Acute kidney injury in an infant with severe combined immunodeficiency: Answers

Georgia Malakasioti MD[1], Nele Alders[2], Giovanna Lucchini[2], Fan Cheng[3], Detlef Bockenhauer MD, PhD[1]

[1]Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

[2]Department of Pediatric Immunology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

[3]Department of Pharmacy, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Corresponding author: Georgia Malakasioti

Current Address: Renal Unit, P. & A. Kyriakou Children's Hospital, Thivon and Levadeias Street, 11527, Athens, Greece

Email address: gwgwm1979@yahoo.gr

Telephone number: +306944537706

Keywords: acute kidney injury; severe combined immunodeficiency; pentamidine

Question 1

The child has experienced an acute rise in plasma creatinine and thus, by definition, has acute kidney injury (AKI) [1].This can be due to impaired blood delivery to the kidney with intact tubules (also called functional or pre-renal AKI) or due to tubular necrosis (also called intrinsic or established AKI). Post-renal AKI, due to urinary tract obstruction is unlikely in this case, considering the preserved urine output and absence of signs of obstruction on ultrasound.

The fractional excretion of sodium (FENa) is often used to distinguish between functional and intrinsic AKI. Under normal circumstances, urine sodium excretion reflects sodium intake and even with a "Western diet" high in salt, intake is usually well below 1% of the filtered sodium. Therefore, a FENa of <1% is usually considered normal. However, this is under the assumption of a normal glomerular filtration rate (GFR). With decreased GFR, less sodium is filtered and thus the same amount of sodium excreted will represent a higher FENa: with a GFR of 10 ml/min a FENa of 10% is equivalent to a FENa of 1% with a GFR of 100 ml/min [2]. Adjusting FENa for GFR is impossible in this case, as the GFR can only be estimated, if kidney function is in steady state, i.e. the creatinine is stable, whereas here, creatinine is still rising. Nevertheless, with intact tubular function, a low FENa would be expected in the context of clinical hypovolemia even with impaired GFR. Thus, a FENa of 12% is suggestive of tubular injury. Similarly, the urine osmolality, roughly isotonic to plasma, is also suggestive of tubular injury, as with intact tubular function, a highly concentrated urine would be expected with hypovolaemia.

In contrast, the low TTKG is a poor indicator of tubular injury, as in hypovolemia this can be just the consequence of decreased distal delivery of sodium to the distal tubule, which in turn is needed for potassium secretion [3]. Reassessment of laboratory indices after restoration of

extracellular volume by fluid supplementation is not only appropriate treatment, but also helps to identify the type of AKI: if creatinine normalises with euvolemia and potassium secretion increases, then AKI was functional, whereas persistent renal dysfunction indicates tubular injury [4].

Question 2

The patient had several factors predisposing to intrinsic AKI. Firstly, she was receiving three nephrotoxic antimicrobials: amikacin, liposomal amphotericin B and daily intravenous pentamidine. Patients with SCID are at risk of invasive bacterial as well as fungal and parasitic infections, hence the need for such a broad coverage in the setting of febrile neutropenia. Therapeutic drug monitoring of amikacin serum trough levels during the previous days did not identify any toxic concentrations, making this agent rather unlikely to be the sole responsible for the AKI. The infant had been on liposomal amphotericin B approximately 10 days prior to the manifestation of AKI also without any changes in her plasma creatinine.

Intravenous pentamidine had been recently introduced to treat *Pneumocystis jirovecii* pneumonia (PJP) and on day 4 of treatment an increase of the child's baseline creatinine by 130% was manifested. There is evidence stemming from adult HIV literature that immunocompromised individuals have a specific predisposition for renal impairment when treated with intravenous pentamidine and more so if amphotericin is concurrently utilized [5]. Our patient experienced a severe non-oliguric AKI with concurrent hyponatremia, hyperkalemia and hyperchloremic metabolic acidosis within five days after initiation of intravenous pentamidine. Urine biochemistry was suggestive of tubular damage as discussed in Question 1

The increased echogenicity seen on renal ultrasound examination is non-specific, but consistent with AKI.

There were additional aggravating factors of the pentamidine-induced renal impairment. Intravascular volume depletion as reflected on the child's weight loss was a significant one; it was precipitated by diarrhea, increased insensible losses due to tachypnea and the imposed fluid restriction. In addition, the newly established polyuric state (urine output 3.6ml/kg/h) was not taken into account when her fluid allowance was set. It has been demonstrated that dehydration serves as a contributor to the known nephrotoxicity of agents such as liposomal amphotericin and amikacin and even more so in the case of pentamidine [6, 7].

There was also strong suspicion of neutropenic sepsis- a clinical diagnosis closely associated with the development of AKI [8].

Question 3

Pentamidine and concurrently administered liposomal amphotericin B were recognised as the most likely causative agents of her AKI and were discontinued. Amikacin was also withdrawn as meropenem was already providing satisfactory antibacterial coverage. The infant received fluid resuscitation with fluid boluses and liberalization of the fluid intake to normal maintenance (130ml/kg/day) in order to restore euvolemia and improve renal perfusion. The fluid regimen was tailored to cover insensible losses, urinary and gastrointestinal output. It was given as a combination of intravenous normal saline in dextrose 5% (50ml/kg/day) and nasogastric tube feeding with a low potassium formula fortified with glucose polymer for extra caloric provision in the setting of azotemia (80ml/kg/day)to minimize catabolism.

Plasma creatinine returned to baseline levels within 72 hours from drug discontinuation and electrolyte abnormalities resolved without the need for dietary potassium restrictions. Of note, liposomal amphotericin B had to be reinstituted a few days later for suspected fungal infection, although without any impact on renal function or electrolyte serum concentrations. Similarly, her previous fluid regimen was resumed after recovery of kidney function and despite some ongoing stool losses plasma creatinine did not deviate from baseline.

The above observations are strongly supportive of pentamidine as the main precipitating factor for the infant's kidney injury; prompt and full recovery is anticipated upon drug discontinuation. Optimizing intravascular volume, nutrition and addressing electrolyte disturbances are general supportive strategies to be kept in mind when treating patients with AKI. Pentamidine is an aromatic diamidine first used in the treatment of trypanosomiasis in the 1930s and later in the 1950s became the drug of choice against PJP. This approach changed after a comprehensive report from the Centers for Disease Control in 1974 demonstrating the high incidence of side effects [9]. In line with this report, Hughes et al suggested that co-trimoxazole had a more favourable safety profile and soon became first line treatment for PJP with pentamidine reserved for resistant cases [10]. Nephrotoxicity was hence considered the commonest adverse effect of this antiprotozoal agent with an incidence of 25% [11].The first case report of a pediatric leukemia patient who developed renal failure over a course of pentamidine was published in 1970 and more cases were described involving not only cancer patients but also children with immunodeficiencies [9, 12, 13].

The issue of pentamidine-induced renal impairment was reignited during the AIDS epidemic in the early 1980s when HIV infected patients seemed more intolerant to co-trimoxazole and thus pentamidine was again widely used for PJP. A much greater propensity

towards AKI with use of pentamidine than previously described was recognised with a frequency ranging between 35-95% [14-19]. Investigators reported special risk factors for this patient population: non-white race, hypoalbuminemia, suboptimal fluid status, co-administration with other nephrotoxic medications, higher cumulative dosing, and longer duration of treatment [7, 14, 15, 18].

To our knowledge, this is the first case of severe pentamidine-related AKI described in a pediatric patient with severe combined immunodeficiency. One might speculate that patients with immunity defects either primary or acquired might be at additional risk in view of their common catabolic state and hypoalbuminemia [14]. Our infant had active infections and diarrhea with a declining serum albumin. Furthermore, the ongoing fluid losses and the strict fluid restriction exacerbated volume depletion. This is consistent with a previous observation in adult AIDS patients: the incidence of AKI was higher among those with diarrhea lacking intravenous access for volume restoration and receiving pentamidine intramuscularly [7].

The importance of simultaneous use of nephrotoxic agents cannot be overemphasised. Antoniskis *et al.* described 4 cases of AKI in HIV patients in whom pentamidine and amphotericin B were given together, all resolving upon discontinuation of both [5]. Interestingly, amphotericin B could safely be reinstituted upon recovery of renal function; this was also the case with our patient who had later further doses of liposomal amphotericin without any renal dysfunction suggesting a causative role in the AKI for the combination of the two drugs.

The special features of pentamidine-induced renal failure are closely related to its pharmacokinetic properties. The aromatic diamidine has a large volume of distribution with very little renal clearance (2-5%) [20]. Due to prolonged elimination half-life, plasma concentration and total tissue load was found to increase with daily dosing even when a lower dose was used

[20]. This is reflected on the timing of AKI anticipated towards the end of first week of treatment and is in line with the occurrence of renal impairment on day 6 of pentamidine treatment in our patient [14, 15, 19]. The child was on a daily intravenous regimen of 4mg/kg/day likely contributing to higher pentamidine levels and consequent toxicity as previously suggested [19, 20]. The long elimination half-life is also mirrored on the re-occurrence of AKI with subsequent administration as well as the minimum of 5-7 days required for renal recovery [15, 21]. Fortunately, our patient's kidney function improved within 3 days probably as a result of prompt recognition of AKI and discontinuation of the inciting agents together with tailoring of the fluid regimen.

The exact mechanism for pentamidine-related kidney injury is unclear. Our patient displayed the typical features of polyuria, poor urine concentrating ability (urine osmolality lower than plasma), hyperkalemia with high TTKG, hyponatremia with elevated urine sodium FE and hyperchloremic acidosis all in keeping with a distal tubular injury. More specifically, hyperkalemia has been a consistent feature of pentamidine-related tubulopathy even in the absence of renal impairment mimicking type 4 renal tubular acidosis [15].

Pentamidine-related tubulotoxicity was reflected in the findings of focal degeneration of convoluted tubular epithelium with preserved glomerular and vascular structures on the kidney autopsy of a pediatric patient with acute lymphoblastic leukemia who succumbed after developing renal failure and toxic epidermal necrolysis whilst on pentamidine for PJP [12]. Feddersen et al studied the effects of pentamidine administration in a rat model where creatinine clearance declined alongside increased shedding of tubular epithelial cells in a dose dependent fashion [21]. Of note, amphotericin was demonstrated to enhance pentamidine adverse effects on tubular cells.

In terms of renal prognosis after pentamidine induced nephrotoxicity, clinical and experimental data indicate full recovery following cessation of treatment [5, 15, 21]. Nevertheless, there are several reports of persistent renal impairment up to one month later and even deaths related to severe kidney failure [9, 14]. The main pitfall of those older studies is the lack of rigorous criteria for AKI definition as well as the several comorbidities in their patient population. Publications related to pentamidine-induced nephrotoxicity along with patient characteristics are summarised in Online Resource 1.

What are the implications of these old observations in the contemporary pediatric patient? With the advances in immunology, the population of surviving pediatric patients with genetic or acquired immune defects will continue growing. Thus, increasing numbers of hematopoietic stem cell and solid organ transplant recipients as well as children with primary immunodeficiencies are at risk of opportunistic infections necessitating treatment with agents like pentamidine. Treating physicians need to be aware of the adverse effects of this drug on kidney function. The recommended strategy to prevent, timely recognise and ameliorate nephrotoxicity is as follows:

1. Assess patient's baseline renal function and recognize any pre-existing renal dysfunction; monitor renal function and plasma electrolytes closely once intravenous pentamidine is commenced with specific attention towards the end of first week of treatment.
2. Optimize fluid status avoiding volume depletion; monitor for any weight changes and adjust drug dosing accordingly.
3. Avoid concomitant use of nephrotoxic agents; be aware of the increased nephrotoxic potential of pentamidine combination with liposomal amphotericin.

4. In the instance of AKI, discontinue the medication and take measures to ameliorate potential hyperkalemia; avoid reusing pentamidine as nephrotoxicity is likely to re-occur.

Further work is needed to determine optimal dosing of pentamidine as for instance alternate day administration perhaps at a reduced dose, in order to improve its renal safety profile albeit not at the expense of efficacy. Whether monitoring of its plasma concentrations during treatment course or using suggested nephroprotective agents could be of clinical benefit also remain to be elucidated.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare

References

1. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120:c179-184.
2. Nguyen MT, Maynard SE, Kimmel PL (2009) Misapplications of commonly used kidney equations: renal physiology in practice. Clin J Am Soc Nephrol 4:528-534.
3. Choi MJ, Ziyadeh FN (2008) The utility of the transtubular potassium gradient in the evaluation of hyperkalemia. J Am Soc Nephrol 19:424-426.
4. Himmelfarb J, Joannidis M, Molitoris B, Schietz M, Okusa MD, Warnock D, Laghi F, Goldstein SL, Prielipp R, Parikh CR, Pannu N, Lobo SM, Shah S, D'Intini V, Kellum JA (2008) Evaluation and initial management of acute kidney injury. Clin J Am Soc Nephrol 3:962-967.

5. Antoniskis D, Larsen RA (1990) Acute, rapidly progressive renal failure with simultaneous use of amphotericin B and pentamidine. Antimicrob Agents Chemother 34:470-472.
6. Hishida A, Nakajima T, Yamada M, Kato A, Honda N (1994) Roles of hemodynamic and tubular factors in gentamicin-mediated nephropathy. Ren Fail 16:109-116.
7. Stehr-Green JK, Helmick CG (1985) Pentamidine and renal toxicity. N Engl J Med 313:694-695.
8. Reilly JP, Anderson BJ, Hudock KM, Dunn TG, Kazi A, Tommasini A, Charles D, Shashaty MG, Mikkelsen ME, Christie JD, Meyer NJ (2016) Neutropenic sepsis is associated with distinct clinical and biological characteristics: a cohort study of severe sepsis. Crit Care 20:222.
9. Walzer PD, Perl DP, Krogstad DJ, Rawson PG, Schultz MG (1974) Pneumocystis carinii pneumonia in the United States. Epidemiologic, diagnostic, and clinical features. Ann Intern Med 80:83-93.
10. Hughes WT, Feldman S, Chaudhary SC, Ossi MJ, Cox F, Sanyal SK (1978) Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of Pneumocystis carinii pneumonia. J Pediatr 92:285-291.
11. Sands M, Kron MA, Brown RB (1985) Pentamidine: a review. Rev Infect Dis 7:625-634.
12. Wang JJ, Freeman AI, Gaeta JF, Sinks LF (1970) Unusual complications of pentamidine in the treatment of Pneumocystis carinii pneumonia. J Pediatr 77:311-314.
13. Siegel SE, Wolff LJ, Baehner RL, Hammond D (1984) Treatment of Pneumocystis carinii pneumonitis. A comparative trial of sulfamethoxazole-trimethoprim v pentamidine

in pediatric patients with cancer: report from the Children's Cancer Study Group. Am J Dis Child 138:1051-1054.

14. O'Brien JG, Dong BJ, Coleman RL, Gee L, Balano KB (1997) A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. Clin Infect Dis 24:854-859.

15. Lachaal M, Venuto RC (1989) Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. Am J Med 87:260-263.

16. Sattler FR, Cowan R, Nielsen DM, Ruskin J (1988) Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A prospective, noncrossover study. Ann Intern Med 109:280-287.

17. Wharton JM, Coleman DL, Wofsy CB, Luce JM, Blumenfeld W, Hadley WK, Ingram-Drake L, Volberding PA, Hopewell PC (1986) Trimethoprim-sulfamethoxazole or pentamidine for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. Ann Intern Med 105:37-44.

18. Briceland LL, Bailie GR (1991) Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. DICP 25:1171-1174.

19. Comtois R, Pouliot J, Vinet B, Gervais A, Lemieux C (1992) Higher pentamidine levels in AIDS patients with hypoglycemia and azotemia during treatment of Pneumocystis carinii pneumonia. Am Rev Respir Dis 146:740-744.

20. Conte JE, Jr. (1991) Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. J Infect Dis 163:169-175.

21. Feddersen A, Sack K (1991) Experimental studies on the nephrotoxicity of pentamidine in rats. J Antimicrob Chemother 28:437-446.