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***ACUTE KIDNEY INJURY IN PORTUGUESE
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ACUTE KIDNEY INJURY IN PORTUGUESE CHILDREN

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ABSTRACT

Introduction: Over the last decade efforts have been made in standardizing the definition and assessment of severity of acute kidney injury (AKI) for early recognition and intervention. The purpose of our study was to understand the etiology, clinical and laboratory features, management and outcomes of AKI in Portuguese children.

Method: A retrospective study including all children (0-18 years old) diagnosed with AKI from January 2002 to December 2011 at a pediatric tertiary care hospital was conducted, based on information from medical records. Acute kidney Injury Network (AKIN) classification system was applied.

Results: Our study comprised 137 children with AKI, 56% males and a median age of 1.1 years. In respect to age, 49% of patients were less than 1 year, 23% 1-5 years, 23% 6-12 years and 5% 13-18 years. A total of 77% were admitted to the intensive care unit. Etiology of AKI was pre-renal in 64%, intrinsic renal in 31% and post-renal in 5%. Pre-renal causes were more prevalent on infants. The commonest causes of AKI were sepsis/ septic shock, followed by heart failure/cardiogenic shock, acute/ rapidly progressive glomerulonephritis, hypoxic-ischemic encephalopathy and hemolytic-uremic syndrome. According to AKIN classification system, 4%, 16% and 78% of patients were classified as stage 1, 2 and 3, respectively. Edema was the most frequent clinical feature being evident in 67% of children and in 45% of cases AKI was nonoliguric. Treatment modality was conservative in 70% and surgical in 4% of cases. Renal replacement treatment (RRT) was performed in 26% of children. Mortality rate during hospitalization was 29% and depended on etiology and age group, being higher in the infants group, due to pre-renal causes in all cases except one. At time of discharge, 23% of children had complete renal recovery. Follow-up was not possible for 57% of children after 3 years. After 3 years, 8% of children had CKD and 2% developed end-stage renal disease. AKIN stage 3 had a positive association with the need for RRT, evolution to CKD and

mortality. There were no statistically significant differences between the first 5 years of the study (2002-2006) and the second period (2007-2011) in respect to etiology, AKIN classification and mortality rate.

Conclusions: The implementation of an AKI classification system on clinical practice is advised in order to evaluate at-risk patients and improve long-term outcomes.

Keywords: Acute kidney injury, Children, Classification, Epidemiology, Etiology, Outcome Assessment.

RESUMO

Introdução: Durante a última década têm sido feitos esforços para uniformizar a definição e a avaliação da gravidade da lesão renal aguda (LRA), no sentido de facilitar o reconhecimento e intervenção precoces. O objetivo do nosso estudo consistiu em compreender a etiologia, características clínicas e laboratoriais e a evolução da LRA nas crianças portuguesas.

Método: Foi conduzido um estudo retrospectivo, incluindo todas as crianças (0-18 anos) diagnosticadas com LRA de Janeiro de 2002 a Dezembro de 2011 num hospital pediátrico terciário, com base na informação dos registos médicos. O sistema de classificação da *Acute Kidney Injury Network* (AKIN) foi aplicado.

Resultados: O nosso estudo incluiu 137 crianças com LRA, 56% do sexo masculino e uma idade mediana de 1,1 anos. Relativamente à idade, 49% dos doentes apresentavam menos de 1 ano, 23% 1-5 anos, 23% 6-12 anos e 5% 13-18 anos. A admissão na unidade de cuidados intensivos foi necessária para 77% das crianças. A etiologia da LRA foi pré-renal em 64%, renal intrínseca em 31% e pós-renal em 5%. As causas pré-renais foram prevalentes no grupo com menos de 1 ano. As causas mais frequentes de LRA foram sépsis/ choque séptico, falência cardíaca/ choque cardiogénico, glomerulonefrite aguda/ rapidamente progressiva, encefalopatia hipóxico-isquémica e síndrome hemolítico-urémico. Ao aplicar o sistema de classificação AKIN, obtivemos 4%, 16% e 78% das crianças nos estádios 1, 2 e 3, respetivamente. O edema foi a característica clínica mais frequente, estando presente em 67% das crianças e em 35% dos casos a LRA foi não-oligúrica. O tratamento foi conservador em 70% e cirúrgico em 4% dos casos. A terapêutica de substituição renal (TSR) foi necessária em 26% dos casos. A taxa de mortalidade durante o internamento foi de 29% e esteve dependente da etiologia e do grupo etário, sendo mais elevada no grupo com menos de 1 ano, devido a causas pré-renais, exceto num caso. Na data da alta, 23% das crianças apresentavam recuperação completa da função renal. Após 3 anos, o seguimento não foi possível para 57%

das crianças, sendo que 8% das crianças tinham desenvolvido doença renal crónica (DRC) e 2% doença renal terminal. O estágio 3 de AKIN teve uma associação positiva com a necessidade de TSR, evolução para DRC e mortalidade. Não se encontrou uma diferença estatisticamente significativa entre os primeiros 5 anos do estudo (2002-2006) e o segundo período (2007-2011) no que respeita a etiologia, classificação de AKIN e taxa de mortalidade.

Conclusões: A implementação de um sistema de classificação da LRA na prática clínica é recomendada, no sentido de avaliar os doentes em risco e melhorar os resultados a longo prazo.

Palavras-chave: Avaliação de resultados, Classificação, Crianças, Epidemiologia, Etiologia, Lesão renal aguda.

LIST OF ABBREVIATIONS

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARF	Acute renal failure
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
HDF	Hemodiafiltration
HUS	Hemolytic-uremic syndrome
ICU	Intensive care unit
PD	Peritoneal dialysis
RIFLE	Risk, Injury, Failure, Loss and End-Stage Renal Disease
RRT	Renal replacement treatment
SCr	Serum creatinine
UOP	Urine output

INTRODUCTION

Acute kidney injury (AKI) is defined by an acute and reversible increment in serum creatinine (SCr) levels associated or not with a reduction in urine output (UOP) to oliguria/anuria. It is a complex disorder with clinical manifestations ranging from mild injury to complete kidney failure ¹. The term AKI is now used in place of acute renal failure (ARF), because this was frequently used to describe an anuric, dialysis dependent state and by the time such a state is recognized, beneficial interventions are significantly delayed which increases mortality ².

Over the last decade much progress has been made in early recognition of kidney injury and intervention prior to the development of oliguria ². International efforts to define AKI and standardize the assessment of its severity have resulted in two classification systems. In 2004, the Acute Dialysis Quality Initiative (ADQI) proposed an AKI classification system called the RIFLE criteria (acronym for Risk, Injury, Failure, Loss and End-Stage Renal Disease) ³ for stratifying patients based on changes in estimated glomerular filtration rate (eGFR) from baseline and/or a decrease in UOP. Three years later, RIFLE criteria were modified to be used in children, thus giving rise to the pediatric RIFLE criteria or pRIFLE ⁴. In 2007, the Acute Kidney Injury Network (AKIN) revised AKI classification and has adopted the percentage SCr increment to diagnose AKI, recognizing that eGFR was not necessary ⁵. This is important because it made it possible to diagnose AKI in retrospective studies, in which the researchers often do not have access to children's length, which is necessary to calculate eGFR ¹. AKIN criteria have also been applied to the pediatric population ⁶⁻⁸.

The epidemiology of AKI has widely varied between different studies due to differences in the country of origin (developing versus developed countries), type of patients attended by the different centers and referral patterns of the center ⁹. Also, there has been a

change over time. Epidemiological studies from the 1980s and 1990s suggested that major cause of acute renal failure in children was primary renal disease, but more recent studies have suggested that the pattern of disease is changing and the most common causes are renal ischemia, nephrotoxins, and sepsis¹⁰.

To our knowledge, no epidemiological study on AKI has been previously conducted in Portugal. The aim of this study was to characterize the pediatric Portuguese population retrospectively regarding etiology, clinical and laboratorial features, treatment modality and short, medium and long-term outcomes using children admitted to the Pediatric Hospital of Coimbra, a tertiary care center. A better understanding of AKI diagnosis and management is important for delineate preventive strategies and improve long-term outcomes.

METHODS

We conducted a retrospective, descriptive study, based on medical records of all children less than 18 years old admitted to the Pediatric Hospital of Coimbra between 1 January 2002 and 31 December 2011. This is a tertiary care center and manages all children from the centre region of Portugal requiring intensive care and acute renal replacement services, including neonates. Clinical records were searched for ICD-9-CM codes 580 (acute glomerulonephritis), 581 (nephrotic syndrome), 582 (chronic glomerulonephritis), 583 (nephritis and nephopathy, not specified as acute or chronic), 584 (acute renal failure), 585 (chronic kidney disease), 586 (renal failure, unspecified), 572.4 (hepatorenal syndrome) and 283.11 (hemolytic-uremic syndrome). In cases with more than one admittance with AKI, only the first episode was considered.

Based on AKIN criteria⁵, AKI was defined as an absolute increase in serum creatinine by either >0.3 mg/dl or an increase of $\geq 50\%$ from baseline within 48 h. In newborns, AKI was

defined as a serum creatinine value higher than 1.5 mg/dl ¹¹. The patient's condition was staged according to AKIN classification system (Table 1) based on changes during one week.

Baseline creatinine level was estimated from the following formula: Mean creatinine (mg/dl)

$$= -0.02324 - 0.14545 * \log_e(\text{age}) * 0.26964 + (\text{age})^{0.5} \text{ }^{12}.$$

Table 1 – AKIN classification/ staging system for acute kidney injury ⁵.

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.4 $\mu\text{mol/l}$) or increase to ≥ 150 – 200% (1.5-fold to 2-fold) from baseline	< 0.5 ml/kg per hour for > 6 h
2	Increase in serum creatinine to > 200 – 300% (> 2 -fold to 3-fold) from baseline	< 0.5 ml/kg per hour for > 12 h
3	Increase in serum creatinine to $> 300\%$ (> 3 -fold) from baseline (or serum creatinine ≥ 4.0 mg/dl [≥ 354 $\mu\text{mol/l}$] with an acute rise of at least 0.5 mg/dl [44 $\mu\text{mol/l}$])	< 0.3 ml/kg per hour for 24 h or anuria for 12 h

For comparison purposes, 4 age groups were established: less than 1 year (infants), 1 to 5 years (preschool children), 6 to 12 years (school age) and 13 to 18 years (adolescents). Also, two periods of five years, 2002-2006 and 2007-2011, were established for comparison.

Information on age, gender, primary disease/condition causing AKI at the time of diagnosis, clinical and laboratorial features, duration of hospital length of stay, requirement for admission to the intensive care unit (ICU), ICU length of stay, renal ultrasounds or biopsy results, modality of treatment and outcome (at discharge and after 1 month, 3 months, 1 year and 3 years) was collected. Clinical manifestations registered included macroscopic hematuria, urine output (non-oliguria, oliguria, oligo-anuria or anuria), hypertension, edema and hypertensive encephalopathy. Laboratory findings included maximum serum creatinine and urea values during stay, serum creatinine and urea values at discharge, hyperkalemia (serum potassium > 5.1 mmol/l; in newborns, it was defined as a serum potassium level > 6.0 mEq/l), hyperuricemia, metabolic acidosis, anemia, proteinuria, and microscopic hematuria.

When renal replacement treatment (RRT) was needed, the duration and complications that occurred were also registered.

Outcome was recorded as complete renal recovery, hypertension, abnormal urinalysis (proteinuria or hematuria), elevated SCr, chronic kidney disease, end-stage renal disease, death and whether follow-up was arranged. Complete renal recovery was defined as normal serum creatinine for age (0.3-0.9 mg/dL for neonates, 0.2–0.4 mg/dL for 1 month to 3 years, 0.3–0.6 mg/dL for 3 to 11 years and 0.4 to 0.8 mg/dL for > 11 years)¹², normal blood pressure and normal urinalysis at discharge.

For the purposes of this study, hypertension was defined as systolic and/or diastolic blood pressure greater than 95th percentile for age, gender and height. When no height data were available, the blood pressure percentile was calculated using the 50th percentile for height for the child's age. Proteinuria was defined as a protein creatinine ratio ≥ 0.2 mg/mg and nephrotic proteinuria when this ratio was ≥ 2 mg/mg or ≥ 300 mg/dl on dipstick. Microscopic hematuria was considered when red cell count/HPF was ≥ 5 . Oliguria was defined as an urine output less than 1 ml/kg/h during 6 h, and oligo-anuria when this value was less than 0.5 mL/kg/h.

Data were statistically analyzed using Microsoft Excel and GraphPad software. Continuous variables were expressed as mean \pm standard deviation or medians and range. Those with a normal distribution, as determined by Kolmogorov-Smirnov test, were compared using Student's t-test, while those that did not have a normal distribution were compared using Mann-Whitney U test. Categorical outcome measures were reported as absolute number of cases or relative frequencies (%) and univariate comparison between groups was performed using Pearson's chi square test or Fisher's exact test, as appropriate. P values less than 0.05 were considered statistically significant.

RESULTS

Study population

We identified a total of 137 cases of AKI in our 10-year study period from 2002 to 2011 and 56.2% (77 cases) occurred on male gender. The median age was 1.1 years (range 1 day to 17.5 years). Mean age was 3.8 ± 4.7 years old, being 3.2 ± 4.1 for male and 4.6 ± 5.3 for female gender, respectively. The highest number of cases occurred on infants age group, a total of 67 (48.9%) and incidence declined with increasing age, being 22.6% for preschool age, 23.4% for school age and 5.1% for adolescents. The male gender was more prevalent in all age groups, except in the adolescents (Figure 1). On the infants group, 58.2% of children were newborns, corresponding to 28.5% of the study population.

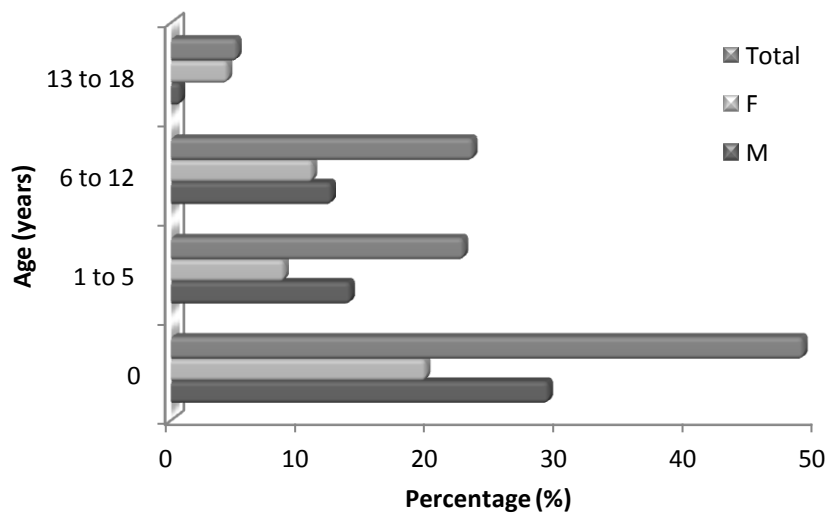


Figure 1 – Distribution of AKI cases according to age group and gender (N = 137). F – Female; M – Male.

Thirty-nine children (28.5%) died during hospitalization (non-survivors group). Mortality rate was higher on the infants group with 25 cases (18.2%). In the preschool age, school age and adolescents groups, the number of children dying during hospitalization were 6 (4.4%), 6 (4.4%) and 2 (1.5%), respectively. Comparing the study period of 2002-2006 with 2007-2011, the mortality rate was 32.4% and 24.2%, respectively ($p>0.05$). There were no statistically significant differences on mortality rate by age distribution between these two periods: 56.5%, 21.7%, 13.0% and 8.7% for infants, preschool age, school age and adolescents in the first period, and 75.0%, 6.3%, 18.8% and 0% for the same group ages in the second period.

Ninety-eight patients (71.5%) had been previously admitted to another hospital and then referred to our hospital. The percentage of patients who needed admission to the intensive care unit (ICU) was 77.4% and 35.8% of the children only stayed at the ICU. The average total hospital length of stay was 21.7 ± 33.7 days and for ICU was 12.5 ± 13.5 days. In those patients needing ICU admission, the percentage of ICU stay in relation to total hospital stay was $70.3 \pm 33.6\%$. Only one child of the non-survivors group was not admitted to the ICU. The difference in the percentage of ICU stay in relation to total hospital stay between survivors and non-survivors, $62.6 \pm 33.6\%$ and $84.0 \pm 29.3\%$, respectively, was statistically different ($p<0.05$).

Etiology

Primary causes of AKI were pre-renal in 88 (64.2%), intrinsic renal in 42 (30.7%) and post-renal in 7 (5.1%) of the patients. Table 2 shows the distribution of AKI causes between different groups of diseases considered for each of the major categories previously mentioned.

Table 2 – Major and specific causes of AKI in number (No.) and percentages (n=137).

Pre-renal AKI	No. (%)	Intrinsic renal AKI	No. (%)	Post-renal AKI	No. (%)
Sepsis/ Septic shock	28 (20.4%)	Acute/ rapidly progressive glomerulonephritis	19 (13.9%)	Obstructive uropathy	7 (5.1%)
Heart failure/ Cardiogenic shock	27 (19.7%)	Hemolytic-uremic syndrome	11 (8.0%)		
Hypoxic-ischemic encephalopathy	13 (9.5%)	Nephrotoxins	6 (4.4%)		
Hepatorenal syndrome	7 (5.1%)	Acute interstitial nephritis	2 (1.5%)		
Hypovolemia	5 (3.6%)	Polyarteritis nodosa	1 (0.7%)		
Post-abdominal surgery	5 (3.6%)	Pyelonephritis	1 (0.7%)		
Post-cardiac surgery	3 (2.2%)	Renal vein thrombosis	1 (0.7%)		
		Tumor lysis syndrome	1 (0.7%)		
TOTAL = 88 (64.2%)		TOTAL = 42 (30.7%)		TOTAL = 7 (5.1%)	

The most prevalent cause of AKI was sepsis/ septic shock, followed by heart failure/ cardiogenic shock, acute/ rapidly progressive glomerulonephritis, hypoxic-ischemic encephalopathy and hemolytic-uremic syndrome (HUS). Acute/rapidly progressive glomerulonephritis included 11 cases (8.0%) of post-infectious glomerulonephritis, 5 cases (3.6%) of IgA nephropathy, 1 case (0.7%) of lupus nephritis, 1 case (0.7%) of Alport syndrome and 1 case (0.7%) of unknown cause.

The cause of AKI varied for specific ages (Figure 2). In infants, the pre-renal cause was the most prevalent (43.1%), while for preschool and school age children intrinsic renal cause accounted for most of the cases (12.4 and 13.1%, respectively). In the adolescents group, pre-renal and intrinsic renal were equally responsible for 2.2% of cases. Post-renal causes were more frequent in the infants group (2.9%) as compared to older children (0.7% for each other age category).

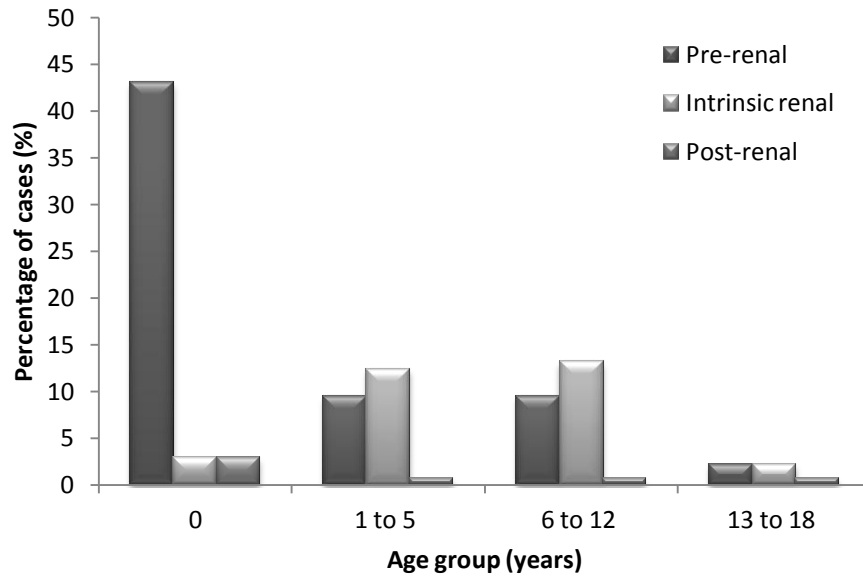


Figure 2 – Major causes of AKI according to age group (N=137).

Between 2002 and 2006 the percentage of pre-renal, intrinsic renal and post-renal causes for AKI were 66.2%, 26.8% and 7.0%, respectively, while in the second period of our study, between 2007 and 2011, these values were 62.1%, 34.8% and 3.0%, respectively. The difference was not statistically significant.

AKIN classification

The results obtained for AKIN classification system applied to the study population are shown in Table 3. There was no statistically significant difference when data was analyzed considering the primary cause of AKI.

In the first period of study (2002-2006) children were classified as AKIN stage 1, 2 and 3 in 2.8%, 16.9% and 80.3% of cases and in the second period of study (2007-2011) these values were 4.5%, 19.7% and 75.8%, respectively. The difference was not statistically significant.

Table 3 – AKIN classification of the study population considering its primary cause (N= 137)

	Total No. (%)	Pre-renal No. (%)	Intrinsic renal No. (%)	Post-renal No. (%)
Stage 1	5 (3.6%)	2 (1.5%)	2 (1.5%)	1 (0.7%)
Stage 2	25 (18.2%)	17 (12.4%)	8 (5.8%)	0 (0.0%)
Stage 3	107 (78.1%)	69 (50.4%)	32 (23.4%)	6 (4.4%)

Clinical and laboratory features

The clinical presentation of AKI was nonoliguric in 44.5%, oliguric in 21.9%, oligoanuric in 13.1% and anuric in 20.4%. Assembling these categories in only two groups considering a normal or decreased UOP, we found that when AKI was due to pre-renal causes, decreased UOP was two-fold higher than normal UOP (67.0% vs. 33.0%) and this relationship was inverse for AKI due to intrinsic renal causes (31.0% vs. 69.0%). This difference was statistically significant ($p < 0.05$). Other clinical and laboratory features, according to their primary cause, are shown in Tables 4 and 5. In respect to hypertensive encephalopathy, if we consider only hypertensive children, its occurrence was 5.7%.

Creatinine and urea maximum serum values decreased to 29.7% and 32.9%, respectively, at discharge ($p < 0.05$). If we apply the AKIN criteria to creatinine values at discharge we found that among the 99 survivors, 59 (59.6%) were not classifiable, 15 (15.2%) were on stage 1, 15 (15.2%) were on stage 2 and 10 (10.1%) were on stage 3. Of these 10 children with AKIN stage 3, 5 were discharged to another hospital and 1 was already classified as having chronic renal disease at discharge.

Anemia was found in 122 children (89.1%), but in 54 cases (39.4%) there was another evident cause for its existence. In the 68 children with anemia possibly attributed to AKI (49.6%), the mean absolute value for hemoglobin concentration was 8.4 ± 2.0 g/dl. A mean relative hemoglobin value was calculated considering the relationship between the registered value and the minimum reference value for each age group and that value was $71.4 \pm 15.3\%$.

Table 4 – Clinical features of AKI patients considering their primary cause.

Clinical feature	Number evaluated	Total (N=137)	Pre-renal (N=88)	Intrinsic renal (N=42)	Post-renal (N=7)
Macroscopic hematuria No. (%)	137	29 (21.2%)	10 (7.3%)	19 (13.9%)	0 (0.0%)
Hypertension No. (%)	137	35 (25.5%)	8 (5.8%)	24 (17.5%)	3 (2.2%)
Edema No. (%)	137	92 (67.2%)	69 (50.4%)	20 (14.6%)	3 (2.2%)
Hypertensive encephalopathy No. (%)	137	2 (1.5%)	0 (0.0%)	2 (1.5%)	0 (0.0%)

Table 5 – Laboratory features of AKI patients considering their primary cause.

	Number evaluated	Total	Pre-renal	Intrinsic renal	Post-renal
SERUM PARAMETERS					
Maximum creatinine (mg/dl) Mean ± SD	137	2.5 ± 1.5	2.3 ± 1.2	2.5 ± 1.9	3.8 ± 1.9
Creatinine at discharge (mg/dl) Mean ± SD	98	0.7 ± 0.5	0.7 ± 0.6	0.8 ± 0.3	0.8 ± 0.4
Maximum urea (mg/dl) Mean ± SD	137	124.8 ± 73.5	118.6 ± 76.8	138.6 ± 68.4	120.1 ± 53.8
Urea at discharge (mg/dl) Mean ± SD	98	41.1 ± 33.4	35.2 ± 29.5	51.4 ± 37.8	24.0 ± 11.2
Anemia with possible relation to AKI No. (%)	137	68 (49.6%)	30 (21.9%)	33 (23.4%)	6 (4.4%)
Hyperkalemia No. (%)	137	66 (48.2%)	47 (34.3%)	15 (10.9%)	4 (2.9%)
Hyperuricemia No. (%)	63	46 (73.0%)	22 (34.9%)	20 (31.8%)	4 (6.3%)
Metabolic acidosis No. (%)	120	62 (51.7%)	48 (40.0%)	10 (8.3%)	4 (3.3%)
URINE PARAMETERS					
Proteinuria – No. (%)	119				
No proteinuria		5 (4.2%)	4 (3.4%)	1 (0.8%)	0 (0.0%)
Nephrotic		55 (46.2%)	24 (20.2%)	29 (24.4%)	2 (1.7%)
Non-nephrotic		59 (49.6%)	44 (37.0%)	11 (9.2%)	4 (3.4%)
Maximum proteinuria (mg/dl) Mean ± SD	119	1125.4 ± 8584.6	1638.7 ± 11030.8	372.7 ± 458.9	110.5 ± 48.5
Microscopic hematuria No. (%)	122	47 (38.5%)	31 (25.4%)	11 (9.0%)	5 (4.1%)

Renal ultrasound and biopsy

Renal ultrasound was performed in 60.9% of children. There were no detectable changes on 35.7% and the most common finding was increased kidney echogenicity occurring in 58.3% of exams. Other changes included decreased corticomedullary differentiation in 7.1%, pyelocaliceal dilation in 6.0%, hydronephrosis/ hydroureter in 6.0% and increased kidney size in 1.2% of exams.

Renal biopsy was performed in only 12 children (8.7%) and pathological diagnosis revealed: IgA nephropathy in 5 cases, rapidly progressive glomerulonephritis in other 4 cases interstitial nephritis in 2 cases and finally class IV lupus nephritis in 1 case.

Treatment modality

Conservative treatment was the choice in 70.1% of children and renal replacement treatment (RRT) was needed for 26.3%. In 3.6% of cases there was need for surgical treatment. In respect to RRT, 12.4% required peritoneal dialysis (PD), 8.8% hemodiafiltration (HDF), and 5.1% were treated by a combination of PD and HDF.

The percentage of need for RRT during AKI episode by age group was 26.9%, 29.0%, 25.0% and 14.3% for infants, preschool, school and adolescents, respectively, and the difference was not statistically significant ($p>0.05$). In the infants group, 55.6% of children who needed RRT performed PD, and 27.8% received HDF, while 16.7% needed PD + HDF. For the preschool age group, these values were 55.6%, 11.1%, and 33.3%. The preferred modality in school age children was HDF, which was used in 62.5% of cases, while PD and PD+HDF were used in 25.0% and 12.5%, respectively. Only one adolescent needed RRT and HDF was the choice in that case.

Considering the primary cause of AKI, we found that conservative treatment and RRT were the choices in 44.5% and 19.7% of children with pre-renal causes, 24.0% and 6.6% of

children with intrinsic renal causes and 1.5% and 0.0% of children with post-renal causes, respectively ($p>0.05$). Surgery was used only in children with AKI due to post-renal causes. On the other hand, when AKIN classification was taken into account we found that 97.2% were at stage 3, 2.8% at stage 2 and none was at stage 1. Moreover, 32.7% of children at AKIN stage 3 needed RRT.

The percentage of need for RRT was 20.4% and 41.0% on the survivors and non-survivors group, respectively, and this difference was statistically different ($p<0.05$). On the survivors group, the average length of RRT was 10.7 ± 10.5 days, ranging from 1 to 48 days.

Considering all the children receiving RRT, there were no registered complications in 86.1% of cases. Complications corresponded to catheter obstruction in 11.1% and filters coagulation in 2.8% of children receiving RRT. On time of discharge only 1 child (2.8%) was dependent on RRT.

Outcomes

At the time of discharge, children were evaluated for the presence of abnormal urinalysis, including proteinuria and hematuria, elevated SCr or hypertension (Table 6). No abnormality was found in 22.6% of cases and these children were considered as having complete recovery. Proteinuria was present in 38.0% of children and hematuria was found in 16.8%, being macroscopic in 5.1%. In many cases, more than one abnormality was found in the same child: hematuria and proteinuria occurred in 15.3%, hypertension associated with abnormal urinalysis was present in 5.1% and elevated SCr with abnormal urinalysis was found in 6.6% of children. Considering only the survivors group, 68% of patients were discharged from hospital with renal impairment.

Differences were observed when the primary cause of AKI was considered. When AKI was due to pre-renal disease, 28.4% had complete recovery at discharge, 12.5% had

elevated SCr, 1.1% had hypertension and 20.5% had abnormal urinalysis. In the group of children having intrinsic renal disease these values were 9.5%, 9.5%, 16.7% and 81.0%, respectively. Finally, when AKI had a post-renal cause those values were 28.6%, 0.0%, 0.0% and 28.3%.

Twenty-three children (16.8%) were transferred to another hospital at discharge and this group presented statistically significant differences in respect to outcomes profile as compared with the non transferred children group. In the transferred group there was complete recovery, elevated SCr, hypertension and abnormal urinalysis in 43.5%, 43.5%, 0.0% and 39.1%, respectively, and these values were 28.0%, 6.7%, 10.7% and 60.0%, respectively, in the non transferred group.

Outcomes after 1 month, 3 months, 1 year and 3 years are shown on Table 6. Follow-up was not possible for 34.7% of children after 1 month, which increased to 43.3%, 46.8% and 57.0% after 3 months, 1 year and 3 years, respectively. The development of chronic kidney disease (CKD) 1 year after the AKI episode occurred in 8 children, corresponding to 5.1% of all children included in this study. After 3 years, 1 more child had CKD, totalizing 9 (6.6%), and 2 of these children (1.5%) progressed to end-stage renal disease. The primary cause of AKI was pre-renal in 25%, intrinsic renal in 50% and post-renal in 25%. The cases of end-stage renal disease were associated with intrinsic renal cause for AKI.

As mentioned previously, 39 children (28.5%) died during hospitalization and in all cases there was an underlying pre-renal cause for AKI which was also the cause of death, except in one case associated to intrinsic renal disease. Deaths occurring 1 and 3 months after AKI episode (Table 6) were correlated with previous pre-renal causes for AKI and were a consequence of the underlying disease. There was only one death occurring one year after the AKI episode, which was associated with an intrinsic renal cause for AKI in a child undergoing chemotherapy. No further deaths were observed. By associating deaths with the

treatment modality, we found that 61.4% occurred in children submitted to conservative treatment and 38.6% in patients where RRT were performed. Considering the percentage of deaths in children submitted to each type of treatment, the mortality rate was 28.1% and 47.2% for children submitted to conservative treatment and RRT, respectively, but this difference was not statistically significant. No deaths occurred on children undergoing surgical treatment during the 3-year follow-up.

Children were classified during hospitalization as AKIN stage 3 in 93.2% of deaths, 87.5% of CKD and 100.0% of end-stage renal disease cases occurring during the 3-year follow-up period. The prevalence of these outcomes on children classified as AKIN stage 3 was 34.6%, 6.5% and 1.9%, respectively.

Table 6 – Outcomes of AKI at discharge and after 1 month, 3 months, 1 year and 3 years.

N.A. – Not applicable.

	At discharge	After 1 month	After 3 months	After 1 year	After 3 years
Total number evaluated	137	98	97	94	93
No follow-up	N.A.	34 (34.7%)	42 (43.3%)	44 (46.8%)	53 (57.0%)
Still hospitalized	N.A.	26 (26.5%)	4 (4.1%)	0 (0.0%)	0 (0.0%)
Complete renal recovery	31 (22.6%)	18 (18.4%)	25 (25.8%)	29 (30.9%)	20 (21.5%)
Abnormal urinalysis	54 (39.4%)	21 (21.4%)	18 (18.6%)	11 (11.7%)	11 (11.8%)
Elevated SCr	15 (11.6%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	8 (5.8%)	3 (3.1%)	2 (2.1%)	2 (2.1%)	0 (0.0%)
Chronic kidney disease	1 (0.7%)	N.A.	6 (6.2%)	8 (8.5%)	7 (7.5%)
nd-stage renal disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Death	39 (28.5%)	1 (1.0%)	3 (3.2%)	1 (1.1%)	0 (0.0%)

DISCUSSION

Many of the previous single center published studies on AKI in children are restricted to specific criteria, such as age (only neonates or do not include this age group) or type of care units (ICUs or Nephrology departments). Our study was conducted on a tertiary care hospital, a referral center for many etiologies, able to treat all patients, including neonates, requiring intensive care or renal replacement services. For this reason, no restrictions to inclusion criteria were made. However, as this study was conducted in a single center, its extension to whole population is limited. Moreover, almost 71% of the patients included in this study were referred from other health services, which could cause a bias, since those corresponded to more severe cases. This is in agreement with our high need for ICU admission (77%).

Our study population had slightly higher male children prevalence, which is similar to other studies in developed countries ^{6,9,13,14}

Almost half of our study population was less than one year of age and 28% were newborns. AKI incidence in critically ill neonates as been estimated to be between 8% and 24% ¹¹. Several features make newborns more vulnerable to AKI in the first days of life as their kidneys are more susceptible to hypoperfusion and have low glomerular filtration rate, high renal vascular resistance, high plasma rennin activity, decreased intercortical perfusion, and decreased reabsorption of sodium in the proximal tubules ¹.

In our study, AKI mainly occurred as a complication of other underlying systemic illnesses. These findings are in agreement with the most recent publications supporting that pattern of disease is changing from primary renal disease to secondary involvement due to systemic illnesses ¹⁰. The distribution of pre-renal, intrinsic renal and post-renal causes on AKI has been estimated to be 60%, 35% and 5% ¹⁵, which is similar to our results (64%, 31% and 5%). Urine sodium values or fractional excretion of sodium are often used to distinguish pre-renal injury from acute tubular necrosis in hypoxic-ischemic insults ¹⁶, however, as our

study was retrospective, we did not have access to those measurements in many patients, so we considered the cause in origin for AKI. Therefore, pre-renal disease may have been overestimated.

The major causes of AKI were sepsis/ septic shock, followed by heart failure/cardiogenic shock, acute/ rapidly progressive glomerulonephritis, hypoxic-ischemic encephalopathy and HUS. This is agreement with other studies from European countries in which sepsis, acute glomerulonephritis and HUS were the commonest causes of AKI ^{14,17}.

Applying AKIN classification to our study population showed us that the great majority of children were diagnosed at AKIN stage 3 (78%). In a retrospective study, Ozçakar *et al.* obtained a patient's distribution using this system classification of 25% in stage 1, 36% in stage 2 and 39% in stage 3 ⁶. We recognize here a limitation of our study, because its retrospective nature relies on diagnoses that were not based on this classification system. For this reason, we hypothesize that many cases classifiable as AKIN 1 and 2 were not included in our study because they were not considered by clinicians as an AKI and were not codified on ICD-9-CM. To clarify the relationship between AKIN stage and prognosis, a prospective study should be planned to better control small increases in creatinine levels and therefore diagnose AKI at early stages. It has been suggested that implementation of a score system in every ICU admission may provide clinicians with an additional instrument to develop preventive and early therapeutic interventions in critically ill children at risk of AKI ¹⁸.

Although serum creatinine is used as a primary biomarker for AKI in clinical practice, it is accepted that this is an insensitive and delayed measure of decreased kidney function following AKI, which limits its value as diagnostic tool for early intervention. Novel early biomarkers of AKI may allow for detection prior to changes in serum creatinine but their clinical use is still experimental ^{2,16}. Currently, the most promising early non-invasive biomarkers of AKI are serum and urinary neutrophil gelatinase-associated lipocalin (NGAL),

urinary interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver type fatty acid binding protein (L-FABP), and serum cystatin C ¹⁹.

An important function of sonographic imaging in pediatric renal injury is to exclude previously undiagnosed chronic renal conditions, such as congenital hypoplasia/dysplasia, cystic disease, or urinary tract dilation ²⁰. Gheissari *et al.* found increased kidney echogenicity the most common ultrasound finding (48%) in a retrospective study including 180 children diagnosed with AKI, which is agreement with our study ²¹.

RRT was needed in 26% of our children and there was no significant influence of age or primary cause of AKI, but AKIN stage had a positive association. This withstands the importance of using a classification system in clinical practice in order to anticipate the diagnosis and prevent complications. Besides, it has been shown that support with RRT should be done early to improve patient survival ²² and applying AKI classification criteria for patient evaluation could help on early recognition of RRT need ⁶. The decision about dialysis modality is based on patient's age, local expertise, resources available, and the patient's clinical status ²³. The preferred modality on infants is peritoneal dialysis, while hemodiafiltration is preferred on older children and this tendency was observed in our study.

Previously published mortality rates in children suffering AKI vary widely from 8 to 89%, depending on country, centre and criteria defining AKI ^{14,24}. In our study, it was 29% during hospitalization and it was mostly due to pre-renal causes except in one case. Also, there was a positive association with the relative ICU length of stay in comparison with total hospitalization time. Therefore, mortality was primarily determined by extrarenal underlying disease and the associated hemodynamic instability. This is in agreement with previous studies that found a more favorable prognosis when AKI is caused by a primary renal disease with no systemic involvement ²⁵. AKI is considered an instigator and multiplier of pulmonary, cardiac, hepatic, and neurologic dysfunction, which likely accounts for the vicious cycle of

AKI and multi-organ failure leading to mortality²⁶. Although the need for RRT has been presented as an independent factor for death²⁷, we found no relationship between mortality rate and need for RRT.

Our study confirmed that children with primary renal diseases were very likely to have abnormalities at discharge. Children with pre-renal causes of AKI previously considered to be reversible also showed evidence of renal dysfunction at discharge, although in less degree. It has previously been thought that patients who have an episode of AKI secondary to other processes, such as ischemic damage, suffer few renal consequences in the long term²⁴. Any episode of AKI, regardless of etiology has the potential to result in short-term abnormalities and thus may predict a degree of future risk. In a meta-analysis including 10 cohort studies reporting long-term outcomes in children after AKI, it was concluded that AKI is associated with a high risk of long-term renal outcomes²⁸. This highlights the need for periodic assessment of renal function in those who survive episodes of AKI to check for the development or persistence of renal abnormalities²⁴. In our study, 68% of surviving patients were discharged from hospital with renal impairment, however follow-up was not achieved for nearly 1/3 of children after 1 month, which increased to more than half after 3 years. This can be partially explained by our high referral rate at admission (72%), which means that some children may have been followed-up elsewhere.

AKI may be a significant risk factor for early childhood CKD development, incurring higher risk for negative health outcomes, including cardiovascular disease²⁹. AKI severity has been correlated with progression to CKD. In a prospective cohort study, 126 children admitted to a pediatric ICU were followed for up to three years after AKI episode and 10% developed CKD. The prevalence had a direct correlation with AKI severity, as defined by AKIN criteria, affecting 17% of patients with AKIN stage 3⁸. In our study, almost all the children who developed CKD and ESRD were classified at stage 3 of AKIN classification

system during hospitalization and the prevalence of CKD in children with AKIN stage 3 was 6.5%.

Moreover, two periods of five years, 2002-2006 and 2007-2011, were established for comparison. There were no significant differences in respect to distribution of primary causes, AKIN classification and mortality rate between the two periods. Although differences have been pointed out along time by others authors^{10,14}, these differences were described before our time span and probably in the last decade the improvement in medical support as not been so evident as before.

In the future, we aim to diagnose AKI at earlier stages, in order to improve outcomes. A classification system, either AKIN or pRIFLE, should be applied as a prognostic tool to evaluate at-risk patients. Moreover, the introduction of new biomarkers in clinical practice may be the next step in achieving this goal.

CONCLUSIONS

AKI in Portuguese children occurred mainly as a complication of other systemic illnesses and nearly two thirds needed to be treated in the intensive care unit. Extrarenal underlying cause for AKI was an important risk factor for mortality. The great majority of children were already in stage 3 of AKIN classification system and this staging level had a positive association with the need for RRT, evolution to CKD and mortality. The implementation of an AKI classification system on clinical practice is advised in order to evaluate at-risk patients and improve long-term outcomes.

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