CASE REPORT

Sepsis-associated renal salt wasting:
how much is too much?

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SUMMARY

We report the case of a patient who presented with an extremely high level of glomerular filtration rate and renal salt wasting during acute severe sepsis. Clinical implications for resuscitation and antibiotics dosage regimens are discussed.

BACKGROUND

Circulatory failure during sepsis is a major problem in the critical care setting and septic shock-related short-term mortality is near 50% even in the recent reports.¹

Guidelines for management of circulatory failure in septic shock have been recently re-evaluated.²

According to these guidelines, one of the end-points reflecting adequate volume resuscitation is urine output of at least 0.5 ml/kg/h.

While in daily clinical practice a subset of septic patients might present with an apparently 'well-resuscitated state' manifested by high urine output despite severe low cardiac output. These are features of renal salt wasting.

Not taking into account this phenomenon might be harmful because renal salt wasting might induce fluid loss and might lower cardiac output which might be a paradoxical response in the setting of acute sepsis where adequate blood volume and cardiac output are early goals of patients' resuscitation.²

CASE PRESENTATION

A 25-year-old woman was admitted to our intensive care unit (ICU) for immediate postoperative management of acute peritonitis and severe sepsis caused by small intestine ischaemia related to small intestine volvulus.

The patient's initial diagnosis and management were accomplished urgently by our hospital surgical team since she presented—6 h earlier—in the emergency room with severe acute abdominal pain associated with intestinal obstruction caused by a small intestine volvulus.

She presented no signs of sepsis during the brief preoperative period.

She had a medical history that was non-contributory.

The patient's weight and height values were 60 kg and 165 cm, respectively.

Her calculated body mass index was 22 and she had a total body surface area of 16.6 m².

Surgery initially consisted of resection of a 10 cm long segment of small intestine necrosis and then, a double ileostomy was performed.

On ICU admission, arterial blood pressure measured continuously by a radial artery catheter was 120/60 mm Hg, heart rate was 155 bpm, central body temperature was 39°C and oxygen saturation was 100%.

Urine output was 400 mL/h (approximately 7 mL/kg/h).

The patient had no catecholamines support but she presented with clinical signs of acute circulatory failure.

She had diffuse skin livedo and cold extremities.

On ICU admission, the patient was sedated with a combination of midazolam (5 mg/h) and sufentanil (25 µg/h).

She was kept sedated with mechanical ventilation because of clinical signs of acute severe circulatory failure.

Mechanical ventilation settings were as follows: tidal volume 7 mL/kg, respiratory rate 15 cycles/min, end expiratory pressure 5 cm H₂O, measured end inspiratory plateau pressure 18 cm H₂O and the fraction of inspired oxygen was set at 30%.

INVESTIGATIONS

The presence of such a high level of urine output despite clinical signs of severe circulatory failure prompted our medical team to explore in detail the kidney functions in conjunction with a detailed haemodynamic assessment.

Blood chemistry showed that serum creatinine level was undetectable because it was below our laboratory detection threshold value set at 27 µmol/L (our lower and upper laboratory adult female reference values are 65 and 95 µmol/L, respectively), serum urea level was 2 mmol/L (our laboratory reference values are 4 and 6 mmol/L).

Mild hyponatraemia (132 mmol/L) was present.

Serum potassium, phosphate and magnesium levels had a tendency to be towards lower limit values but the patient's electrolyte levels remained within the normal limits with supplementation as needed.

Serum uric acid was not measured.

Serum glucose level was 6 mmol/L and was within the normal reference values.

Arterial blood gas analysis showed that partial pressure of oxygen was 120 mm Hg, partial pressure of carbon dioxide was 40/mm Hg. Mild metabolic acidosis was present with arterial pH value of 7.33 and a base excess value of −5 mmol/L.

Liver function tests were within the normal limits.

Complete blood count showed hyperleucocytosis with a total white cell count of 25 000/mm³.

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To cite: Saleh M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201838

Urine analysis showed no proteinuria and urine glucose level was undetectable. Neither uric acid nor phosphate urinary excretion fractions were measured.

Assuming the patient's serum creatinine level was at least 27 $\mu\text{mol/L}$ (our laboratory detection threshold value), we estimated glomerular filtration rate by the creatinine clearance calculation method via a 24-h urine collection specimen analysis.

This method showed a very high creatinine clearance value (at least 350 mL/min) and a high renal sodium output value (UNa^+ : 170 mmol/L) despite hyponatraemia. These findings indicated glomerular hyperfiltration and renal salt wasting, respectively.

Microbiological analysis of peritoneal fluid showed numerous leucocytes and bacterial culture showed *Enterococcus gallinarum*.

Haemodynamic assessment was based on three times a day transthoracic echocardiography and continuous invasive arterial blood pressure measurement.

No other invasive haemodynamic monitoring device was used because our medical team relies on regular echocardiography-based haemodynamic assessment for the majority of our patients presenting with acute circulatory failure.

Echocardiography on admission showed small inferior vena cava diameter (10 mm, our reference range is set between 15 and 20 mm for patients under mechanical ventilation) and normal left ventricular systolic function (ejection fraction 70%, our reference range is set above 50%).

Cardiac index value estimation by echocardiography was 1.9 L/min/m² (our reference range is set between 2.8 and 4.2 L/min/m²).

These haemodynamic findings were consistent with low cardiac output secondary to hypovolaemia.

DIFFERENTIAL DIAGNOSIS

Some differential diagnosis could be discussed to explain renal fluid and salt wasting.

One of these might be renal tubular and/or glomerular injury.

The absence of proteinuria and the documented high level of glomerular filtration rate argue against this diagnosis.

Also, the diagnosis of fluid loss due to osmotic diuresis could not be an explanation because of normal serum glucose level and the absence of any context of osmotically active agent administration or ingestion.

Finally, one might assume creatinine clearance might overestimate glomerular filtration rate as in cases of severe chronic renal failure. In our case there was no medical history of chronic renal failure, in addition the unexpectedly high level of amikacin clearance we documented later argued for the presence of a real glomerular hyperfiltration.

TREATMENT

Treatment consisted of volume resuscitation to initially achieve our haemodynamic resuscitation endpoints based on our unit's 'Echocardiographic reference values' and regression of clinical signs of circulatory failure.

To achieve these endpoints the patient initially received 2000 mL of normal saline solution infusion.

Second, to maintain these endpoints in time, our protocol called for intravenous fluid replacement for urine output exceeding 1 mL/kg/h.

Our patient received between 6000 and 7000 mL of normal saline per 24 h for three consecutive days.

Antibiotics therapy regimen was based on piperacillin/tazobactam (16 g/day) and amikacin combination.

Owing to glomerular hyperfiltration we documented, amikacin was given at the dosage of 50 mg/kg (instead of our traditional dosage of 30 mg/kg).

Serum amikacin level measured only 12 h after injection was undetectable confirming the presence of glomerular hyperfiltration.

Piperacillin serum concentration measurement was not available in our hospital.

OUTCOME AND FOLLOW-UP

Outcome was marked by persistent uncontrolled sepsis on the fourth day with persistent intestinal occlusion and the absence of any significant source of extra abdominal sepsis.

Ventilatory settings and sedation remained unchanged.

A second look surgery was performed. It documented unexplained persistent peritonitis. An abundant peritoneal lavage was carried out.

Microbiological peritoneal fluid analysis confirmed persistent peritonitis caused by the same piperacillin-sensitive *E. gallinarum* despite conventional piperacillin dosage administration.

After the second look surgery, the renal fluid loss response gradually regressed within a few hours.

The same antibiotic dosage regimen of piperacillin was continued for eight additional days since within a few hours after surgery the glomerular hyperfiltration started to regress as well.

Serum creatinine level became detectable and rose within a few hours to reach a plateau value around 60 $\mu\text{mol/L}$ within 4 days.

Glomerular filtration rate estimated by the aforementioned creatinine clearance method decreased gradually and reached a stable value around 120 mL/min within 5 days.

Serum sodium level gradually increased and reached a normal range plateau value of 137 mmol/L within 4 days.

DISCUSSION

Glomerular hyperfiltration in the critical care setting has been mentioned only in one recent study.³ No management strategy aiming to reduce glomerular hyperfiltration was mentioned in this observational study.

Only the possible impact of glomerular hyperfiltration on antibiotics dosing regimens was mentioned.

In the present case we documented via creatinine clearance calculation a glomerular filtration rate of 350 mL/min.

To our knowledge, such a high level had never been documented before.

We also documented antibiotic treatment failure despite the conventional dosage regimen. This might be related to an insufficient antibiotic serum concentration level due to glomerular hyperfiltration and higher renal antibiotic clearance.

The cerebral salt wasting syndrome has been recently renamed the renal salt wasting syndrome⁴ since its description in association with acute non-brain injury-related illnesses. In fact, other acute illnesses have been associated with renal salt wasting.^{4,5}

Our patient presented marked features of renal salt wasting in addition to glomerular hyperfiltration.

One might suppose that during acute sepsis both glomerular hyperfiltration and renal salt wasting are two manifestations of one process characterised by imbalance between glomerular filtration rate and renal salt retention capacity.

This process might be due to functional and reversible alterations in local renal haemodynamics and might not be associated with any kidney damage.

In one recent study⁶ pharmacological modifications of local renal haemodynamics induced significant changes in the glomerular filtration rate.

One could suppose that endogenous sepsis-associated cytokines or other vasoactive substances might modify local renal haemodynamics in the same manner and finally induce glomerular hyperfiltration and/or renal salt wasting.

The apparent beneficial effect of the second look surgery in our case might be due to the reduction—by abundant peritoneal lavage—of the residual bacterial inoculum and subsequently the reduction of the systemic levels of inflammatory cytokines or vasoactive mediators responsible for the renal haemodynamic alterations.

One might question the physiological origins of increased salt and fluid loss in sepsis where increased cardiac output is needed.

Is it the need for high level of toxins clearance by the kidneys during sepsis? Is it a paradoxical response with harmful consequences?

Before answering this question, one might suppose that during acute sepsis high urine output might be as alarming as low urine output and estimation of glomerular filtration rate by 24 h urine collection would be helpful in antibiotic dose adjustment if glomerular hyperfiltration is documented.

From a strict haemodynamic point of view, in the presence of signs of circulatory failure during sepsis or acute illness, no defined quantity of urine output could be qualified as excessive or 'too much'.

Only haemodynamic monitoring can tell clinicians how much is too much.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Renal salt wasting may be responsible for high volume fluid loss in septic patients.
- ▶ Apparently 'good' urine output might not reflect 'really' good cardiac output.
- ▶ Also, 'good' urine outputs do not mean the kidney is functioning normally during sepsis.
- ▶ Glomerular hyperfiltration in the critically ill might be responsible for antibiotic treatment failure.
- ▶ Correction of antibiotics dosage and antibiotic serum level monitoring are mandatory in these cases.

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