Case report

Elimination of *Staphylococcus aureus* from the bloodstream using a novel biomimetic sorbent haemoperfusion device

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SUMMARY

Removal of bacteria from the blood by means of extracorporeal techniques has been attempted for decades. In late 2019, the European Union licensed the first ever haemoperfusion device for removal of bacteria from the blood. The active ingredient of Seraph 100 Microbind Affinity Blood Filter is ultrahigh molecular weight polyethylene beads with endpoint-attached heparin. Bacteria have been shown to bind to heparin as they would usually do to the heparan sulfate on the cell surface, thereby being removed from the blood stream. We describe the first case of a female chronic haemodialysis patient in which this device was clinically used for a *Staphylococcus aureus* infection that persisted for 4 days despite antibiotic therapy. After a single treatment, the bacterial load decreased and the blood cultures at the end of a 4 hour haemoperfusion exhibited no bacterial growth.

BACKGROUND

More than 100 years ago, it had been shown that in case of infection the bacterial burden is associated with the clinical outcome.[1] In theory, a rapid reduction of infectious agents from the blood could be accomplished by combining effective antibiotic treatment with extracorporeal means of pathogen removal. After failed attempts of such a strategy in the 1980s,[2] several approaches to this task such as filtration,[3] use of human opsonin mannose-binding lectin,[4] magnetic nanoparticle separation[5] bendable polycrystalline nanowires/carbon foam[6] and a biomimetic device[7] have been developed. The later one uses covalently end-point-attached heparin-coated ultrahigh molecular weight polyethylene that mimics heparan sulfate on cell surfaces, thereby binding and removing pathogens from the blood stream.[8] After a first in men study in chronic dialysis patients where the Seraph 100 Microbind Affinity Blood Filter was used in combination with haemodialysis only, the device received clearance by the European authorities in summer of 2019.

CASE PRESENTATION

We report the case of a 70-year-old Caucasian woman who started maintenance haemodialysis via her arterio-venous fistula 3 months ago for a failed renal allograft graft that she received 16 years earlier. She was admitted to our tertiary care hospital with fever and diarrhoea during outpatient haemodialysis. Her body weight was 51 kg, which was 1.7 kg below her normal post dialysis weight. With a height of 166 cm, her body mass index was calculated to be 18.5 kg/m^2. She had a blood pressure of 130/70 mm Hg, a heart rate of 76/min and a respiratory rate of 23/min. Her ear temperature was 37.7°C. She was confused and not oriented to time and situation. Hence, she had 2 points on the quick Sequential Organ Failure Assessment Score. Of note was her severe steroid-induced skin atrophy with skin defects. Crucial laboratory findings included increased inflammatory markers—C reactive protein (CRP) 153 mg/L (<5 mg/L); leucocytes 11.3×10^9/L (4–10×10^9/L) anaemia with a haemoglobin 98 g/L(133–153 g/L) and hyponatremia—sodium 129 mmol/L (132–146 mmol/L). Blood culture drawn and empiric antibiotic treatment with ceftriaxone (2 g/day) were started.

INVESTIGATIONS

On the hospital day 2, blood cultures revealed Gram-positive cocci with time to positivity of 11 hours. CRP increased from 153 to 192 mg/L (<5 mg/L) and leucocytes increased from 11.3 to 13.8×10^9/L (4–10×10^9/L). On day 4, a *Staphylococcus aureus* resistant to penicillin G and amoxicillin was identified. Bacteria were sensitive against ampicillin/sulbactam, cefuroxim, levofloxacin, gentymicin, erythromycin, clarithromycin, vancomycin, clindamycin, fosfomycin, rifampin, doxycyclin and cotrimoxazole. Antibiotic regimen was changed from ceftriaxone (2 g/day), which the patient had received four times, to flucloxacillin 1.5 g four times per day, which was given until discharge on hospital day 10. The dosing of the antibiotics was tailored to the residual renal function and the dialysis dose according to www.dosing.de website

Under this regimen, CRP decreased from 192 to 114 mg/L (<5 mg/L) and leucocytes decreased from 13.8 to 6.8×10^9/L (4–10×110^9/L). A day later, another blood culture had been drawn that again grew *S. aureus* with a time to positivity of 36 hours.

DIFFERENTIAL DIAGNOSIS

The diagnosis of a persistent bloodstream infection with *Staphylococcus aureus* despite adequate antibiotic treatment according to a resistogram was made. To identify the source of the ongoing infection, we performed an echocardiography, a chest X-ray and an ultrasound examination of the abdomen. None of those investigations showed a source of the

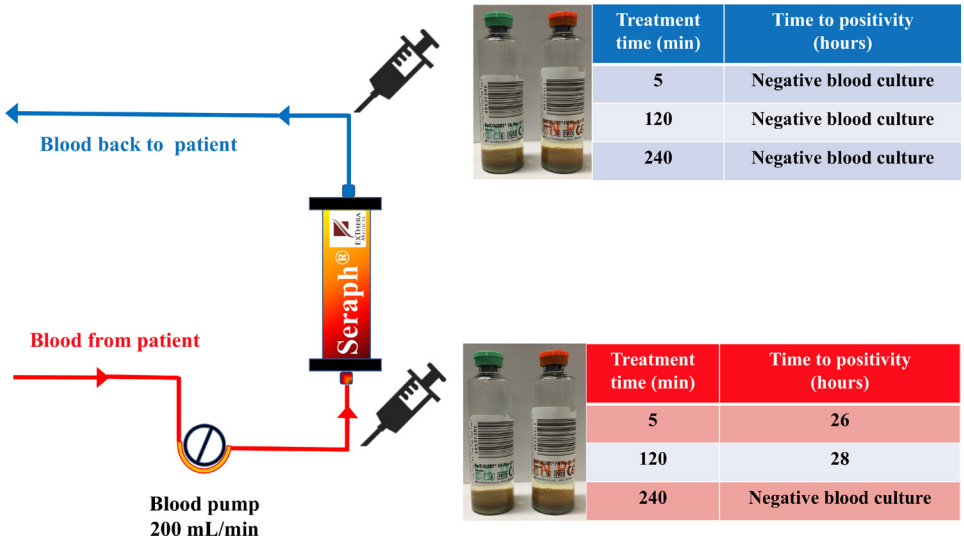

Figure 1 Six blood cultures have been taken at three different time points before and after the Seraph 100 Microbind Affinity Blood Filter to evaluate the bacterial burden in the blood by measuring time to positivity.

infection. An infected tunnelled dialysis catheter could be ruled out as the patient had a native arteriovenous fistula on her left arm as dialysis access. All in all, the skin lesions on the patient's extremities seem to be the only possible port of entrance for the *S. aureus*.

TREATMENT

On day 5 of the hospital stay, the patient underwent haemoperfusion with the Seraph 100 Microbind Affinity Blood Filter (Exthera Medical, California, USA) using a multiFiltrate machine (Fresenius Medical Care, Bad Homburg, Germany). The combination with dialysis was not necessary as the last dialysis session commenced 24 hours earlier. Vascular access was obtained by insertion of two needles into the native arteriovenous fistula of the patient. Blood flow rate was set to 200 mL/min and treatment lasted 4 hours. Heparin was used as anticoagulant.

To monitor the treatment effect of the Seraph 100 Microbind Affinity Blood Filter, blood cultures were taken at three time points during the treatment before and after the Seraph to allowing to asses bacterial clearance (figure 1). There was no apparent effect of the treatment on routine laboratory parameters as shown in table 1. The previous *in vitro* data have shown that the Seraph 100 does not remove a wide array of antiinfective; however, flucloxacillin was not tested.[9]

Of note, despite the fact that the haemoperfusion with the Seraph 100 Microbind Affinity Blood Filter did not remove any fluid, the peripheral oxygen saturation under ambient air improved from 96% to 100% and lactate level (0.63–2.44 mmol/L) decreased from 1.0 mmol/L at the beginning of the treatment to 0.7 mmol/L at the end of the treatment.

OUTCOME AND FOLLOW-UP

Intravenous antibiotic treatment was continued until hospital day 10 leading to a decrease of inflammatory markers (leucocytes 6.4×10^9/L ($4–10\times110^9$/L). The patient could be discharged 10 days after admission.

DISCUSSION

Infections are the second leading cause of hospitalisations and death in chronic dialysis patients. One study showed that from 1996 to 2001, 32% of haemodialysis patients had been

Table 1 Routine clinical chemistry parameters before and after the treatment with the Seraph 100 Microbind Affinity Blood Filter

	Reference range	Pre Seraph treatment (0 min)	Post Seraph treatment (240 min)
CRP (mg/L)	<5	41.8	45.1
Leucocytes, $\times10^9$/L	4–10	6.1	6.6
Haemoglobin (g/L)	123–153	82	79
Erythrocytes, 10^{12}/L	4.1–5.1	3.08	3.02
Haematocrit (%)	35–47	26.4	25.7
MCV (fL)	80–96	85.7	85.1
Platlets, $\times10^9$/L	149–409	187	167
Creatinin (µmol/L)	44–106	174	179
Urea (mmol/L)	2.1–8.9	9	9
Sodium (mmol/L)	132–146	134	135
Potassium (mmol/L)	3.7–5.4	5.3	5.6
Phosphorus (mmol/L)	0.87–1.45	0.75	0.82
Calcium (mmol/L)	2.15–2.55	2.22	2.15
Cholesterol (mg/dL)	<200	96	88
LDL-cholesterol (mg/dL)	<120	48	48
HDL-cholesterol (mg/dL)	>55	26	28
Uric acid (mg/dL)	2.4–5.7	3.7	4
CK (U/L)	<200	34	27
Bilirubin (mg/dL)	<1.0	0.3	0.3
LDH (U/L)	135–214	197	185
y-GT (U/L)	5–39	51	49
Alk. phosphatase (U/L)	35–104	77	73
LDL-cholesterol (mg/dL)	<120	48	48
HDL-cholesterol (mg/dL)	>55	26	28
Lipase (U/L)	13–60	90	79
Triglycerides (mg/dL)	<200	153	107
GPT (ALT) (U/L)	10–50	28	27
GOT (AST) (U/L)	10–50	34	30
Serum protein (g/L)	64.0–83.0	63.1	61.1

CK, creatine kinase; CRP, C-reactive protein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HDL-cholesterol, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-cholesterol, low-density lipoprotein cholesterol; MCV, mean corpuscular volume; y-GT, gamma-glutamyl transferase .

hospitalised for infection related causes within the first year after start of haemodialysis therapy.[10] The hospital mortality of infected dialysis patients ranges between 7% for catheter infections and 30% for endocarditis.[11] Staphylococci represent the most frequent bacteria found in 31% of isolates from the dialysis patients. The Achilles heel of the dialysis patient in terms of infections is the dialysis access. Patients with a tunnelled haemodialysis catheter have a 10-fold increased risk of bloodstream infections as compared with patients with native arteriovenous fistulas.[12] In a sizeable percentage of dialysis patients, the focus of the infection cannot be identified, as in our patient.

We are not aware of a prior report in which it had been attempted to remove the bacteria from the blood in addition to antibiotic therapy. The rapid decrease of bacterial load, as evidenced by the blood cultures turning negative during the 4-hour treatment, suggests a marked added effect of this treatment in addition to the targeted antibiotic therapy, which should, however, not be abandoned.

Patient's perspective

Frankly, I did not notice any difference to a regular haemodialysis session except for the fact that there were no alarms during this treatment. Also the hours after the treatment did not feel different from my day after my mid-week dialysis session.

Learning points

- Persistent bacteremia despite adequate choice and dose of antibiotics is a clinical relevant problem.
- The Seraph 100 Microbind Affinity Blood Filter a newly licensed extracorporal device that is able to reduce the number of circulating bacteria in the blood.
- Combining antibiotic treatment with extracorporeal removal of bacteria might lead to faster clinical cure/resolution of blood stream infections.
- The early use of such a device might help to prevent an inadequate response of the body to infections with life-threatening organ dysfunction, that is, sepsis.

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