Port J Nephrol Hypert 2019; 33(1): 72-74 • Advance Access publication 29 March 2019

A child with acute kidney injury

Rui Domingues[1], Tânia Moreira[1], Telma Francisco[2], Sara Nóbrega[3], António Pedro Campos[3], Raul Silva[3], Margarida Abranches[2]

[1] Unidade Funcional de Pediatria Médica, Área da Mulher, Criança e Adolescente, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central
[2] Unidade de Nefrologia Pediátrica, Área da Mulher, Criança e Adolescente, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central
[3] Unidade de Cuidados Especiais Respiratórios e Nutricionais, Área da Mulher, Criança e Adolescente, Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central

CASE PRESENTATION

We present the case of an 18-month-old boy born with intestinal atresia type IIIa, resulting in short bowel syndrome, treated with home parenteral nutrition by an indwelling central line and weighing 8.300 kg (<3rd centile).

He was admitted to the hospital with a catheter-related bloodstream infection (CRBSI) caused by methicillin-resistant *Staphylococcus aureus*. The patient was treated with intravenous vancomycin and gentamicin for 14 days.

Three days after finishing this course of antibiotics, the patient presented a second CRBSI caused by *Pseudomonas aeruginosa* and *Candida albicans*, and therefore intravenous amphotericin B, gentamicin and ceftazidime were initiated.

On day 24 of hospitalization (8 days after starting the second antibiotic cycle), the patient started vomiting (five episodes, small amount) and having diarrhea (two liquid stools, small amount), followed by prostration, pallor and poor peripheral perfusion. Laboratory workup at this time and a few days after showed anemia, leukocytosis with neutrophilia, increasing C-reactive protein (CRP), metabolic acidosis, hypokalemia, hypophosphatemia, hypomagnesemia, hypoalbuminemia, elevated serum urea and creatinine, glycosuria and proteinuria. Estimated glomerular filtration rate (eGFR) was 52 mL/min/1,72 m$^{2.}$ (Table I). Astrovirus was isolated from stools. Hydroelectrolytic disorders were treated with intravenous fluids and sodium bicarbonate, potassium chloride and magnesium sulphate; red cells and albumin transfusions were prescribed.

In the context of central line infection and worsening inflammatory markers, nephrotoxicity caused by amphotericin B and gentamicin was suspected, so both medicines were stopped and replaced by intravenous fluconazole, piperacillin/tazobactam, metronidazole and vancomycin.

On day 27 of hospitalization (and day 3 of the third antimicrobial cycle) the patient developed oliguria (minimum of 0.5 milliliters/kg/hour), anasarca (edema, weight gain of 1.2 kg, bilateral pleural effusion and ascites) and worsening metabolic acidosis with respiratory compensation, despite improvement in kidney function. He was treated with intravenous sodium bicarbonate and vancomycin was stopped. Hydric restriction and furosemide, with strict evaluation of enteric fluid losses and diuresis, were started, with significant improvement after 48 hours.

WHY DID THIS PATIENT DEVELOP HYPOPHOSPHATEMIA AND HYPOKALEMIA, DESPITE AN ACUTE KIDNEY INJURY?

Acute kidney disease (AKI) is defined by Kidney Diseases Improving Global Outcomes (KDIGO) as an increase in creatinine of ≥50% or an absolute increase of creatinine of 0.3 mg/dL or an eGFR ≤35 ml/min per 1.73 m^2 or a urine output <0,5mL/kg/hour in 6-12 hours (stages 1-3 are defined according to severity of theses alterations).[1] AKI is characterized by an increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate the fluid and electrolyte homeostasis appropriately[2], causing metabolic acidosis, hyperkalemia and hyperphosphatemia. However, our patient presented hypokalemia, hypomagnesemia and hypophosphatemia, along with metabolic acidosis, glycosuria, and proteinuria. Altogether, these results indicate a tubular disorder.

WHAT'S THE MOST PROBABLE CAUSE OF RENAL LESION IN THIS CASE?

This patient has a severe chronic condition (short bowel syndrome) leading to intestinal failure, poor oral feeding, had a multi-agent CRBSI and simultaneously a viral gastroenteritis, which could lead to dehydration. However, the Astrovirus gastroenteritis was not serious enough (only a few episodes of vomiting through the day, in small amount, and two small liquid stools) to cause, by itself, AKI, acidosis and electrolytic disorders.

Furthermore, the patient was treated with several nephrotoxic drugs: amphotericin B, gentamicin, piperacillin/tazobactam and vancomycin. Several studies indicate that among hospitalized children, nephrotoxic drug exposure is one of the most common contributors to AKI.[3]

Drug-induced tubular disorders have been described with several medications that are handled through tubular transport mechanisms.[4] Several patterns have been described, ranging from isolated abnormalities (e.g. phosphate leak) to more generalized lesions contributing to a proximal renal tubular acidosis or an acquired Fanconi syndrome. By recognizing the wide spectrum of tubular dysfunction, we must include abnormalities in urinary losses of phosphate, glucose, magnesium, potassium, and tubular proteins or water handling.

In aminoglycosides, nephrotoxicity is associated with a varying degree of renal tubular dysfunction that may, in the most severely affected patients, lead to AKI.[1]

Received for publication: Feb 2, 2019 • Accepted in revised form: Mar 26, 2019 • http://doi.org/10.32932/pjnh.2019.04.014

Table I

Relevant laboratory findings, follow-up and medicines used.

Day of admission	D1	D23	D24	D25	D26	D27	D29	D31	D40	Reference range
Medicines	VAN GEN	AMB GEN CAZ	AMB GEN CAZ **STOP**	FLC TZP MTZ VAN	FLC TZP MTZ VAN	FLC TZP MTZ VAN **STOP**	FLC TZP MTZ	TZP MTZ	MTZ **STOP**	
Clinical evolution		5 episodes of vomiting Normal diuresis and hydration status	2 small amount liquid stools Prostration Pallor Normal diuresis Normal blood pressure	Edema Normal diuresis Normal blood pressure	Edema Oliguria	Anasarca (edema, bilateral pleural effusion, ascitis) Oliguria	Mild edema Diuresis ↑ (furosemide)			
Weight	8.300 kg	8.230 kg		8.440 kg	9.400 kg	9.600 kg	8.600 kg	8.300 kg		
Hemoglobin (g/dL)	9.7	9.5	11.4	7.3	9.1	8.9	10	11.3	10.6	10.5 – 13.5
Leukocytes (/L)	13 120	22 710	51 700	29 120	16 070	15 060	16 370	16 940	8 510	6000 – 16000
Neutrophils (/L)	5 230	11 440	39 650	18 030	8 350	7 150	5 020	5 180	1 420	1000 – 7000
Platelets (/L)	440 000	317 000	548 000	330 000	264 000	275 000	371 000	454 000	295 000	200000 – 550000
CRP (mg/L)	30.8	13.8	37.2	34.7	31.2	15.8	7.3	3.1	4.4	<5
Glucose (mg/dL)		76		96	84		57			
Creatinine (mg/dL)	0.41	0.82	0.82	0.75	0.68	0.58	0.50	0.45	0.41	0.1 – 0.36
Urea (mg/dL)	28	94	104	88	64	49	24	19	39	10.9 – 36.0
Sodium (mEq/L)	136	135	134	141	149	145	144	136	137	136 – 145
Potassium (mEq/L)	4.3	3	2.7	3.2	2.8	3.5	3.5	4.2	4.3	3.4 – 4.7
Chloride (mEq/L)	103	101	102	117	119	118	107	104	104	98 – 107
Phosphate (mg/dL)	–	4.3	–	3.7		–	3.5	4.5	5.2	4.3 – 6.8
Magnesium (mg/dL)	–	1.34	–	1.47	2.07	–	1.4	1.65	1.79	1.7 – 2.3
Ca^{++} (mmol/L)	–	1.32	1.31	1.32	1.21	1.27		1.28	1.28	1.1 – 1.35
Albumin (mg/dL)	–	–	–	–	27.5	31.7	35.4	36.7	40.1	38.0 – 54.0
Venous pH	–	7.42	7.32	7.26	7.37	735	–	7.42	7.38	7.31 – 7.41
Venous HCO_3 (mmol/L)-	–	20.1	16.6	13.6	18	16.2	–	22.2	22.1	23 – 27
Venous pCO_2 (mmHg))	–	29.2	30.2	27.1	54.7	26.3	–	35.0	37.9	40 – 52
Anion gap	–	16.5	13.9	13.6	14.9	16.7	–	11.8	16.2	8 – 16
Base excess	–	-5.7	-10.8	-14.9	-8.5	-11.3	–	-2.1	-3	-4 – +2
Urine pH				6		6	–			
Urine glucose	–	–	–	100		500	–	–	–	negative
Urine protein	–	–	–	100		100	–	–	–	negative
Urinary casts				Hyaline and pathologic casts						
Blood culture			negative							
Urine culture				negative						
Treatment		Intravenous fluids Intravenous KCl and magnesium sulphate	Intravenous fluids Intravenous KCl, sodium bicarbonate and magnesium sulphate	Furosemide Red cell transfusion Reduction of intravenous fluids Intravenous KCl, sodium bicarbonate and magnesium sulphate	Furosemide Albumin transfusion Intravenous KCl and sodium bicarbonate	Fluid restriction Furosemide Intravenous KCl and sodium bicarbonate	STOP furosemide			

D (day). VAN, vancomycin; GEN, gentamycin; AMB, amphotericin B; CAZ, ceftazidime; FLC, fluconazole; TZP, piperacillin/tazobactam; MTZ, metronidazole.

Aminoglycosides cause damage primarily to tubular epithelial cells[3] (particularly proximal tubular cells[5]), but can also have an adverse effect on renal function via activation of the renin-angiotensin-aldosterone system and changes of glomerular endothelial cells.[3] Other mechanisms involved are the direct and indirect effects on the mitochondria that lead to the disruption of electron transport and ATP production and the production of reactive oxygen species.[1] Patients may present with oliguric AKI, along with proximal tubule dysfunction, resulting in loss of enzymes, proteins, glucose, calcium, potassium and magnesium. Most patients recover but some can progress to chronic interstitial nephritis.[5] There are several risk factors that can increase the nephrotoxic potential of aminoglycosides, such as pre-existing renal disease, treatment for more than 10 days, higher trough levels and hypoalbuminemia.[4]

The role of vancomycin as a nephrotoxin remains controversial, particularly in the context of monotherapy with appropriate drug monitoring levels.[5] However, there is evidence that vancomycin has detrimental oxidative effects on proximal tubule cells.[3] The exact mechanism of nephrotoxicity remains unclear, but may be related to oxidative effects on the proximal tubule.[6] Moreover, simultaneous use of vancomycin and piperacillin/tazobactam has been linked to the development of AKI in non-critically ill children. There is even more evidence suggesting substantial nephrotoxicity associated with piperacillin/tazobactam, independent of vancomycin use.[6] Furthermore, the combined use of vancomycin and aminoglycoside may increase nephrotoxicity.[6]

Nephrotoxicity represents the most significant side effect of amphotericin B (80% of patients[5]) and results from a combination of vasoconstriction and direct distal tubular toxicity.[5] The direct toxicity and increased tubular membrane permeability accounts for the characteristic electrolyte abnormalities that can be seen after amphotericin B administration (hypokalemia, hyponatremia, acidosis and hypomagnesemia).[5] In our patient, the hypomagnesemia found on day 23 (table I) was most probably related with treatment with amphotericin B, as this drug was prescribed seven days before.

WHICH RISK FACTORS FOR DRUG NEPHROTOXICITY CAN BE FOUND IN THIS CASE?

In hospitalized children, predisposing factors such as age[3,6], low weight-for-age[3], severity of illness, pharmacogenetics, dosage, duration, and concomitant nephrotoxic medication determine and influence the severity of nephrotoxic insult.[6] In this case, several risk factors can be identified for AKI, such as low weight, young age (<5 years), sepsis, dehydration, low serum albumin, association of several nephrotoxic drugs (aminoglycosides, vancomycin, piperacillin/tazobactam and amphotericin B) and a prolonged treatment with gentamicin. As a critically ill patient, he is at the highest risk for drug-induced comorbidities of AKI, sepsis, hypotension, polypharmacy, and poor estimation of renal function.[3] Regular assessment of serum creatinine levels, urine output and drug monitoring (peak and trough drug levels for aminoglycosides and vancomycin) allow early recognition of the development of AKI with the need to further adjustment of drug dosing to the eGFR.

CASE FOLLOW-UP

The patient showed progressive improvement of his clinical condition, and after three days, acidosis and the other tubular disorders were solved. Urea and creatinine blood levels showed progressive improvement and, on hospital discharge, he had nearly normal renal function (Table I).

With this case, authors intend to warn of the potential nephrotoxic effects of some drugs currently used in everyday practice. A high index of suspicion is required to identify potential at-risk children for drug-associated AKI. As there is no specific treatment for AKI, preventive measures include assuring an adequate hydration status, avoiding nephrotoxic medications and adjusting drug dosing to eGFR, particularly when a combination of nephrotoxic agents is required and the patient presents many risk factors for AKI.

Disclosure of potential conflicts of interest: none declared.

References

1. McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. *Pediatr Nephrol* 2017; 32:2015–2025
2. Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol* 2009; 24:253–263
3. Joyce EL, Kane-Gill SL, Fuhrman DY, Kellum JA. Drug-associated acute kidney injury: who's at risk? *Pediatr Nephrol* 2017; 32:59–69
4. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerdad J, Chakaravarthi R, Holden AL, Goldstein SL. Phenotype standardization for drug-induced kidney disease. *Kidney Int* 2015; 88:226–234
5. Faught LN, Greff M, Rieder MJ, Koren G. Drug-induced acute kidney injury in children. *Br J Clin Pharmacol* 2015; 80(4): 901–909
6. Hanna MH, Askenazi DJ, Selewski DT. Drug-induced acute kidney injury in neonates. *Curr Opin Pediatr* 2016; 28:180–187

Correspondence to:
Rui Pereira Domingues; MD
Área da Mulher, Criança e Adolescente, Hospital Dona Estefânia, CHULC, Rua Jacinta Marto, 1169-045 Lisboa.
E -mail: rp.domingues87@gmail.com