

## GENTAMICIN, INFECTIONS, AND ACUTE TUBULAR NECROSIS IN CHILDREN

MIHAELA BALGRADEAN<sup>1,2</sup>, ELIZA CİNTEZA<sup>1,2</sup>, FLORIN FILIPOIU<sup>3\*</sup>, VIOREL JINGA<sup>4,5</sup>

<sup>1</sup>*Pediatrics Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

<sup>2</sup>*"M.S. Curie" Emergency Children's Hospital, Bucharest, Romania*

<sup>3</sup>*Morphological Sciences Department, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

<sup>4</sup>*The Third Department of Urology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

<sup>5</sup>*"Th. Burghel" Hospital, Bucharest, Romania*

\*corresponding author: [ffilipo58@yahoo.com](mailto:ffilipo58@yahoo.com)

### Abstract

The incidence of acute kidney injury (AKI), previously called acute kidney failure (ARF), in emergency hospitals worldwide is highly independent of its different underlying causes. The use of certain antibiotics, like gentamicin, which determines the rapid loss of kidney ability to remove waste and stabilize the balance of fluids and electrolytes, finally causing AKI in child, is well known, and far from uncommon. Acute tubular necrosis (ATN) is a medical condition that consists of kidney disorder and involves the death of tubular cells. ATN is clinically characterized by AKI, which is defined as a rapid (ranging from hours to days) decline in the glomerular filtration rate (GRF), and classified as an intrinsic, or renal, cause of kidney injury. The tubules are responsible for transporting urine to the ureters, and concentrating the metabolic byproducts and salts by reabsorbing ninety-nine percent of the water. The terms ischemic and nephrotoxic ATN are frequently used synonymously with ischemic or nephrotoxic AKI. We report three cases of AKI induced by ATN diagnosed in complicated pediatric infectious diseases, in relation with gentamicin treatment.

### Rezumat

Incidența leziunii acute renale (AKI), numită anterior insuficiența renală acută (ARF), este independentă de cauzele etiologice. Implicarea anumitor antibiotice, precum gentamicina, în apariția pierderii abilității rinichiului de a elimina produșii de metabolism și de a stabili balanța lichidelor și electroliților, generând în final AKI la copil, este bine cunoscută și des întâlnită. Necroza tubulară acută (ATN) este o afecțiune care constă în tulburări renale și implică moartea celulelor tubulare. ATN este caracterizată clinic prin AKI, care este definită ca un declin rapid al ratei filtrării glomerulare (de la ore la zile) și clasificată ca o cauză intrinsecă de leziune renală. Tubulii sunt responsabili de transportul urinei către uretere și concentrarea produselor secundare de metabolism și a sărurilor prin reabsorbția a 99% din apă. Termenii ATN ischemică sau nefrotoxică sunt frecvent folosiți ca sinonime pentru AKI ischemică sau nefrotoxică. Raportăm trei cazuri de ARF induse de ATN în relație cu tratamentul cu gentamicină la copii cu boli infecțioase complicate.

**Keywords:** acute tubular necrosis (ATN), infections, gentamicin, young child

## Introduction

Acute Kidney Injury (AKI) is a common pathology among critically ill patients and carries significant morbidity and mortality. The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group has defined and stratified acute renal failure and described the RIFLE criteria. RIFLE is an acronym comprising Risk, Injury, Failure, Loss and End-Stage Kidney Disease, aiding in the staging of patients with AKI [2,4,12].

- Risk: Glomerular Filtration Rate (GFR) decrease >25%, serum creatinine increased 1.5 times or urine production of < 0.5 ml/kg/hr for 6 hours
- Injury: GFR decrease >50%, doubling of creatinine or urine production < 0.5 ml/kg/hr for 12 hours
- Failure: GFR decrease >75 % tripling of creatinine or creatinine > 355  $\mu\text{mol/L}$  (3.5 mg/dL) with a rise of > 4mg/dL or urine output below 0.3ml/kg/ hr for 24 hours.
- Loss: persistent AKI or complete loss of kidney function for more than 4 weeks
- End-Stage Renal Disease: need for replacement therapy for more than 3 months

The two major causes of AKI developing in hospitalized children are pre-renal diseases due to dehydration, sepsis, or septic-shock, and acute tubular necrosis (ATN) due to ischemia or direct nephrotoxic medications[20].

ATN is a medical condition, which consists of kidney disorder and involves the death of tubular cells. ATN can occur in both children and adults and can lead to severe kidney injury and ARF if not treated properly [9,10,21]. Renal failure is noted 8-17 days after the beginning of gentamicin therapy. ATN means creatinine clearances of 4 to 10 mL/min, urinary fractional excretion of sodium (FENa) > 2-4%, and urinary sodium concentrations between 16 and 60 mEq/L, low proteinuria, and, sometimes, cylindruria [6]. The terms ischemic and nephrotoxic ATN are frequently used synonymously with ischemic or nephrotoxic AKI. Although the common classification defines two types of ATN (toxic and ischemic) depending on the underlying causes, in current clinical pediatric and emergency pediatric practice there are frequent situations where the two ATN types overlap.

The prevalent causes of ATN in neonates and in older children are: perinatal asphyxia, respiratory distress syndrome, shock/sepsis and severe

dehydration, third-space losses in nephrotic syndrome, severe cardiac or pulmonary diseases. Ischemia is the primary and major pathophysiological explanation in all these pediatric entities[11]. Nephrotoxic ATN is caused by exogenous toxins, drugs that impair autoregulation (angiotensin-converting-enzyme inhibitors (ACEI), Non-steroidal anti-inflammatory drugs (NSAIDs)), or direct nephrotoxins (aminoglycosides, Amphotericin B, contrast agents, etc.). Although uncommon, irreversible loss of renal function may appear in ATN in those cases which present an unfortunate combination of repeated ischemic insults and /or nephrotoxin administration [5,13,15].

Gentamicin is a common pediatric prescription in the treatment of susceptible gram-negative (*Pseudomonas*, *E.coli*, *Proteus*) and gram-positive (*Staphylococcus*) bacterial infections, including septicemia, respiratory tract infections, CNS infections, as well as abdominal and urinary tract infections [9]. Because of the well-known nephrotoxicity of aminoglycosides, it is recommended that gentamicin should be used with caution in children of all ages, and especially in newborns. Precaution in the prescription of this antibiotic to neonates is imperious because of renal immaturity that may result in a prolonged serum gentamicin half-life, particularly in children with congenital reno-urinary, or even with mild, kidney abnormalities [7,19]. Gentamicin nephrotoxicity determines decrease in urine specific gravity, urinary casts, electrolyte wasting, proteinuria, elevated serum creatinine, reduction in glomerular filtration rate – all of which predict an ATN, even when administered in recommended doses. Oliguria or anuria is not always noticeable, feature which may impair recognition of kidney damage [17,18]. Clinical recovery requires an average of 40–60 days and may be complete in the majority of the cases. The major causes of unfavorable prognosis in ATN are infection and underlying disease, not renal failure itself [3,4,8,13].

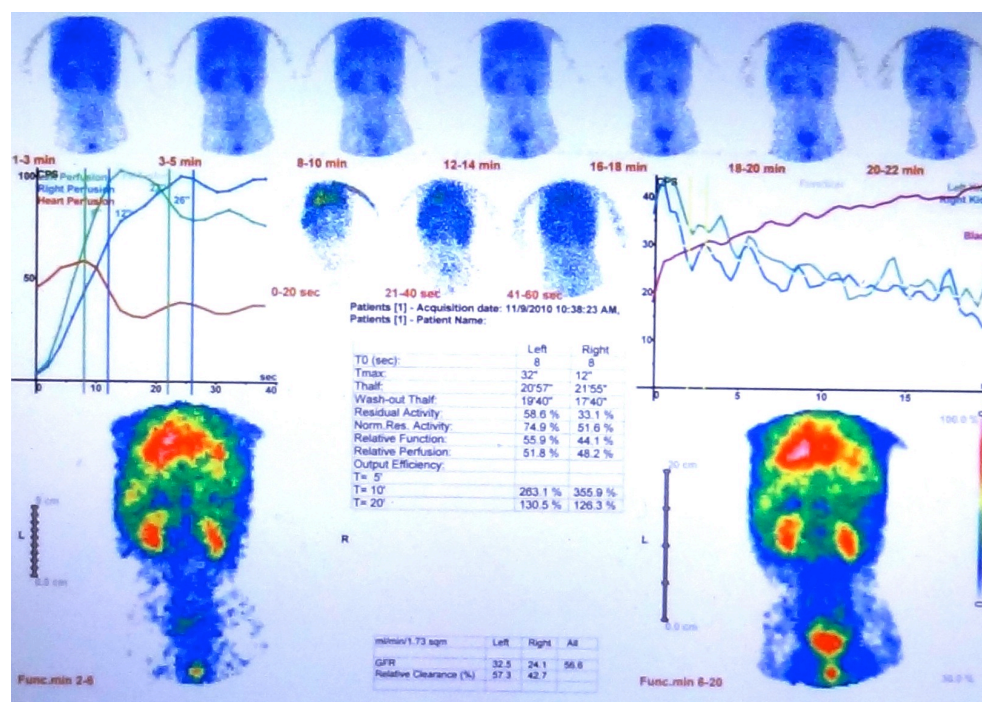
#### **ATN pathophysiology**

In most cases, drug-induced acute renal toxicity primarily affects the proximal tubular epithelium. Toxic ATN is characterized by proximal tubular epithelium necrosis caused by a toxic substance (organic solvents, drugs, etc.). The typical findings include patchy loss of tubular epithelial cells with resultant gaps and exposure of denuded basement membrane, diffuse effacement, and loss of proximal tubule brush border [6]. Necrotic cells fall into the tubule lumen, thus causing a tubular obstruction which triggers AKI. Acute necrosis of moderate numbers of proximal tubule cells is a reversible process. Tubular dilatation and intraluminal casts in the distal

nephron segments, and evidence of cellular regeneration are also significant ATN findings.

The clinical course of ATN may be divided in three phases: initiation, maintenance, and recovery. The initiation phase corresponds to the period of exposure to ischemia or nephrotoxins, when renal tubular damage begins and glomerular filtration rate (GFR) starts declining. During the maintenance phase, renal tubular injury is established and GFR stabilizes at a low level, while the urine output may be low or absent. ATN due to nephrotoxins is always non-oliguric. This phase usually lasts between 2 and 4 weeks, sometimes more. The recovery phase of ATN is characterized by polyuria, the gradual return of urea and plasma creatinine concentration near the previous baseline level, and gradual normalization of the GFR. It also involves the restitution of cell polarity, removal of the dead cells by apoptosis, reestablishment of tubular fluid flow, and regeneration of lost renal epithelial cells [7,10].

*Case 1.* A 3-year-old girl was admitted in the Intensive Care Unit of Marie Curie Emergency Children's Hospital, Bucharest, Romania, with high fever, important respiratory distress, generalized edema and anuria. One year before admittance the child was diagnosed with cortico-dependent nephrotic syndrome. A corticoid therapeutic schedule was in place at the moment of hospitalization. Laboratory data demonstrated leukocytosis ( $23900/\text{mm}^3$ ), C reactive protein ( $100\text{mg/L}$ ), high blood sedimentation rate ( $120\text{ mm/h}$ ), metabolic acidosis ( $\text{pH } 7.01$ ;  $\text{HCO}_3^- 18\text{ mmol/L}$ ), hyponatremia ( $118.3\text{ mmol/L}$ ), hyperpotassemia ( $5.36\text{ mEq/L}$ ), hiperazotemia (urea  $200\text{mg/dL}$ , creatinine  $4\text{ mg/dL}$ ), hypoproteinemia ( $3\text{ g/dL}$ ), and a high amount of urinary proteins ( $5\text{ g/L}$ ). The child's physical exam and clinical symptoms, the laboratory data, a chest X-ray, and abdominal ultrasound examination pointed to septic AKI. The right-lung extensive pneumonia detected by X-ray, the clinical appearance of anasarca, and the loss of renal cortico-medullary differentiation revealed by ultrasonography, all of which were considered in the context of the child's disease history, confirmed the necessity of intensive parenteral treatment. Ceftriaxone and gentamicin ( $7\text{mg/kg/day}$ ) were included in the therapeutic schedule. Two days later, the patient was anuric, and the levels of azotemia and urinary FENa (fractional excretion of sodium) ( $12.2\%$ ) were high, despite the complexity of treatment (oxygen, hydration, antibiotics, diuretics, adrenergic and antihypertensive medication). The diagnosis of intrinsic renal failure was thus made and a hemodialysis program was started. An emergency Tc99m Diethylene Triamine Pentacetic Acid (DTPA-renal) scan demonstrated the seriousness of the ARF (Figure 1).



**Figure 1**

Renal scan 99m Tc-DTPA: left kidney GRF=32.5 ml/min/1.73 m<sup>2</sup>, right kidney GRF=24.1 ml/min/1.73 m<sup>2</sup>, suggesting left reflux nephropathy. The important amount of radiocontrast substance still visible in the bloodstream indicates acute renal failure

The gentamicin treatment was stopped. The plasma level of gentamicin was 14.6 µg/mL (gentamicin normal serum level is < 2 µg/mL). After seven days of hemodialysis and antibiotic treatment the medical team noted a favorable clinical evolution of the pulmonary and renal disease, with amelioration of inflammatory tests and azotemia level values. Two months after the ATN episode, ultrasound examination revealed kidneys of normal appearance, and the creatinine clearance measured using Schwartz formula [17] was normal for age (86 mL/min/1.73 m<sup>2</sup>), indicating normal renal function.

*Case 2.* A 10-day-old prematurely born girl was admitted in the Intensive Care Unit of "Marie Curie" Emergency Children's Hospital, Bucharest, Romania, with fever 39°C. The blood and urinary analyses (high leucocytosis, anemia, positive inflammatory tests), and the positive blood and urine cultures confirmed a group-B streptococcal pyelonephritis in a pathological context of sepsis. A treatment combining ampicillin and gentamicin, in the recommended dosage for age, and intravenous

administration of hydration and medication were started. The renal ultrasound identified right renal agenesis and left ureterohydronephrosis, as well as the loss of left-kidney cortico-medullary differentiation.

Eight days after hospital admission, physical examination revealed progressive edema and oliguria. Remarkably high blood levels of urea (80 mg/dL) and creatinine (4.3 mg/dL), hyponatremia (119.2 mmol/L), and metabolic acidosis (pH 6.3,  $\text{HCO}_3^-$  16 mmol/L) confirm an ARF. A creatinine clearance (Schwartz formula) of 6.2 mL/min/1.73 m<sup>2</sup>, the high value of urinary FENa (17.8%), low urinary density (1008), and gentamicin blood dosage of 12.6 µg/mL underlined a severe ATN. Ten days of peritoneal dialysis were necessary to restart diuresis, correct the electrolyte imbalance, and ameliorate azotemia. The antibiotic prescription was changed to intravenous ceftriaxone.

A micturating urethrocytography effectuated in the second month of life demonstrated left dilated vesicoureteral reflux as underlying cause of the severe, repetitive pyelonephritis, and as risk factor in the evolution of ATN (Figure 2).



**Figure 2**

Micturating cystography: right dilated vesicoureteral reflux.

*Case 3.* A 24-day-old boy is hospitalized in the Neonate Intensive Care Unit of Marie Curie Emergency Children's Hospital for sudden weight

gain (450 g in two days), low appetite, drowsiness, oliguria (20 mL in the previous 18 hours) hypertension (120/80 mmHg), high level of urea (82 mg/dL) and creatinine (4.3 mg/dL), hyponatremia (120 mmol/L), hyperpotasemia (5.7 mEq/L), and low urine density (1010). The recent history of the patient mentioned a ten-day gentamicin treatment (2.5 mg/Kg/dose two times a day) for a problematic lower-respiratory-tract infection. At admission, the gentamicin serum level was 22.1 µg/mL, urinary FENa was high (26.2%), and the creatinine clearance (Schwartz formula) was 3.9 mL/min/1.73 m<sup>2</sup>. Over the following 14 days, the newborn's general state of health improved under diuretic and antihypertensive treatment and a normal nutrition (his mother's milk). Blood pressure, diuresis, and the urinary electrolyte and seric levels were normalized. Normal seric creatinine status was noted six weeks after the start of ATN.

### Results and Discussion

AKI, formerly named ARF, is a rapid and progressive decrease in renal function, which results in the inability of the kidney to maintain homeostasis (hydric and electrolyte balance), metabolic acidosis, and azotemia [4]. Studies of renal failure, as defined by RIFLE, indicate that AKI requiring renal replacement therapy, is associated with mortality rates of 28% to 85% [16].

In spite of the decrease in mortality due to severe infections and sepsis in recent years, these latter still remain a major cause of morbidity and mortality in children under five [9,14, 20]. The kidney is constantly affected in this pathology, bacterial infections being the main cause of disease. The main precipitating factors for severe infections, as in the presented cases, are: small age, premature birth, neonatal respiratory distress, underlying congenital renourinary abnormalities, nephrotic syndrome, or systemic diseases.

AKI is often the major manifestation of the disease, being at the same time a priority of the therapeutic approach [14]. The tissue hypoxia and consecutive ischemia are induced by anaerobic metabolism, with lactate formation and metabolic acidosis. Adenosine, nitric oxide and vasoactive metabolites tend to accumulate, while compensatory vasoconstriction fails in the presence of hypoxia. The consequence of this complex physiopathological mechanism is multi-organic hypoperfusion.

ATN often occurs in the context of multiple organ dysfunction. In such cases, regeneration of renal tissue may be severely impaired and renal

function is totally compromised. In the absence of multi-organ failure, most patients with ATN regain sufficient renal function [1].

### Conclusions

Gentamicin is well known as an efficient antibiotic prescription in various severe pediatric infections in all ages, but precautions are recommended in neonates and in cases of already diagnosed underlying reno-urinary abnormalities. Gentamicin nephrotoxicity may determine ATN even when the antibiotic is administered in normal dosage, due to immaturity of the renal function in child. In the great majority of pediatric illnesses, the major causes of unfavorable prognosis in ATN are infection and underlying reno-urinary disease, and not renal failure itself.

Despite this reality, gentamicin-associated AKI remains a common and potentially serious clinical problem. Early diagnosis and timely treatment are important to avoid further kidney damage, especially in neonates and young children.

*All authors have equally contributed to this paper.*

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