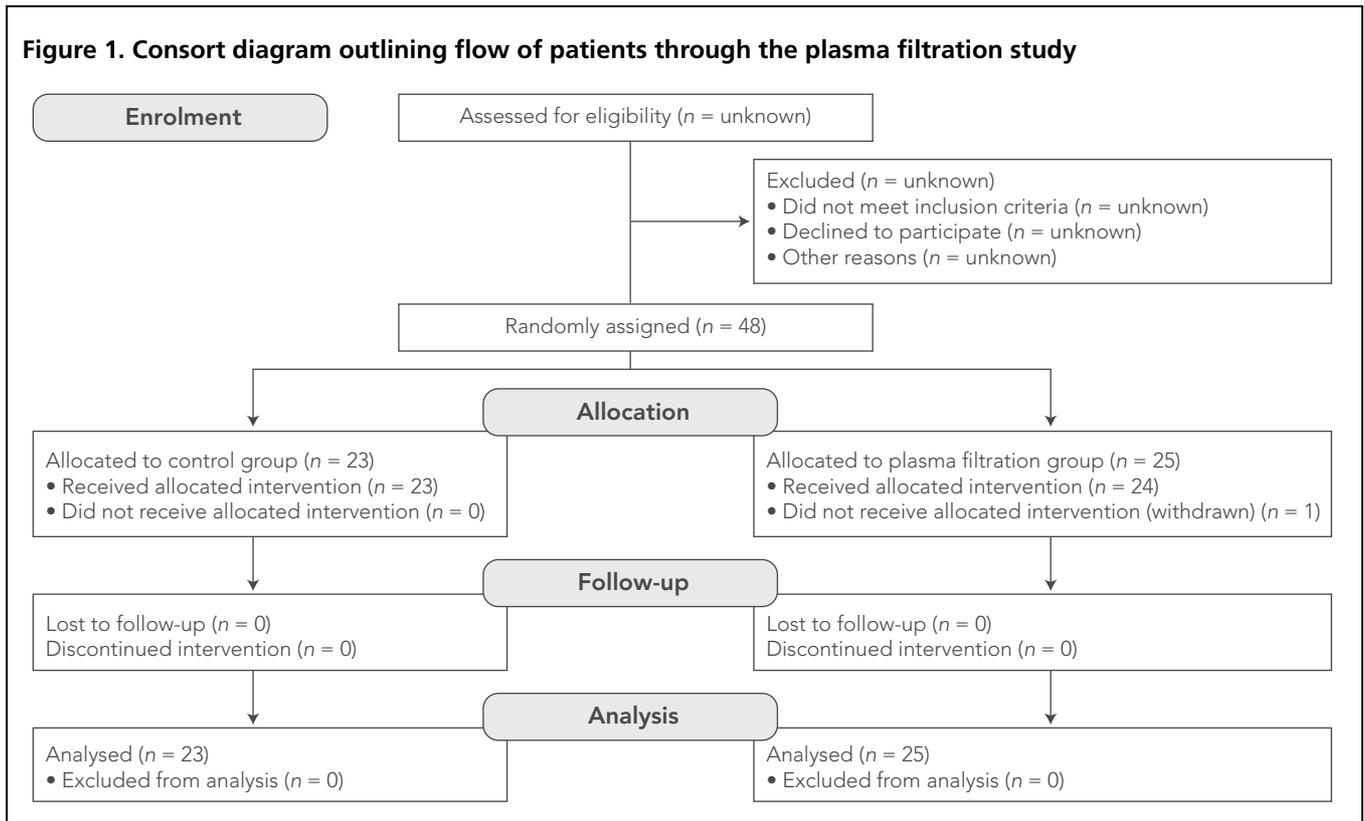
poorly matched for sex, initial serum lactate level (the first lactate level obtained), initial inotrope score and MGOS (Table 1). The differences in baseline characteristics were probably due to the small sample size. In the control group, 15 patients had a causative organism identified: *Neisseria meningitidis* in 10, with the remainder being one each of *Haemophilus influenzae*, *Pseudomonas*, *Streptococcus pneumoniae*, *Enterobacter* and *Serratia*. In the plasma filtration group, the causative organism was identified in 18 patients: *N. meningitidis* in 13, *S. pneumoniae* in two, and one each of Group A streptococcus, *Escherichia coli* and *Streptococcus pyogenes*.

Renal failure led to the use of haemofiltration in four patients enrolled in the control group for a mean of 121 hours, and in five patients in the plasma filtration group for a mean of 303 hours.

The primary and secondary outcome measures are reported in Table 2. No patients in the control group had died by Day 7, while three had died in the plasma filtration group. Patients who died before Day 7 were included in the analysis of number of organs failing on Day 7. Patient records at 6 months were missing for three patients in the plasma filtration group and one patient in the control group, thus they were excluded from the MGOS analysis.

With multiple logistic regression, there was a non-significant trend towards increased mortality with increased serum lactate level (odds ratio, 1.2; 95% CI, 0.92–1.45) and a high prior MGOS (odds ratio, 1.8; 95% CI, 0.93–3.48). Sex and time (early versus late in the trial) were not significant predictors of mortality in multiple logistic regression analysis. Initial lactate level, ventilation index, inotrope score and MGOS were unequally distributed between the plasma filtration and control groups. With intention-to-treat analysis and adjustment for initial lactate level, ventilation index, inotrope score and MGOS using logistic regression, the odds ratio for death with plasma filtration was 1.20 (95% CI, 0.23–6.20; *P* = 0.82). Ten of 25 patients died in the plasma filtration group versus four of 23 in the control group (Table 2), giving a crude (unadjusted) risk ratio of 2.30 (95% CI, 0.84–6.33).

Discussion

This small study did not show a reduction in 28-day mortality, requirement for ECMO, number of failed organ systems or 6-month MGOS in the plasma filtration group. This lack of effect persisted despite correction for known confounding variables that were not equally distributed between the plasma filtration and control groups (initial serum lactate level, initial ventilation index, initial inotrope score and initial MGOS).

Table 1. Patient characteristics at randomisation

	Plasma filtration (*n* = 25)	Control (*n* = 23)
Age (years), median (IQR)	2.8 (1.2–9.6)	2.8 (0.9–5.0)
Boy, number (percentage)	17 (68%)	10 (43%)
Immunosuppressed, number (percentage)	2 (8%)	3 (13%)
Number of organs failing, median (IQR)	2 (2–3)	2 (2–3)
Initial serum lactate level (mmol/L), median (IQR)	5.7 (2.8–9.9)	4.4 (2.8–5.7)
Initial ventilation index, median (IQR)*	19.8 (14.0–27.3)	19.3 (13.6–26.4)
Initial inotrope score, median (IQR)†	18.8 (15.0–28.0)	12.0 (9.1–25.5)
Modified Glasgow outcome score, median (IQR)‡	1 (1–3)	1 (1–1)

IQR = interquartile range. RR = respiratory rate. PIP = peak inspiratory pressure. * Ventilation index was calculated as: $pCO_2 \times RR \times PIP \div 1000$ if pCO_2 in mmHg, $pCO_2 \times RR \times PIP \div 131.7$ if pCO_2 in kPa. † Inotrope score was calculated as: (1 × dopamine dose [μg/kg/min]) + (1 × dobutamine dose [μg/kg/min]) + (20 × adrenaline dose [μg/kg/min]) + (20 × noradrenaline dose [μg/kg/min]) + (25 × 10% calcium gluconate dose [mL/kg/h]) + (150 × vasopressin dose [units/kg/h]). ‡ Modified Glasgow outcome score comprises six categories: 1, normal; 2, functionally normal but requiring medication; 3, mild handicap but likely to lead an independent existence; 4, handicapped and dependent on care; 5, totally dependent on care or vegetative; 6, dead.

This study is severely compromised by a small sample size. This resulted in wide confidence intervals for the primary and secondary outcome measures, and no statistically significant conclusions can be drawn from the study. The small sample size is likely to have contributed to the unequal distribution of confounding variables between the plasma filtration and control groups. Several known and measured confounding variables (initial lactate level, ventilation index, inotrope score and MGOS) were adjusted for using logistic regression. There may have been other unmeasured confounding variables that were also unequally distributed between treatment groups that could not be taken into account.

This study did not enrol enough patients, largely due to the substantial additional work required to include patients in an unfunded study, and the requirement for long and detailed written consent that was imposed by the primary study centre's ethics committee.

Support for the use of extracorporeal blood purification in the treatment of severe sepsis is limited to case reports and underpowered randomised controlled trials. Animal models of endotoxin-mediated septic shock have yielded mixed results.[24-36] Nine uncontrolled human case reports involving a total of 44 patients have been published.[21,37-44] Several patients had improvements in markers of cardiac performance, inotrope score and ventilation index following treatment with plasma filtration. Four small prospective studies in adults with retrospective controls have been published, involving a total of 41 plasma-filtered patients and 55 controls.[45-48] Overall mortality was 29% in the plasma-filtered groups and 45% in the control groups. Improved outcome was associated with early plasma filtration, plasma filtration of patients in haemorrhagic shock and plasma filtration of patients in non-surgical septic shock. Two prospective randomised controlled trials of plasma filtration in sepsis have been conducted.[15,49] The first study included 30 patients (adults and children), 14 of whom were randomly assigned to receive plasma filtration. No significant difference in mortality between the two groups was shown, although there was a trend towards

Table 2. Primary and secondary outcome measures

	Plasma filtration (*n* = 25)	Control (*n* = 23)	Risk ratio or odds ratio (95% CI)
28-day mortality, number (percentage)	10 (40%)	4 (17%)	1.20 (0.23–6.20)*
Extracorporeal membrane oxygenation, number (duration)	2 (mean 63 h†)	1 (45 h)	1.8 (0.2–19.0)‡
Number of organs failing on Day 7, median (IQR)	2 (1–4)	2 (1–3)	0.9 (0.1–6.0)‡
6-month modified Glasgow outcome score, median (IQR)§	4 (2–6)	2 (1–4)	1.8 (0.4–9.1)‡¶

IQR = interquartile range. * Odds ratio adjusted for the effects of initial serum lactate level, ventilation index, inotrope score and modified Glasgow outcome score at admission. † Durations for the two patients were 2.5 h and 123 h. ‡ Risk ratio. § Modified Glasgow outcome score comprises six categories: 1, normal; 2, functionally normal but requiring medication; 3, mild handicap but likely to lead an independent existence; 4, handicapped and dependent on care; 5, totally dependent on care or vegetative; 6, dead. ¶ Patient records at 6 months were missing for three patients in the plasma filtration group and one patient in the control group, thus they were excluded from the MGOS analysis.

fewer organs failing in the plasma filtration group.[15] The second study of 106 adult patients with severe sepsis or septic shock reported a 28-day mortality of 54% in the control group and 33% in the plasma-filtered group ($P =$ 0.049).[49] It is unclear which filters were used in this study, and filtration occurred as one or two "exchanges" of 30–40 mL/kg of plasma, whereas patients in our study underwent continuous plasma filtration for 24–36 hours (20 mL/kg/h for 6 hours, then 10 mL/kg/h for 30 hours) using Gambro PF1000 or PF2000 filters.

All patients in the study by Busund et al[49] received fresh frozen plasma as the replacement fluid, while immunoglobulin was not used in either group. In contrast, all patients in our study received immunoglobulin, and all those in the plasma filtration group of our study received fresh frozen plasma. Evidence for survival benefit from immunoglobulin in neonatal sepsis is conflicting,[50,51] while in adults no survival benefit exists.[52] There may be significant differences in the paediatric response to sepsis that may make children less responsive to plasma filtration than adults. These include developmental differences in haemodynamics, resulting in an increased incidence of shock caused by high systemic vascular resistance in children,[53] differences in the coagulation cascade and the development of disseminated intravascular coagulation,[54] differences in the cytokine response to sepsis,[55] and immaturity of the innate and adaptive immune systems in children.[56,57]

Three important questions regarding plasma filtration are yet to be answered. First, it is unclear whether plasma filtration is beneficial in all cases of severe sepsis, or whether certain subgroups would benefit more than others — for example, those with lipopolysaccharide-mediated gram-negative sepsis. Second, it is unclear whether benefit comes through removal of host immune factors, or through replacement of depleted host factors with fresh frozen plasma. Third, it is unclear whether plasma filtration is safe for use in routine clinical practice in the larger patient population, or whether this highly invasive procedure should still be considered an experimental therapy in sepsis.[58]

This study adds to the available evidence relating to the use of plasma filtration for the treatment of severe sepsis in children. The small sample size prevents conclusions being drawn regarding potential benefit of or harm from this treatment.

Competing interests

None declared.

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Appendix. Protocol for patient management in plasma filtration and control groups

Management should be identical in both groups, except for the plasma filtration.

Cardiovascular

Use echocardiography to monitor volume status and myocardial contractility:

- Aim to keep mean arterial pressure > 40 mmHg (1–4 months), > 45 mmHg (5 months – 5 years), > 50 mmHg (6–7 years), > 55 mmHg ($\geqslant$ 8 years)
- Give hydrocortisone 1 mg/kg 8-hourly intravenous
- Use fluids to keep central venous pressure 10–15 mmHg
- Give dobutamine to maximum 15 µg/kg/min, then if still hypotensive add noradrenaline 0.1–1.0 µg/kg/min

If, despite the above, diastolic blood pressure < 25 mmHg (< 12 months) or < 30 mmHg (12 months to $\leqslant$ 8 years) or < 40 mmHg ($\geqslant$ 9 years):

- Contractility acceptable: add vasopressin 0.02–0.06 µ/kg/h (1 µ/kg in 50 mL, run at 1–3 mL/h)
- Contractility poor: 10% calcium gluconate 0.4 mL/kg/h, then adrenaline 0.1–1.0 µg/kg/min
- Consider extracorporeal membrane oxygenation if poor contractility despite dobutamine 15 µg/kg/min, 10% calcium gluconate 0.4 mL/kg/h, and adrenaline 0.5–1.0 µg/kg/min

Respiratory

- Use minimum FiO_2 to maintain SaO_2 > 90% (apply positive end-expiratory pressure as needed)
- Ventilate to keep pH > 7.25 (but minimum pCO_2 35 mmHg, and maximum peak inspiratory pressure 30 cmH_2O if < 12 months, or 35 cmH_2O if $\geqslant$ 12 months)
- If pH < 7.25 and base deficit > 10 mmol/L, consider bicarbonate (intravenous over 1 hour)

Immunoglobulin and antibiotics

- Immunoglobulin 0.5 g/kg intravenous over 2 hours at time of entry to the trial, and after 36 hours (but not before filtration has finished in the filtration group)
- Use specific antibiotic(s) if organism known
- Unknown organism, immunocompetent host: flucloxacillin or oxacillin (or vancomycin if *Streptococcus* or *Staphylococcus* resistance is common in your area), cefotaxime, and metronidazole
- Unknown organism, immunocompromised host: vancomycin (or teicoplanin if vancomycin resistance common), piperacillin ± tazobactam (or imipenem if gram-negative resistance common), and gentamicin (or amikacin if gentamicin resistance common)

Renal replacement

- If creatinine > 0.4 mmol/L or increasing > 0.1 mmol/day, consider continuous venovenous haemofiltration or haemodiafiltration
- DO NOT HAEMO(DIA)FILTER IN THE FIRST 36 HOURS AFTER RANDOMISATION (unless potassium is > 7 mmol/L despite sodium polystyrene sulfonate and insulin plus dextrose)

Nutrition

- Use enteral feeding as soon as possible
- If total parenteral nutrition is needed, give dextrose (Day 1) + add amino acids (Day 2) + add lipids (Day 3)

Plasma filtration

- Cannula: 8.5 Fr in child (blood flow, 30–60 mL/min), 11 Fr in teenager (blood flow, 50–100 mL/min)
- Filter: Gambro PF1000 or PF2000 (or equivalent)
- Filtrate: 20 mL/kg/h for 6 hours, then 10 mL/kg/h for 30 hours
- Replace any filter that clots before 24 hours, electively discontinue any filter still functioning at 36 hours
- Heparin: 100 units/kg in 50 mL saline at 1–10 mL/h prefilter, 10 units/kg in 50 mL saline at 1–10 mL/h postfilter; keep activated clotting time 1.5 × normal (Hemotec machine, 130–150 s, Hemochron machine, 160–180 s)
- Acid citrate dextrose, formula A: 1 mL/h prefilter for every 1 mL/min of blood flow
- Replacement fluid: dextrose 0.3%, sodium 135 mmol/L, potassium 3.5 mmol/L, calcium 2.0 mmol/L, magnesium 0.7 mmol/L, bicarbonate 25 mmol/L, phosphate 1.5 mmol/L, chloride 100 mmol/L, acetate 9.2 mmol/L, albumin 30 g/L; give 1 bag of fresh frozen plasma (about 230 mL) after every 800 mL of replacement fluid, and cryoprecipitate 5 mL/kg (1 bag/4 kg) if blood fibrinogen level < 2.0 g/L