REGULAR ARTICLE

The incidence and aetiology of acute kidney injury in children in Norway between 1999 and 2008

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ABSTRACT

Aim: Primary acute kidney injury (AKI) is a direct cause of hospitalisation in children, but can also result from other conditions. There is limited information on the epidemiology of this condition. Our aim was to describe the national incidence rate and aetiology of acute kidney injury in children under the age of 16 in Norway from 1999 to 2008.

Methods: We carried out a retrospective study of medical records provided by all 18 of the paediatric hospital departments that specialise in treating paediatric patients with AKI.

Results: We identified 315 cases of AKI (53% male), with an estimated average annual incidence rate of 3.3 cases per 100 000 children and a median annual occurrence of 33 cases. Most cases (43%) were in children under five. We identified 53 aetiologies and classified these into 30 aetiological groups: 24% of the cases were prerenal (n = 75), 74% were intrinsic/renal (n = 234) and 2% were postrenal (n = 5). Nephritic syndromes was the major cause (44%) of AKI, followed by haemolytic-uraemic syndrome (HUS) (15%).

Conclusion: Nephritic syndromes and HUS are the most common aetiologies of AKI in Norway. Although our results could indicate a low incidence of paediatric AKI in Norway, the lack of other national studies makes comparisons difficult.

BACKGROUND

Acute kidney injury (AKI), previously referred to as acute renal failure, is defined as a sudden decline in kidney function, with falling glomerular filtration rate and the inability to regulate the acid, electrolyte balance and to excrete waste and fluid (1). It is an important contributor to mortality and morbidity in paediatric patients with critical illnesses and may also be associated with mortality in mild cases of kidney failure (2). AKI can be divided into three categories, prerenal, intrinsic/renal and postrenal, depending on the pathophysiological mechanism leading to the decline in function. Some cases are difficult to categorise, due to the complex nature of different underlying conditions.

The main causes of AKI in Africa and Asia are of prerenal origin, due to dehydration, which is often caused by gastroenteritis and infections. However, with improving living conditions, the pattern is also changing in these countries (3–6). In Europe, the most common cause of AKI is haemolytic-uraemic syndrome (HUS), a clinical syndrome characterised by the triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute oliguric or anuric renal failure, often characterised as either diarrhoea-associated or non-diarrhoea-associated, also called atypical, HUS (7). Outbreaks of HUS, particularly the large Northern European outbreak originating in Germany in 2011 (8), and a national outbreak in Norway in 2006 (9,10), have increased public awareness of the condition in recent years.

To our knowledge, no national reports or nationwide studies are available on the incidence of AKI, as they are usually performed at specific centres or regions, based on limited surveillance networks and registries and focusing on the incidence in hospital populations (11,12). There is an

Abbreviations
AKI, acute kidney injury; HUS, haemolytic-uraemic syndrome.

Key notes

- This study examined the national incidence rate and aetiology of paediatric acute kidney injury (AKI), with data from all 18 Norwegian paediatric hospital departments that provide specialist AKI treatment.
- Most cases (43%) were in children under five, and the major causes were nephritic syndromes (44%) and haemolytic-uraemic syndrome (15%).
- The incidence rate seemed low, at 3.3 cases per 100 000, but the lack of other national studies make comparisons difficult.

increasing interest in national registries on different diagnoses, but so far, no national registries on AKI in children exist, in contrast to registries on dialysis and transplantation. National data on AKI does not exist in Norway, but it was possible to collect data on a national basis, as the country has five million inhabitants and only a limited number of hospitals treat children with AKI.

We recognise the need to describe the importance and burden of AKI in a national context, as it plays a key role in the mortality and morbidity in paediatric patients and such data are not currently available. The incidence of HUS is relatively low in Norway (13), despite being recognised as the most common cause of AKI in Europe. We wanted to compare the incidence of AKI to other countries to see whether Norway's rate was, in fact, lower than other countries or whether the incidence rates reflected that HUS is a less important contributor to AKI in Norway. Therefore, the aim of this study was to estimate the incidence of AKI in children in Norway and describe the epidemiology. We also wanted to determine the distribution of different aetiologies of the condition.

METHODS

This was a retrospective, descriptive study, based on data from patient medical records. Potential cases were identified by searching the medical record archives at the Norwegian paediatric departments that specialise in treating children with AKI. We gathered data directly from 18 of the country's 24 paediatric departments, having confirmed that the remaining six used these centres as secondary or tertiary hospitals and referred children with AKI to them.

Search criteria were ICD-10 codes N17 (AKI), D59.3 (HUS), N00 (acute nephritic syndrome), N01 (rapidly progressive nephritic syndrome) and N05 (unspecified nephritic syndrome).

We included children who were under the age of 16 years when they were first admitted to a Norwegian hospital between 1 January 1999 and 31 December 2008. AKI cases were defined as: (i) a primary or secondary initial diagnose of acute kidney injury (ICD-10: N17) and/or haemolytic-uraemic syndrome (ICD-10: D59.3), and/or acute nephritic syndrome / rapidly progressive nephritic syndrome / unspecified nephritic syndrome (ICD-10: N00/N01/N05) plus (ii) a confirmed history with a serum creatinine increase of >35 μmol/L if the patients were under the age of one or >80 μmol/L if they were aged 1–15 years.

A HUS case was defined as a case with a clinical picture that included all of the following: (i) thrombocytopenia, with a low platelet count (<150 × 10^9/L), (ii) anaemia (Hgb <10.5 g/dL) of haemolytic origin, with increased serum lactate dehydrogenase (>500 U/L) and (iii) acutely reduced renal function, with serum creatinine of >35 μmol/L if the patient was under the age of one or >80 μmol/L if the patient was 1–15 years. To be included, the patients also had to have either: (i) a reported presence of fragmented red blood cells (schistocytes) on peripheral blood smear, a sign of microangiopathic

changes consistent with haemolysis and an important part of HUS pathophysiology (14), or if peripheral blood smear was missing from their records, a probable clinical diagnosis of HUS confirmed by consulting a clinician with expertise in paediatric nephrology.

In cases with multiple admittances and/or, occurrences of AKI, only the initial episode was included. Exclusion criteria were AKI related to birth asphyxia or acute post-kidney-transplantation graft failure.

Statistical analysis

Calculations were performed using Microsoft Excel. Descriptive statistics are presented as proportions, median and annual average values with ranges and as incidence rates calculated using population numbers provided by official Statistics Norway registries.

Ethical considerations

This study was approved by the Regional Ethical Committee South East A. The Norwegian Ministry of Health granted us exemption from patient confidentiality regulations requiring informed consent to access patient medical records.

RESULTS

During the 1999 to 2008 study period, we identified 315 cases of AKI in children in Norway under the age of 16. Of these, 167 (53%) were male (Fig. 1). The estimated average annual AKI incidence rate was 3.3 cases per 100 000 children, ranging from 1.8 in the lowest year to 5.2 in the highest year. The median annual occurrence of AKI was 33 cases. The highest occurrence was in 2006, with 50 cases (16% of the total study) and the lowest was in 2000, with 17 (5%) cases (Fig. 2).

The median age at occurrence was 6 years for both male and female patients, with a range of zero to 15 years. The age-related distribution by gender can be seen in Fig. 1.
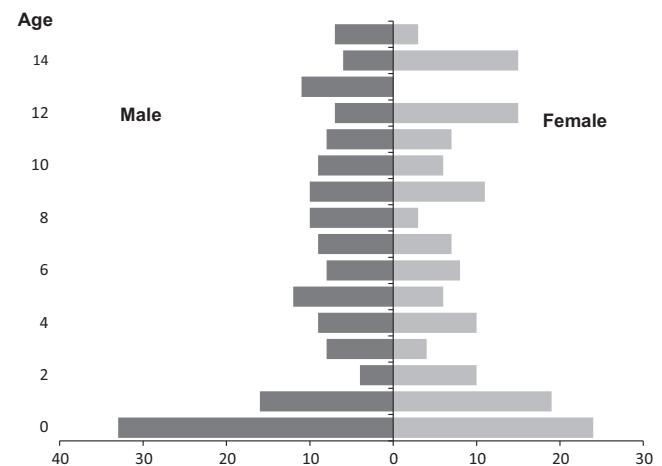
Figure 1 Distribution of cases of acute kidney injury by age and gender in children under 16 years of age in Norway, 1999–2008 (N = 315).
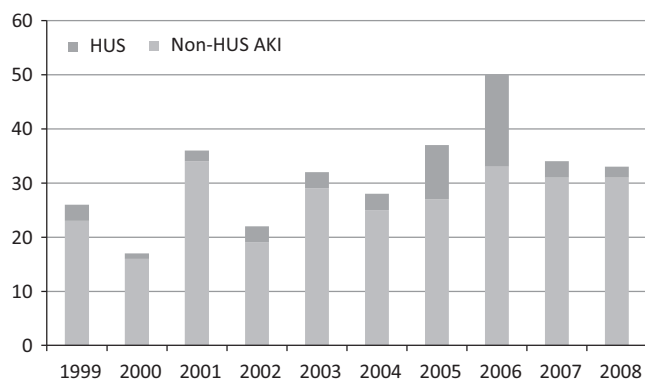
Figure 2 Yearly occurrence of acute kidney injury (AKI) and share of cases caused by haemolytic-uraemic syndrome (HUS) in children under 16 years of age in Norway, 1999–2008 (N = 315).

The highest percentage of cases was found in patients under the age of five (43%), and this age group had an estimated average annual incidence rate of 4.7 cases per 100 000 children, ranging from 1.7 to 6.9 (Table 1).

When we divided the cases into probable pathophysiological causes of kidney failure, the 315 AKI cases were distributed as follows: 24% prerenal (n = 75), 74% intrinsic/renal (n = 234) and 2% postrenal (n = 5). One case had an unknown cause.

A total of 53 different aetiologies were identified and classified into 30 different aetiological groups (Table 2), with nephritic syndromes accounting for 138 (44%) cases. It is notable that 71 of these nephritis syndrome cases occurred in patients who did not have an ICD-10 AKI diagnosis, just an episode of marked serum creatinine increase.

A further 47 (15%) AKI cases were related to haemolytic-uraemic syndrome (HUS). Of these, 9 (3%) were atypical, 38 (12%) were associated to diarrhoea. Only 24 (51%) of the HUS cases had an ICD-10 AKI diagnosis code registered in their medical record. There was a link between HUS cases and the year with the highest occurrence of AKI (Fig. 2).

Apart from HUS and nephritic syndromes, the most frequent causes identified were the 24 (8%) cases with prerenal causes in relation to septicaemia and the 23 (7%)

Table 1 Age-related occurrence, percentage and incidence rate of acute kidney injury in children in Norway, 1999–2008 (N = 315)

Measures			Average annual incidence rate per 100 000
Age group	Cases	Percentage of total, %	children (range)
0–4 years	137	43	4.7 (1.7–6.9)
5–9 years	84	27	2.7 (1.6–5.6)
10–15 years	94	30	2.6 (2.0–3.7)
Total	315	100	3.3 (1.8–5.2)

cases of dehydration that were specified as the cause in the medical record but were either related or not related to other conditions. Table 2 presents an overview of identified aetiologies.

DISCUSSION

We identified 315 cases of AKI in children during the period 1999–2008, with an estimated overall average annual incidence rate of 3.3 cases per 100 000 children. The highest incidence was found in patients under the age of five, with 137 (43%) cases and an estimated average annual incidence rate of 4.7. The year with the highest occurrence of AKI occurred in 2006 and coincided with the highest HUS occurrence (Fig. 2) (13), related to the Norwegian outbreak (9,10). We also found that the most common type of AKI was of an intrinsic/renal nature most commonly related to nephritic syndromes, followed by HUS.

In our study, we present data from patients from all 18 Norwegian hospitals capable of managing AKI. This is, to our knowledge, the first national study on the epidemiological aspects and aetiology of AKI in children in Europe. Most published studies are confined to intensive care units, tertiary centres or specific regions of a country (11,12,15). In our opinion, describing the epidemiological aspects of this serious condition makes an important contribution to evaluating the national relevance and burden of AKI.

The lack of similar national studies makes it difficult to compare our findings with other countries and state whether our incidence is high or low. However, the annual incidence rate and occurrence of cases seemed to slowly increase during the ten-year study period (Fig. 2) and this trend might reflect the suggestion in certain published papers that paediatric AKI is increasing (1). We should point out that this finding should not be considered conclusive, as we did not carry out a statistical analysis to confirm a significant increase adjusted for potential population growth. A relatively stable, yet generally increasing number of cases can be seen, with the exception of 2006, when there was a national outbreak of *Escherichia coli* O103:H25 and nine children developed HUS (9,10).

Nearly half of the cases in our study were under the age of five, and this may reflect the fact that small children are more vulnerable to gastroenteritis and other infections and more likely to suffer from dehydration and volume depletion.

With regard to the aetiological findings, nephritic syndromes was a notable and very comprehensive aetiological group and provided the most common cause of AKI, which agrees with some studies (11,12,16), and contradicts others (15,17). Of the 138 cases in this group, 71 did not have an ICD-10 code that specified the occurrence of AKI. However, 67 (21% of all AKI) cases were specified as AKI. It is therefore justifiable to consider that this was the most common cause of AKI in children in Norway.

Table 2 Distribution of aetiologies in number and percentage of cases in acute kidney injury in children in Norway, 1999–2008 (n = 315)

Prerenal			Renal			Postrenal		
Aetiological group	N	%	Aetiological group	N	%	Aetiological group	N	%
Sepsis	24	7.6	Nephritic syndromes	138	43.8	Congenital anomalies of the kidney and urinary tract	3	1.0
Dehydration	23	7.3	Haemolytic-uraemic syndrome	47	14.9	Vesicoureteral reflux	1	0.3
Cardiological aetiologies	11	3.5	Oncological	16	5.1	Pelvic tumour	1	0.3
Medical/surgical complications	5	1.6	Drug related	8	2.5			
Systemic shock	2	0.6	Congenital anomalies of the kidney and urinary tract	7	2.2			
Drowning (multiple organ failure)	2	0.6	Genetic disorders	5	1.6			
Meningitis	2	0.6	Rhabdomyolysis	5	1.6			
Acute on chronic	1	0.3	Nephropathia epidemica	2	0.6			
Appendicitis	1	0.3	Unknown renal	2	0.6			
Encephalitis	1	0.3	Severe combined immunodeficiency	1	0.3			
Hypophyseal defect	1	0.3	Intoxication	1	0.3			
Diabetes complications	1	0.3	Wegeners granulomatosis	1	0.3			
Respiratory failure	1	0.3	Cerebral palsy complications	1	0.3			
Total prerenal	75	23.8	Total renal	234	74.2	Total postrenal	5	1.6
Unknown	1	0.3						

Discovering that HUS and septicaemia leading to prerenal AKI were two of the most common causes of AKI was not unexpected and is in line with the findings of studies from other countries with comparable conditions, notably other European countries (11,12,16).

Most larger studies that compare the incidence and aetiology in a population are based on single centres and/or hospitals and are often based on children who need renal replacement. However, our study describes a national distribution of aetiologies and is based on the presence of AKI regardless of required therapeutic measurements. This means that our research covers a wider geographic and aetiological area than existing studies.

One of the advantages of carrying out a national study of AKI incidence based on medical records was the possibility of identifying all cases admitted during the study period. Another possible data source would have been the National Patient Register, but this did not contain identifiable data by patient before 2008 and we would have been limited to the number of consultations and not the number of patients diagnosed. This issue was avoided by systematically gathering data from all Norwegian hospitals capable of treating children with AKI.

There are certain limitations to this study. First, our data were retrospectively collected from medical records and, in many cases, it was difficult to identify an aetiology because complicated medical conditions meant that there were many possible factors that could have led to renal insufficiency. This meant that we had to assume that the

clinician in charge of the patient had identified the main cause of the AKI. One of the prime examples of this was the aetiological group called hypovolaemia, which in theory can cause renal insufficiency as a complication of a wide range of medical conditions. We had to separate cases caused primarily by fluid loss and/or low fluid intake from those caused by pathophysiological changes from an underlying condition that in itself caused the hypovolaemic state.

Another limitation was that the number of AKI cases was probably underestimated. Only 51% of HUS cases had an ICD-10 code for AKI (N17) in their medical records, which suggests that the diagnosis code is often left out of medical records where AKI is part of a more prominent and/or severe clinical diagnosis or where it is included in a clinical syndrome with a separate ICD-10 code. As we had to limit our search to the usual ICD-10 codes for AKI, some of these cases would not have been picked up by our search criteria and would not have been included in our study.

The underestimation of AKI cases was partly reduced by including nephritic syndrome cases with marked serum creatinine increase, without the N17 diagnosis code. Although a few of these cases had miscoded ICD-10 diagnoses and were originally meant to be registered as AKI, most of them did not have sufficiently grave renal insufficiency at the time of admission. They were included in our study as they matched our inclusion criteria. However, it must be noted that the decision to include nephritic syndrome was made after we determined which of

the hospitals should be approached for direct data. There-fore, these cases were identified in the 18 hospitals where direct data were collected for this study. Although it is highly unlikely, it is possible that there were missing nephritic syndrome cases, potentially matching our inclusion criteria, in the other six hospitals with paediatric departments who referred their patients to the 18 hospitals involved in the study. Another potential problem with including the nephritic syndrome cases was that it could have overestimated the role that nephritic syndrome plays in the aetiology of AKI. However, there were two subgroups of nephritic syndrome cases that we included in our study: one in which AKI was diagnosed and the cases were tagged with an appropriate AKI ICD-10 code and another where the cases had experienced a clear rise in serum creatinine above reference values, including some that were directly described as AKI in the medical records, but were not tagged as AKI. While this may have led to the total number of nephritic syndrome cases being high, or overestimated, they are still clearly the largest group and thus the most common cause of AKI in children in Norway.

Some studies have reported that the major cause of AKI is prerenal (18), but our retrospective study revealed that most cases were renal. This could be because temporary rises in creatinine in children without septicaemia and dehydration/hypovolaemia, who do not need dialysis, are not reported, even if measures such as fluid resuscitation were performed. In addition, dehydration as a result of gastroenteritis is not a common cause of AKI in Norway.

Our decision about how to define kidney injury was based on a pilot project where data were collected to adjust the included parameters. This was performed as difficulties with collecting data on a retrospective method were probable. The pRIFLE criteria were introduced in 2004, to measure paediatric risk, injury, failure, loss and end-stage renal disease, and are based on both creatinine levels and urinary output. They define the risk of kidney injury as a 25% decrease of estimated creatinine clearance, injury as a 50% decrease and failure as a 75% decrease (19). However, our pilot project revealed obtaining data on urinary output was difficult, as they were often absent or incomplete. Thus, a creatinine level of 35 in children below 1 year of age would not overestimate the condition and a level of 80 after 1 year of age would include all.

CONCLUSION

This study estimated the incidence of acute kidney injury (AKI) in children in Norway and determined the distribution of the aetiologies involved in the development of the condition. Our study has some obvious limitations, particularly due to the retrospective design of the study, resulting in a probable underestimation of the number of AKI cases. In the future, the focus needs to be on better registration of children with AKI. The pRIFLE criteria have now been implemented and provide a standard for all paediatric departments, which should lead to better diagnosis and improved possibilities for long-term follow-up. Prospective studies are needed to provide accurate data and evaluate the outcome of AKI. HUS is considered to be the most common cause of AKI in Europe, but this was not the case in our study. Although HUS did constitute a large proportion of our cases, nephritic syndrome was the most common cause of AKI in Norway.

Throughout this study, we were also able to assess the limitations involved in this type of national epidemiological study. We hope that our observations may prove useful in future studies with similar designs and aims.

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