UNIVERSITY OF LIVERPOOL

DRUG-INDUCED ACUTE KIDNEY INJURY IN CHILDREN

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy by

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Abstract

Background

Acute Kidney Injury (AKI) is common in adults and children and has a range of aetiologies. AKI is associated with patient outcomes including mortality, length of hospital stay, and chronic kidney disease. Mitigation of AKI has been shown to improve these outcomes. Nephrotoxic medication-associated AKI (NTMx-AKI) is reported to be a common, but potentially preventable cause of AKI in children. Research to date has described associations with nephrotoxin exposure and outcomes including length of stay and mortality.

Methods

This thesis involved a systematic review of the epidemiology of NTMx- AKI in children, followed by an audit of data at Alder Hey Children's Hospital (AHCH), to describe nephrotoxin exposure and AKI in non-critically ill children at a specialist children's hospital in the United Kingdom (UK).

We conducted a systematic review to appraise the epidemiology of drug-induced AKI in children. Two reviewers searched three electronic databases (EMBASE, MEDLINE and CINAHL) from January 2000 until November 2020. Eligible studies for this review included in-hospital exposure to NTMx in children (0 to <18 years of age) treated as inpatients, and reported AKI as an outcome. Papers were categorised according to patient population, and homogenous papers were compared and included in meta-analysis where possible.

We conducted an audit of all non-critically ill inpatients over a one week period at a specialist paediatric hospital in the UK to identify the prevalence of AKI and NTMx-AKI, and to identify risk factors for AKI in this population. All non-critically ill inpatients who stayed for at least one night at a specialist paediatric hospital in the UK between 12th and 18th April 2021 were included in this study. Patients aged 0 to 18 years were included. Critically ill children were defined as those admitted to the intensive care unit, and were excluded. Data collected for each child included: demographics, specialty of admission, maximum number of nephrotoxins received on one day during the admission, and maximum AKI stage during admission (Kidney Disease: Improving Global Outcomes (KDIGO) definition). High

nephrotoxin exposed patients were defined as those receiving three or more nephrotoxins in any one day.

Results

21 papers were included in our systematic review, 12 of which were included in 3 separate meta-analyses by patient population. Results showed that in various paediatric populations, the risk of AKI is high, and higher in those exposed to nephrotoxic medications. Other risk factors were identified including but not limited to younger age (although in children with nephrotic syndrome, older age and longer disease duration was a risk factor), lower weight and nephrotoxin exposure. AKI was shown to impact patient's outcomes including increased length of stay, and higher rate of mortality.

314 non-critically ill inpatients were included in our audit which accounted for 1127 inpatient hospital days. Our findings showed that children with AKI were more likely to be admitted under cardiology or haematology and oncology, and were exposed to a higher number of nephrotoxins in a day of their admission than children without AKI. Significant differences were also seen when comparing nephrotoxin-exposed and non-exposed patients. Nephrotoxin-exposed patients were more likely to be admitted under cardiology or haematology and oncology, were more likely to be female, and were more likely to develop an AKI during an admission than their non-exposed counterparts.

Conclusion

This thesis has allowed us to combine current research and build on this with our audit. Our findings from this thesis demonstrate that the risk of AKI is high in at-risk patients (such as those exposed to nephrotoxins) and highlights the importance of earlier identification of these patients. We have described the positive impact that earlier identification, increased renal function monitoring, and reduction in nephrotoxin exposure can have on children's outcomes. It has also helped us identify areas with scope for further research, and begin to make recommendations for further work based on this.

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ACEI – Angiotensin Converting Enzyme Inhibitor

ADQI – Acute Dialysis Quality Initiative

AG – Aminoglycoside

AHCH – Alder Hey Children's Hospital

AKI – Acute Kidney Injury

ARB – Angiotensin Receptor Blocker

ARF – Acute Renal Failure

ARR – Adjusted Risk Ratio

ATN – Acute Tubular Necrosis

AWAKEN – Assessment of Worldwide Acute Kidney Injury in Neonates

BAPN – British Association of Paediatric Nephrology

BMI – Body Mass Index

CA-AKI – Community-Acquired Acute Kidney Injury

CG – Cockcroft-Gault

CHS – Congenital Heart Surgery

CI – Confidence Interval

CINAHL – Cumulative Index to Nursing and Allied Health Literature

CKD – Chronic Kidney Disease

CNI – Calcineurin Inhibitors

COVID-19 – Corona Virus Disease 19

CPB – Cardiopulmonary Bypass

CyA – Cyclosporin A

DOB – Date of Birth

eCCl – Estimated Creatinine Clearance

eGFR – Estimated Glomerular Filtration Rate

EMBASE – Excerpta Medica dataBASE

EMR – Electronic Medical Record

ESKD – End Stage Kidney Disease

ESRD – End Stage Renal Disease

FSGS – Focal Segmental Glomerulosclerosis

GFR – Glomerular Filtration Rate

HA-AKI – Hospital Acquired Acute Kidney Injury

HDAS – Healthcare Databases Advanced Search

HDU – High Dependency Unit

HER – Health Electronic Record

HR – Hazard Ratio

IBM SPSS – International Business Machines Statistical Package for the Social Sciences

ICU – Intensive Care Unit

IUGR – Intrauterine Growth Restriction

IV – Intravenous

JBI – Joanna Briggs Institute

KDIGO – Kidney Disease: Improving Global Outcomes

MDRD – Modification of Diet in Renal Disease

MEDLINE – Medical Literature Analysis and Retrieval System Online

MeSH – Medical Subject Headings

MI – Myocardial Infarction

MSAF – Meconium-Stained Amniotic Fluid

NCEPOD – National Confidential Enquiry into Patient Outcomes and Death

NE – Neonatal Encephalopathy

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NICU – Neonatal Intensive Care Unit

NINJA – Nephrotoxic Injury Negated by Just-in Time Action

NS – Nephrotic Syndrome

NSAID – Non-Steroidal Anti-Inflammatory Drug

NTMx – Nephrotoxic Medication

NTMx-AKI – Nephrotoxic Medication-Associated Acute Kidney Injury

OR – Odds Ratio

PCI – Percutaneous Coronary Intervention

PD – Peritoneal Dialysis

PICO – Population, Intervention, Comparator, Outcome

PICU – Paediatric Intensive Care Unit

PIGN – Post-infections Glomerulonephritis

pRIFLE – Paediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

PRISM – Paediatric Risk of Mortality

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

PTZ – Piperacillin-Tazobactam

QIP – Quality Improvement Project

QNS – Quantity Not Sufficient

RASi – Rein-Angiotensin System Inhibitor

RCPCH – Royal College of Paediatrics and Child Health

RIFLE – Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

RR – Risk Ratio

RRT – Renal Replacement Therapy

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

SCr – Serum Creatinine

SD – Standard Deviation

SDNS – Steroid-Dependent Nephrotic Syndrome

SE – Standard Error

JP-SHINE – Japanese Paediatric Survey Holding Information of Nephrotic Syndrome

SMX/TMP – Sulfamethoxazole; Trimethoprim

SRNS – Steroid-resistant Nephrotic Syndrome

SSNS – Steroid-sensitive Nephrotic Syndrome

UK – United Kingdom

UO – Urine Output

US/USA – United States of America

UTI – Urinary Tract Infection

VLBW – Very Low Birth Weight

Chapter 1 Introduction

1.1 Background

Acute Kidney Injury (AKI) is a common problem seen in both children and adults, across a range of specialities and patient populations, with many associated short and long-term sequalae. Diagnosis can prove challenging due to a lack of early symptoms, and clinical biomarkers taking time to rise after injury. Along with other factors discussed in this thesis, these difficulties contribute to the limitations seen in current literature. General recommendations for practice have been made based on available evidence, however it is recognised that these guidelines[1] are based upon the best available information. Experts have made these recommendations with the primary goal to improve patient care, and note that clinicians should take into account the needs of individual patients, resources and setting and evaluate the appropriateness to each patient[1].

1.1.1 Defining AKI

AKI is a sudden episode of kidney damage that happens within a short time period – typically within a few hours, or few days[2], reducing kidney function. The build-up of waste products as a result of AKI causes difficulty in fluid balance maintenance, and can lead to symptoms and signs such as reduced urine output, oedema and fatigue[2]. Several accepted definitions of AKI have been proposed, the most widely accepted being the Kidney Disease: Improving Global Outcomes (KDIGO) definition[1] which was proposed in 2012. We will review the progression to the KDIGO definition subsequently.

1.1.1.1 RIFLE

The Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification of AKI was published in 2004[3], and classifies AKI through the use of Glomerular Filtration Rate (GFR) and Urine Output (UO). Until the publication of the RIFLE criteria in 2004, there was no recognised criteria for defining and staging AKI. A patient can fulfil criteria for a stage by meeting either the GFR or the UO criteria (whichever leads to the worst (highest) classification should be used)[3]. This staging system was developed to consider important features including a change from baseline, definitions for acute on chronic kidney disease and consider both sensitivity and specificity[3], as seen in **table 1.1**.

Furthermore, two clinical outcomes (Loss and End-Stage Renal Disease (ESRD)) are included as well as the three tiers of renal dysfunction (Risk, Injury, and Failure). The purpose of this separation is to acknowledge adaptations that occur in ESRD that are not seen in persistent Acute Renal Failure (ARF)[3]. Persistent ARF (Loss) is defined as the need for Renal Replacement Therapy (RRT) for more than 4 weeks, whilst ESRD is the need for dialysis for more than 3 months[3].

The classification also defines two additional descriptions of the Failure stage. Firstly, the use of RIFLE-F_C to denote acute-on-chronic disease, and the use of RIFLE-F_O to denote meeting the Failure category due to oliguria.

Table 1.1: RIFLE criteria, adapted from Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group[3]

	GFR criteria	Urine output criteria	
Risk	Increased SCr x 1.5 OR GFR decrease >25%	<0.5ml/kg/h for 6 hours	High sensitivity
Injury	Increased SCr x 2 OR GFR decrease >50%	<0.5ml/kg/h for 12 hours	
Failure	Increased SCr x 3 OR GFR decrease 75% OR SCr ≥4mg/dl	<0.3ml/kg/h for 24 hours OR Anuric for ≥12 hours (Oliguria)	
Loss	Persistent ARF = complete loss of kidney function >4 weeks		High specificity
ESKD	End Stage Kidney Disease (>3 months)		

The RIFLE criteria (table 1) is designed to demonstrate high sensitivity at the lower categories. As a result, it will include some who do not actually have renal failure (and therefore specificity here is lower). Fewer patients will meet the higher categories (lower sensitivity), but these criteria are designed to be more specific in identifying patients with renal failure.

1.1.1.2 pRIFLE

The RIFLE criteria have been modified several times, the first in 2007 being an adaptation for use in children – the Paediatric RIFLE (pRIFLE) criteria[4]. pRIFLE classifies AKI using Estimated Creatinine Clearance (eCCl) and UO, and importantly considers patient's size (height) in the calculation for eCCl (using the Schwartz formula)[4]. This classification is displayed in **table 1.2**.

Table 1.2: Paediatric-modified RIFLE (pRIFLE) criteria, adapted from pRIFLE criteria seen in Modified RIFLE criteria in critically ill children with acute kidney injury[4]

	Estimated creatinine clearance (eCCl)	Urine output
Risk	eCCl decrease by 25%	<0.5ml/kg/h for 8 hours
Injury	eCCl decrease by 50%	<0.5ml/kg/h for 16 hours
Failure	eCCl decrease by 75% OR eCCl <35ml/min/1.73m^2	<0.3ml/kg/h for 24 hours OR Anuric for ≥12 hours
Loss	Persistent failure >4 weeks	
End stage	End-stage renal disease (persistent failure >3 months)	

1.1.1.3 AKIN

The AKI Network (AKIN) criteria[5], published in 2007, is another modification of the RIFLE criteria[3] and can be seen in **table 1.3**. The AKIN criteria expand diagnosis of AKI to include patients experiencing a ≥0.3-mg/dl increase in serum creatinine in a 48-hour period – a change in Serum Creatinine (SCr) that would not be captured by RIFLE (and therefore is presumed to be more sensitive).

This being said, several studies to date have compared the use of the AKIN criteria to the RIFLE criteria, assessing the relative sensitivity and specificity.

As recognised in the KDIGO guidelines, Joannidis et al[6] conducted a large-scale prospective multicentre cohort analysis in 2009, assessing changes in SCr and UO for both AKIN and RIFLE during the initial 48 hours of adults admitted to the Intensive Care Unit (ICU). Of their cohort of 14,356 patients, they found that 4093 patients (28.5%) met AKIN AKI criteria,

compared to 5093 (35.5%) meeting the RIFLE criteria – a difference of 1000 patients (7%) between the two systems. Mortality in patients classified as non-AKI by AKIN that were classified as AKI according to RIFLE was increased compared to the patients confirmed as non-AKI according to both systems. They concluded that the RIFLE criteria resulted in a higher detection rate of AKI within 48 hours of ICU admission, despite the presumed increased sensitivity by the AKIN system to capture acute changes in SCr.

More recently in 2018, Huber et al[7] validated both RIFLE, AKIN, and also a modified AKIN described as the 'backward classification' (for patients without a baseline SCr value) in a retrospective single-centre cohort analysis of 321 patients. In 87% of AKI cases, both the RIFLE and AKIN systems classified patients in consistent stages according to SCr changes. Findings were comparable to those seen by Joannidis et al[6], with 22 patients (6.9%) classified as AKI by AKIN that were not detected by the RIFLE criteria[7].

Table 1.3: AKIN criteria, adapted from Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury[5]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3mg/dl (≥26.4μmol/l) OR increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5ml/kg/h for more than 6 hours
2	Increase in serum creatinine of more than 200% to 300% (2- to 3-fold) from baseline	Less than 0.5ml/kg/h for more than 12 hours
3	Increase in serum creatinine of more than 300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0mg/dl [≥354μmol/l] with an acute increase of at least 0.5mg/dl [44μmol/l]) OR	Less than 0.3ml/kg/h for 24 hours OR Anuria for 12 hours

	Initiation of RRT (irrespective of the stage they were in at the time of RRT)	

1.1.1.4 KDIGO

The KDIGO definition[1], proposed in 2012, has provided a universally accepted means of defining and staging AKI in both adults and children. It was produced and published in the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury[1] by an international workgroup, to assist practitioners caring for children and adults with or at risk of AKI with evidence-based recommendations. KDIGO is the end result of the development of the previous AKI definitions discussed, and combines the RIFLE, pRIFLE and AKIN definitions. The increase in creatinine required to meet the KDIGO criteria is slightly higher than for the RIFLE criteria[3] meaning RIFLE could potentially classify more patients as having AKI than if they were classified with the KDIGO criteria. This is displayed in **table 1.4**.

Table 1.4: KDIGO staging of AKI, adapted from KDIGO 2012 Clinical Practice Guideline for AKI[1]

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3mg/dl (≥26.5μmol/l) increase	<0.5ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0mg/dl (≥353.6μmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35ml/min per 1.73m^2	<0.5ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

1.1.1.5 Limitations

One difficulty arises as patients present with acute kidney injury without having a previous SCr recording to use as the baseline measure of renal function – therefore being unable to

calculate the percentage increase or decrease in SCr or estimated GFR (eGFR) respectively. Some studies will adapt to this by estimating a baseline SCr by assuming a normal GFR, and calculating using body surface area.

In adults, there are two commonly used formulas used to estimate GFR. The Modification of Diet in Renal Disease (MDRD) group formula takes into account age, race and sex[8], whilst the Cockcroft-Gault (CG) formula takes into account age, weight and gender[9]. The CG is no longer recommended as it has not been expressed using standardised creatinine values.

In the paediatric population (from 1 year to 18 years old), the Schwartz equation is considered the best method for estimating GFR and is based on height[10].

1.1.1.6 Summary

The KDIGO classification system proposed in 2012, combines RIFLE, pRIFLE and AKIN classifications and is the most widely accepted staging system today.

1.1.2 AKI and associated outcomes

1.1.2.1 Adults

AKI in adults has been described in more depth than in children, and important statistics are widely available. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) AKI report (assessing 700 cases)[11] estimated that up to 10,000 in-hospital deaths in the UK per year could be associated with AKI. The report states that up to 30% of these deaths could be prevented with the right care and treatment. Wang et al[12] estimated that one in five emergency admissions to hospital per year has an AKI. Although in these cases the cause for admission may not specifically be AKI, these data highlight how common AKI is and how frequently it is associated with hospital admissions.

An in-depth systematic review and meta-analysis of 13 studies (including adult patients) from 2012[13] displayed an increased risk of death and other long-term consequences, including progression to End Stage Renal Disease (ESRD) and Chronic Kidney Disease (CKD) in patients with AKI compared to those without. The results shown in adult literature

emphasise the importance of recognising and promptly treating AKI as part of the overall management of patients, in addition to the need for further research into the aetiology, risk factors, prevention and treatment options in both adults and the paediatric population.

1.1.2.2 Children

AKI is common in children admitted to hospital[14], and has many recognised associations. Studies have so far conveyed the association of AKI with poor short- and long-term outcomes[14-18], such as residual kidney damage following an acute deterioration in kidney function. A large cross-sectional analysis[14] showed the incidence of AKI in hospitalised children to be 3.9 in 1000 admissions, with 19% of the cohort being less than 1 month of age. Importantly, this study displayed that the in-hospital mortality in admissions complicated by AKI was 15.3%, compared to 0.6% in hospitalised children without AKI. Additionally, a multinational prospective study[18] showed that a worsening severity of AKI positively correlated with an increase in 28-day mortality in children and young adults. Research so far has begun to demonstrate some of the factors associated with poorer outcomes from paediatric AKI, for example the in-hospital mortality in AKI patients is higher in children less than 1 month of age, children requiring critical care, and children needing dialysis[14].

1.1.3 Nephrotoxic AKI

Studies have shown several associations with AKI including cardiac surgery in patients with congenital heart disease[1, 19], nephrotoxic drug exposure[1, 17, 20, 21], radiocontrast agents[1, 20], and circulatory shock and septicaemia[1, 14]. Nephrotoxin exposure is common in neonates (particularly common in the neonatal intensive care unit), and accounts for the most potentially avoidable cause of AKI in this cohort[22]. Premature infants are at increased risk for the development of CKD due to nephrogenesis being incomplete at birth[22].

The KDIGO guidelines[1] suggest that nephrotoxic medication associated AKI (NTMx-AKI) is commonly seen in children and accounts for some part of AKI in 20-30% of patients[1]. However, there is a lack of research and available data surrounding nephrotoxic drug exposure and its role in AKI development. One factor in this is that it can be challenging to

establish the contribution that some nephrotoxic agents have on the natural history of AKI, due to patients at high risk of AKI often being prescribed these agents (e.g., antimicrobials and radiocontrast).

1.1.3.1 Nephrotoxic AKI in adults

The KDIGO guidelines[1] recognise that nephrotoxin exposed patients are often those already at increased risk of AKI, resulting in difficulty quantifying the contribution nephrotoxins have on the development of AKI in these patients.

Research into nephrotoxicity as a result of particular nephrotoxins including aminoglycosides (used to treat gram-negative and some gram-positive pathogens), amphotericin B (used to treat fungal infections), and contrast media (used for radiological examinations) has allowed prevention and treatment recommendations to be produced and outlined in the guideline[1].

A lot of the current literature and studies have focussed on the adult population. Research into wider cohorts including critically ill patients is also more extensive in adults than in the paediatric population. A large multicentre case control study[23] (n=1001) concluded that 617 adult patients (62%) received at least one nephrotoxin during their initial week in the intensive care unit (ICU)), of which 303 (30%) received 2 or more nephrotoxins. Authors concluded that the subsequent development of AKI was significantly associated with nephrotoxic burden, with AKI developing in 609 patients (61%). Nephrotoxic medication associated AKI is an iatrogenic cause of AKI, and is one of the most avoidable. This thesis hopes to discuss whether there is scope to reduce exposure and improve outcomes in the paediatric population, which could be extrapolated to adult centres.

1.1.3.2 Nephrotoxic AKI in children

The research into nephrotoxic AKI in children is less extensive than in adults. However, from the literature available and findings such as the increased risk of mortality in hospitalised children with AKI[14], we can begin to understand the scale and importance of the problem.

However, US data has given valuable insight into the problem of NTMx-AKI in children. One study reports that NTMx-AKI is the second most common (to renal ischaemia) cause of AKI in children and the most common cause of AKI in children aged 6 years and above[24]. Findings from this study also demonstrated that survival was lower in children with AKI admitted to ICU and those requiring RRT than in the entire cohort. Another study[17] found that 6 months after NTMx-AKI, 70% of patients had evidence of residual kidney damage (reduced eGFR, hyperfiltration, proteinuria or hypertension), with 33.7% patients having confirmed CKD (proteinuria or eGFR <60 ml/min/1.73m^2. These findings give us an insight into the short and long-term effects of AKI on children's outcomes, and emphasise the need to understand and identify and prevent children at increased risk developing long-term problems.

1.1.3.3 Nephrotoxic mechanisms of renal injury

An in-depth review by Uber and Sutherland[20] reviewed the mechanisms of renal injury that can occur following nephrotoxin exposure. There are several recognised modes of injury including vasoconstriction and haemodynamic alterations from medications such as Non-Steroidal Anti-Inflammatories (NSAIDs), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB) and calcineurin inhibitors (CNI), direct tubular toxicity from medications such as aminoglycosides (AG), amphotericin, calcineurin inhibitors and intravenous (IV) contrast, interstitial nephritis from NSAIDs, sulphonamides, and diuretics, and crystal formation leading to Acute Tubular Necrosis (ATN) from methotrexate, acyclovir and sulphonamides to mention a few. Although these most commonly described mechanisms of nephrotoxicity are appreciated, it is evident that there are still areas for further research in understanding the mechanism of injury development at a molecular level. Furthermore, challenges arise after identifying nephrotoxins, in assessing how nephrotoxic particular drugs can be. For example, drugs such as ACEi or ARBs can, in some situations, be considered nephrotoxins, but are at other times considered nephroprotective and are used in managing conditions such as CKD[25].

Mehta et al[26] described the mechanisms of drug-induced kidney disease and classified these into four phenotypes based on current knowledge: AKI, glomerular, tubular and nephrolithiasis. They also classified based on whether reactions were dose-dependent or

unpredictable. Finally, drugs were categorised again by the time course for biomarker change: acute (within 7 days of drug initiation), sub-acute (within 4 weeks of drug exposure and may take up to 90 days to resolve), and chronic (injury persisting beyond 90 days). We have adapted the tables produced by Mehta et al[26] to display the mechanisms of nephrotoxins described, which can be seen in **table 1.5**.

Table 1.5: Common Nephrotoxins and their mechanism of injury, adapted from Mehta et al 2015[26]

AKI	Dose-dependent	Acute	Cidofovir	Pamidronate
		Acute/sub-acute	Aminoglycosides Amphotericin Cyclosporin Foscarnet	NSAIDs Tacrolimus Vancomycin
		Sub-acute	Colistin	Nafcillin
	Idiosyncratic	Acute	Abacavir	
		Acute/sub-acute	Cyclosporin NSAIDs Piperacillin/tazobactam (PTZ)	Sulfamethoxazole; Trimethoprim (SMX/TMP) Tacrolimus Vancomycin
		Sub-acute	Amoxicillin Ampicillin Cefazolin Ceftazidime Ciprofloxacin	Levofloxacin Oxacillin Penicillin Rifampicin
		Sub-acute/chronic	Propylthiouracil	
Glomerular	Dose-dependent	Sub-acute	Bevacizumab	Pamidronate
		Sub-acute/chronic	Lithium	
	Idiosyncratic	Sub-acute	Rifampicin	
		Sub-acute/chronic	Hydralazine	
Tubular	Dose-dependent	Sub-acute	Didanosine Foscarnet Lamivudine	Ritonavir Tenofovir
		Sub-acute/chronic	Cisplatin Ifosfamide	Lithium
Nephrolithiasis	Dose-dependent	Sub-acute	Acyclovir Atazanavir	Indinavir

Furosemide is not included the list of nephrotoxic medications in **table 1.5**, nor in the list of nephrotoxins identified by the Cincinnati group[21, 27-30] (**table 4.1**). The authors of the Cincinnati group state in their earliest paper documenting a list of nephrotoxins in 2011[21], that furosemide was not included due to its common use as a treatment for AKI. Due to its use in treating AKI, quantifying the contribution of furosemide to the course of AKI can prove challenging. Furosemide is included in the list of nephrotoxins used at Alder Hey and therefore was recognised as a nephrotoxin in our audit in Chapter 3. At AHCH, furosemide is frequently used, and previous audits have demonstrated its association with AKI in the trust.

Trimethoprim is not included as a stand-alone nephrotoxin in either Mehta et al[26] or the Cincinnati group[21, 27-30]. Current literature suggests trimethoprim possesses minimal, if any, true nephrotoxicity and instead causes a reversible rise in SCr due to its effect in inhibiting renal tubular secretion of creatinine[31]. However, combinations such as sulfamethoxazole/trimethoprim (commonly referred to as co-trimoxazole) are recognised as nephrotoxic by Mehta et al[26]. We can suggest that one reason for the inclusion of trimethoprim on the list developed for use at AHCH could relate to the lack of research relating to different drug combinations with trimethoprim and any associations with AKI. For internal use at our trust, it may prove useful to include trimethoprim on the list as a caution, raising awareness among physicians of the potential nephrotoxic burden of polypharmacy prescriptions.

1.2 Importance of the work/Conclusion

The findings from available literature emphasise the importance and impact of early identification of AKI in children to initiate prompt intervention and treatment, which has been shown to improve patient's outcomes. Existing management strategies of AKI focus on avoidance and prevention[1, 32 33]. This is for the reason that AKI is difficult to diagnose at an early stage unless suspected, due to a lack of signs and symptoms until the injury progresses. Currently, serum creatinine (SCr) is used as a biomarker for the diagnosis and staging of AKI[1], and raises 24-72 hours after an injury has occurred[34]. As explored in more detail in the rest of this thesis, identifying and monitoring patients at risk of NTMx-AKI could improve patient outcomes in both the short- and long-term. The aetiology and contributing

factors to AKI in children is complex. To be able to continue to encourage the mainstay of treatment towards prevention of AKI, we must further understand the factors that can contribute to both the development and the disease course of AKI. Further research is required to further quantify the extent and impact of prevention and treatment strategies on patients' long-term outcomes.

1.3 Aims

- The main aim of this thesis is to provide an overview of the epidemiology of NTMx-AKI in children, and to begin to understand how this influences and affects short- and long-term outcomes.
- Chapter 2 is a systematic review and meta-analysis, which aims to provide an overview of the current literature of the epidemiology and outcomes of NTMx-AKI in children. The meta-analysis will allow us to combine available data and compare outcomes. The conclusions drawn from this systematic review will help contribute to the current literature available, and to inform the audit completed in Chapter 3.
- Chapter 3 consists of the data analysis of inpatients during one week at Alder Hey Children's Hospital (AHCH), intending to contribute to improving current understanding and guide future research and recommendations.
- Chapter 4 will discuss the main findings from the systematic review, meta-analysis and AHCH data analysis. The importance of these findings in relation to clinical practice will be discussed, and recommendations for future research will be made.

Chapter 2 What is the epidemiology of drug-induced Acute Kidney Injury in Children? A systematic review and meta-analysis

2.1 Background

AKI is common across a range of paediatric populations, and NTMX-AKI is a potentially preventable cause of AKI in children. As discussed in **section 1.1**, risk factors for the development of AKI (such as nephrotoxic medications) and predictors of patient outcomes have been described in various groups of patients. This chapter details a systematic review, aiming to provide a comprehensive summary of the current literature surrounding NTMx-AKI in children.

2.2 Aims

The aim of this chapter is to identify studies that have analysed NTMx-AKI in children. The research questions of the systematic review were:

- **Full Review Question**: What is the epidemiology of drug-induced Acute Kidney Injury in children?
- **Primary objective:** Describe the epidemiology of drug-induced AKI in children
- **Secondary objectives:** In addition to the primary outcome, we:
    - Conducted a quantitative analysis of the primary outcome
    - Described outcome measures to report AKI epidemiology in children
    - Described identified risk factors for the development of AKI in children
    - Described strategies that have demonstrated improvements/have been shown to mitigate AKI

2.3 Methods

A systematic review protocol was written and registered with the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42020215439. The registration to PROSPERO can be seen in Appendix 1, and the systematic review protocol can be seen in Appendix 2.

2.3.1 Inclusion and exclusion criteria

Eligibility criteria for studies included in this systematic review are detailed in the PICO format below, in **table 2.1.**

Table 2.1: Inclusion and exclusion criteria to determine relevant studies

PICO	Inclusion Criteria	Exclusion Criteria
Population	Children admitted to hospital / children treated as inpatients in hospital	Non-human Outpatients Over the age of 18
Intervention	Documentation of in-hospital nephrotoxin exposure	No exposure to any nephrotoxins documented Consideration only of a specific nephrotoxin or nephrotoxin combination
Comparator	N/A	N/A
Outcomes	Diagnosis of AKI	N/A
Publication type	Reported in full text format Published in English	Narrative reviews

2.3.2 Identification of relevant studies through search engines

After scoping searches, three bibliographic databases (EMBASE, Medline and CINAHL) using NICE Healthcare Databases Advanced Search (HDAS)[35] were searched by one reviewer (CH) for full text, English literature from January 2000 until November 2020.

HDAS allows searching of nine databases and supports the creation and storage of search strategies[35] which has been useful to create comprehensive searches. This was also useful when repeating searches at a later date to identify any newer studies. Each of the three databases were searched individually rather than in combination using HDAS, to allow the searching of Medical Subject Headings (MeSH) terms. MeSH terms were manually identified from the thesaurus of each individual database.

EMBASE is a database consisting of three separate databases and is produced by Elsevier. It is a widely used major biomedical and pharmaceutical database indexing journals from 1974 to present.[35]

CINAHL covers all aspects of nursing and seventeen allied health disciplines (which can be found on the HDAS help page) from 1981 to present. CINAHL also scans selected journals for relevant articles.[35]

PubMed was not searched due to ongoing maintenance at the time of searching (Nov 2020) resulting in less MeSH terms, and so Medline was used instead. Medline is a medical database derived from biomedical and life science journals, from 1946 to present.[35]

The Cochrane database of Systematic Reviews (Cochrane Reviews)[36] was not searched as systematic reviews were excluded from this review. Furthermore, all results on Cochrane are indexed on Medline, meaning any new findings would have been duplicates of the search results.

Reference lists of included systematic reviews were not examined for additional relevant literature as the database searches were comprehensive.

2.3.3 Design of search strategy

The search strategy was developed from three concepts from the research question. Concept 1 described the outcome (AKI), concept 2 described the intervention (nephrotoxin exposure), and concept 3 described the population (children). A limit on date was applied from January 2000 until November 2020, a limit on publication language was applied to include only studies published in English. This search strategy was designed with Fariba Bannerman (FB) from Alder Hey library and knowledge service, who also reviewed the search syntax following completion of searches. The search syntax for each database can be seen in Appendix 3.

MeSH terms for each concept were identified from the thesaurus of each individual database through HDAS. Boolean operators OR and AND were used to combine the three

concepts and their related MeSH terms. Truncation of any suitable terms was done to ensure a comprehensive search. We then applied a limit to search titles and abstracts for these terms. Narrative reviews were excluded due to the nature of the research question.

2.3.4 Selecting eligible studies for inclusion

After database searches were carried out and duplicates removed, a list of articles potentially meeting the eligibility criteria were produced independently by two reviewers (CH and SM), using the titles and abstracts. Any disagreements were discussed between CH and SM, and failing this would have been resolved by a third reviewer (LO). Full text review and quality assessment was carried out independently by the same reviewers (CH and SM).

2.3.5 Data extraction

Data extraction and critical appraisal of identified studies was then conducted by one reviewer (CH), taking into account the inclusion and exclusion criteria.

The following data was collected from studies meeting the eligibility criteria: Author, Title, Year, Type of study, Number of patients per study, Patient age, Patient demographics (anything available including Body Mass Index (BMI), ethnicity, primary renal disease, weight), Treatment modality (RRT), AKI alerts, Peak AKI Stage, Stages of AKI when alert flagged, Exposure to nephrotoxins, Length of hospital stay, Mortality, Reason for admission, Critical care admission.

2.3.6 Assessment of quality of studies and risk of bias assessment

To assess the risk of bias and check the quality of studies identified after searching, the checklists developed by the Joanna Briggs Institute (JBI)[37, 38] were used, along with personal consideration. This checklist involved assessing characteristics including but not limited to: recruitment; exposure measures in exposed and unexposed groups; identification of confounding factors; measurement of outcomes; appropriateness of statistical analysis. The findings of the quality assessment are discussed in the results section of this chapter, and can also be seen in Appendix 5.

Quality assessment was performed independently by two reviewers (CH and SM). Any differences in assessment outcome were initially discussed between the two reviewers, with any disagreements resolved by a third reviewer (LO).

2.3.7 Data analysis

We aimed to report:

1) The overall incidence of AKI
2) The incidence of AKI in children exposed to nephrotoxic medications
3) The relative risk of AKI in children exposed to nephrotoxic medications compared to those not exposed to nephrotoxic medications

The aim was to provide a quantitative analysis where the data allowed. Where this was not possible, the review provides a comprehensive summary and descriptive narrative of the current literature.

As part of the data synthesis, we included a summary table of data extracted from eligible papers, part of which initially aimed to include effect estimates (adjusted and raw), and standard errors, if the data displayed in included papers allowed. This was adapted to include the data in **table 2.2** after the main searches had been conducted and we knew what data were to be analysed in the time frame available.

2.3.8 Additional analysis – Meta-analysis

In papers that were sufficiently homogenous (defined as including the same patient population, and defining AKI episodes in a consistent way), we conducted a quantitative analysis of the primary outcome of the epidemiology of drug-induced AKI in children. This included subgroup analysis for different patient populations including children with nephrotic syndrome, non-critically ill children, and limited data in critically ill children. The papers were first screened for homogeneity by an independent reviewer (CH) and then discussed with the primary supervisor (SM) and Professor Andrea Jorgensen (of biostatistics) from the University of Liverpool (AJ), where final decisions were made regarding which papers could be included in separate meta-analyses.

To conduct the meta-analysis, Review Manager (RevMan)[39] was chosen to create the forest plots required for this project.

Firstly, we identified papers with the same population of patients (for example children with Nephrotic Syndrome) and used the data summary table to identify any outcomes or risk factors reported in two or more of those papers.

The following statistical analysis was done in conjunction and with the support from AJ. We inputted data for one of each type of variable (incidence, dichotomous and continuous) to create a forest plot during a video call using the screen sharing function. The remaining analyses were then carried out by CH, and reviewed by AJ after completion. We firstly looked at incidence, and for each study we inputted the number of events (n= 1 AKI diagnosis) and total sample size into an excel spreadsheet, and from this calculated the log of the incidence and the standard error (SE) of the log of the incidence (**figure 2.1**). This data was then inputted into RevMan, selecting the 'Generic Inverse Variance' option for outcome type, with random rather than fixed effects to calculate a pooled incidence and p- value with 95% confidence interval (CI).

$$\text{Log of incidence} = \text{LN}\left(\frac{\text{Number of events}}{\text{Sample size}}\right)$$

$$\text{SE} = \frac{(1 - \text{incidence}) \times \text{incidence}}{\text{Number of events}}$$

$$\text{SE log of incidence} = \frac{\text{LN}(\text{incidence} + (1.96 \times \text{SE})) - \text{LN}(\text{incidence} - (1.96 \times \text{SE})}{3.92}$$

Figure 2.1: Formulas used for incidence calculations in Microsoft Excel

To compare dichotomous factors, including exposure to nephrotoxins and mortality, between cases (AKI) and controls (no AKI), we input the total events (i.e., nephrotoxin

exposures or deaths) for the case and control groups separately. This allowed us to produce a forest plot to visualise the results. 'Dichotomous' data type was selected, and the statistical method used was 'Mantel-Haenszel', with random rather than fixed effects applied as the analysis model. A pooled odds ratio (OR) along with 95% confidence interval and p- value was also calculated for each factor.

Finally, continuous variables including age and length of hospital stay were compared between cases and controls. This involved inputting the mean and standard deviation of the variable for both cases and controls into RevMan, which produced a forest plot. 'Continuous' data type was selected, and the statistical method used was 'Inverse Variance', with random effects as the analysis model. This produced a pooled estimate for the mean difference, 95% confidence interval, and p- value for each variable.

As described above, for continuous variables, three pieces of data were needed (mean, SD, total patients) to input for meta-analysis. Several papers identified to be included in the meta-analysis displayed results as median and interquartile ranges (IQR) rather than the desirable mean and standard deviation (SD). The reason that a study may present results as a median and IQR rather than a mean and SD may be because the data was skewed. For this reason, it is sometimes advised against using these values to calculate an estimated mean and SD from a median and IQR. However, we chose to use the Cochrane Handbook[40] advice on estimating mean and SD, in order to be able to conduct the meta-analysis with the limited studies identified. When sample sizes are large and the distribution of the outcome is similar to the normal distribution, the width of the IQR is approximately 1.35 standard deviations. This means that the difference between IQR figures can be divided by 1.35, giving an estimated SD. Median can then be inputted in place of the mean.

2.4 Results

2.4.1 Study selection

Electronic searches in November 2020 identified 258 citations, leaving 205 unique results from three databases after 53 duplicates were removed. These 205 citations were screened using titles and abstracts according to the eligibility criteria (**table 2.1**). After the titles and abstracts were screened for potential citations meeting the eligibility criteria, 28 citations were retained. Full texts of 4 papers were not obtainable (due to being abstract presentations at conferences), meaning 24 citations were obtained and screened again against inclusion and exclusion criteria, and also quality assessed. Three citations were excluded; 2 did not examine the appropriate intervention and 1 reported data from a patient population outside of the eligibility criteria. The reasons for exclusion of each of these papers can be seen in Appendix 4. Ultimately, 21 citations were included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**figure 2.2**) displays the number of papers included and excluded at each stage.

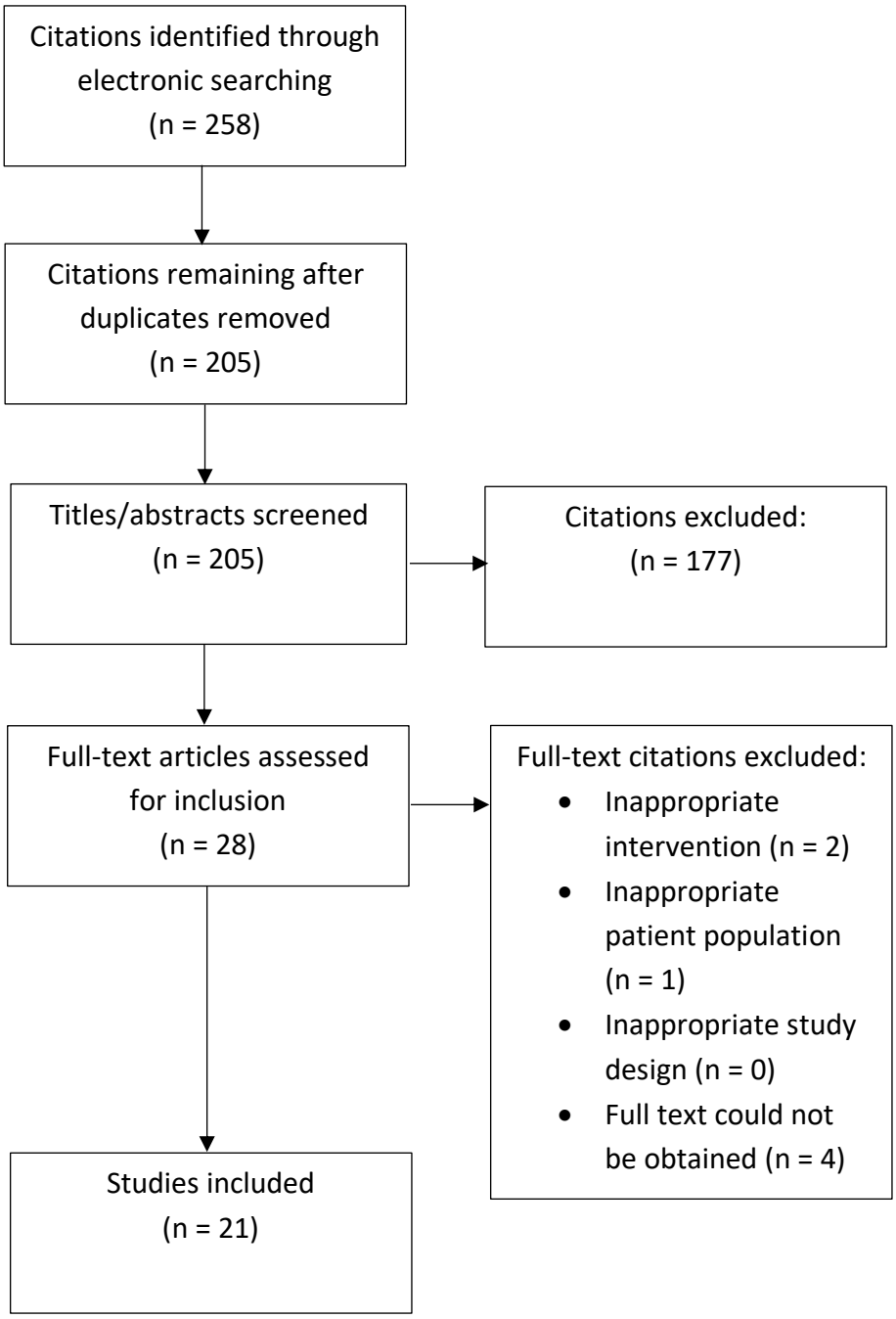


Figure 2.2: PRISMA flow diagram displaying the identification of included studies in the systematic review.

2.4.2 Quality of included studies

As described under Methods, the JBI checklists[37, 38] were used by independent reviewers (CH and SM) to assess the quality of eligible studies. Any differences were discussed and failing this, resolved by a third reviewer (LO). The study design informed the choice of checklist used, so that suitable checks were performed. All retrospective and prospective cohort studies recruited cases and controls from the same populations, measured exposures between cohorts similarly, and defined AKI and other outcome measures in a reliable way. No studies were designed to only include participants free of the outcome measure (AKI) at the start of the study, so this part of the checklist was not relied on so much in the appraisal due to the nature of our systematic review. Four papers did not report how they measured exposure (to nephrotoxins); however this was not a primary outcome measure of these studies. Five papers did not describe how or whether confounding factors were adjusted for. Lastly, the factors in the quality assessment regarding follow up were not relied on so much in the appraisal due to the nature of available literature. Although we wanted to describe and analyse data regarding both short and long-term outcomes where available, this has proved difficult to report in the majority of included studies as this would require a longer follow-up period than many of the included studies were designed for. The detailed outcomes of the quality assessment can be seen in a table adapted from the JBI checklists, in Appendix 5.

2.4.3 Study Characteristics

The characteristics of studies included in the systematic review are displayed in **table 2.2**.

Table 2.2: Study characteristics of eligible papers

Study	Study design	Setting (number of centres)	Dates conducted	Country (State/Region)	Population size (by number of children)*	Population	AKI definition	Outcome measures used (for AKI and nephrotoxin exposure)
Benoit 2019[41]	Prospective cohort analysis (Quality Improvement Project (QIP))†	Single quaternary inpatient hospital	Jan 2014 – Dec 2017	US (Ohio)	Not stated – 222 SCTs reported pre-intervention, and 203 post-intervention, so we could propose 425 patients were included	Stem cell transplant (SCT)	KDIGO	AKI incidence in just in nephrotoxin exposed (%) Rate of nephrotoxin associated AKI (per 1000 patient-days) Rate of nephrotoxin exposure per 1000 patient-days)
Goldstein 2016[28]	QIP†	Single quaternary inpatient hospital	Sept 2011 – March 2015	US (Ohio)	1749	Non-critically ill hospitalised	KDIGO	AKI prevalence rate (per 1000 patient-days) High nephrotoxic medication exposure prevalence rate (per 1000 patient-days) Rate of patients with high nephrotoxic medication exposure who develop AKI (%)

								AKI intensity rate (per 100 exposed patient-days)
Goldstein 2020[29]	QIP†	Multicentre (9)	July 2015 – June 2017	US (Ohio)	4513	Non-critically ill hospitalised	KDIGO	AKI prevalence rate (per 1000 patient-days) High nephrotoxic medication exposure prevalence rate (per 1000 patient-days) Rate of patients with high nephrotoxic medication exposure who develop AKI (%) AKI intensity rate (per 100 exposed patient-days)
Kim 2018[42]	Retrospective cohort study	Single tertiary care centre	Jan 2015 – July 2017	South Korea (Seoul)	65	Nephrotic syndrome	KDIGO	AKI incidence (%) Nephrotoxin exposures by individual nephrotoxins (n, %)
Kirkley 2018[43]	Retrospective cohort study	Multicentre (Assessment of Worldwide Acute Kidney Injury in Neonates (AWAKEN) study is 24 Neonatal Intensive	Jan 2014 – March 2014	US (although AWAKEN is a worldwide database)	113	Neonatal encephalopathy	KDIGO	AKI incidence (%) Nephrotoxin exposure (n, %)

		Care Units (NICUs))						
McGregor 2016[44]	Retrospective cohort study	Single tertiary care centre	Jan 2011 – Dec 2012	US (Tennessee)	2374	Non-critically ill hospitalised	KDIGO	AKI incidence (%) Nephrotoxin exposure (median, IQR)
Moffett 2011[21]	Retrospective case control study	Single quaternary inpatient hospital	During 2008	US (Texas)	714	Non-critically ill hospitalised	pRIFLE	AKI incidence (%) Nephrotoxin exposure (n, % and median, range) Days of nephrotoxin therapy (median, range) Nephrotoxin exposure intensity (median, range) Nephrotoxin doses (median, range) Doses per therapy day (mean ± SD) Medication doses per admission day (mean ± SD)
Prasad 2019[45]	Prospective observational study	Single tertiary care centre	Feb 2016 – Jan 2017	India (Delhi)	73	Nephrotic syndrome	KDIGO	AKI incidence (%) Nephrotoxin exposures by individual nephrotoxins (n, %)
Rheault 2015[46]	Retrospective cohort study	Multicentre collaborative (17)	Jan 2010 – Dec 2012	America (North)	336	Nephrotic syndrome	pRIFLE	AKI incidence (%) Nephrotoxin exposure (%) Nephrotoxin exposures by individual nephrotoxin (mean ± SD) Nephrotoxin exposure intensity (mean ± SD)

Rhone 2014[47]	Retrospective cohort study	Single tertiary care centre	April 2011 – March 2012	US (Virginia)	107	Very low birth weight infants	KDIGO	AKI incidence (%) Nephrotoxin exposure (n, %)
Safder 2020[48]	Prospective observational study	Multicentre collaborative (3)	March 2014 – Feb 2016	Saudi Arabia (Jeddah)	1367	Critically ill	KDIGO	AKI incidence (%)
Schaffzin 2014[49]	Retrospective cohort study	Single quaternary inpatient hospital	Jun 2011 – June 2012	US (Ohio)	28753	Non-critically ill hospitalised	pRIFLE	AKI incidence (%) Nephrotoxin exposure (n, %)
Shalaby 2015[50]	Retrospective cohort study	Single tertiary care centre	Jan 2011 – Dec 2011	Saudi Arabia (Jeddah)	102	Critically ill (whole cohort with AKI)	pRIFLE	AKI incidence (%) not reported but can calculate from available data Nephrotoxin exposure was not reported but % of patients with drug toxicity as the aetiology was reported
Sharma 2018[51]	Retrospective cohort study	Single tertiary care centre	Jan 2012 – Dec 2015	India (Guwahati)	355	Nephrotic syndrome	pRIFLE	AKI incidence (%) Nephrotoxin exposure (n)
Stoops 2019[52]	QIP†	Single centre level IV neonatal intensive care unit	March 2015 – Sept 2017	US (Alabama)	432	Neonates/infants (all exposed to nephrotoxins)	"the most widely used SCr-based definition for neonatal AKI was used" – a SCr of $\geq$0.5	AKI prevalence rate (per 1000 patient-days) High nephrotoxic medication exposure prevalence rate (per 1000 patient-days) Rate of patients with high nephrotoxic medication exposure who develop AKI (%)

							mg/dL was defined as meeting AKI criteria	AKI intensity rate (per 100 susceptible patient-days)
Tresa 2017[53]	Prospective observational study	Single tertiary care centre	April 2014 – March 2015	Pakistan (Sindh)	116	Hospitalised children (whole cohort with AKI)	pRIFLE	Whole cohort had AKI so no incidence was reported. Nephrotoxin exposure was not reported but % of patients with drug induced AKI was reported
Uber 2018[54]	Retrospective cohort study	Single tertiary care centre	June 2014 – Sept 2014	US (California)	154	Congenital cardiac surgery	KDIGO	AKI incidence (%) Nephrotoxin exposure (n, %)
Xiong 2020[55]	Retrospective cohort study	Multicentre collaborative (25)	Jan 2013 – Dec 2015	China (Southern, Central and Northern)	9828	Oncology	KDIGO	AKI incidence (%) Nephrotoxin exposures by individual classes of nephrotoxins (%)
Yang 2020[56]	Retrospective cohort study	Multicentre collaborative (14)	Jan 2013 – Dec 2017	South Korea	363	Nephrotic syndrome	KDIGO	AKI incidence (%) Nephrotoxin exposure (n, %)
Yaseen 2017[57]	Prospective observational study	Single tertiary care centre	March 2014 – October 2015	Pakistan (Sindh)	119	Idiopathic nephrotic syndrome (whole cohort with AKI)	pRIFLE	Whole cohort had AKI so no incidence was reported. Nephrotoxin exposure was not reported but % of patients with drug toxicity as the aetiology was reported
Young 2020[58].	Prospective interventional study	Single quaternary	July 2014 – July 2018	US (Ohio)	273	Oncology	KDIGO	Rate of AKI episodes associated with nephrotoxic

	(Describes the targeted interventions, following the quality improvement initiatives described in 2016[28])†	inpatient hospital						medication exposure (per 1000 patient-days) Rate of nephrotoxic medication exposure (per 1000 patient-days)

*We have stated the total population size by number of patients for eligible studies. Some studies use 'episodes of AKI' or 'hospitalisations' to define their population and calculate rates, however for the purpose of cohort size comparison we have reported in this table the number of included patients per study

†The studies conducted by the Cincinnati group are often referred throughout this thesis to as "interventional studies" and are further described in **table 2.4**. The team did not necessarily enforce interventions in all studies (except Young 2020[58], who describes targeted interventions), instead provided information to teams to drive behaviour change.

2.4.3.1 Summary

A summary of the features of the studies included in the systematic review is detailed in **table 2.3**.

Table 2.3: Summary of study features

Feature	Number of studies
Included studies	21 (total of 52331 patients)
Study design	
QIP	4
Retrospective cohort study	11
Retrospective case control study	1
Prospective observational study	4
Prospective interventional study	1
Method of defining AKI	
KDIGO	13
pRIFLE	7
Other*	1*
Setting	
Single tertiary care centre	9
Multicentre collaborative	6
Single quaternary inpatient hospital	5
Single centre level IV neonatal ICU	1
Country	
US	11
South Korea	2
India	2
America	1
Saudi Arabia	2
Pakistan	2
China	1

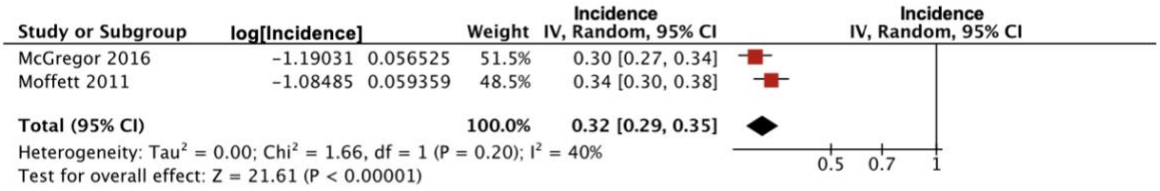
*This particular study was in a cohort of neonates. The authors stated a SCr of $\geq$0.5 mg/dL was defined as meeting AKI criteria (referred to as the most widely used SCr based definition for neonatal AKI)

2.4.4 Primary Outcome – describe the epidemiology of drug-induced AKI in children

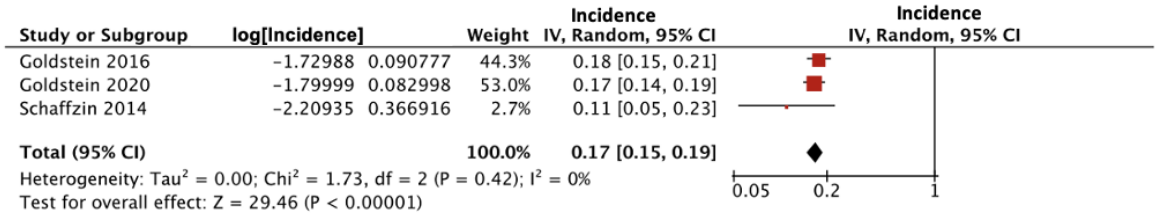
The primary outcome is described in this section for the various populations from studies included in the systematic review. The results from included studies that had sufficient evidence (reported number of AKI episodes and total cohort size) and homogeneity (defined as including the same population and defining AKI episodes consistently) to be included in meta-analysis, are displayed as forest plots (**figures 2.3, 2.4 and 2.5**) alongside the relevant patient population. This meta-analysis was performed with the support of AJ, who has also reviewed all forest plots on completion of this section.

2.4.4.1 Non-critically ill hospitalised children

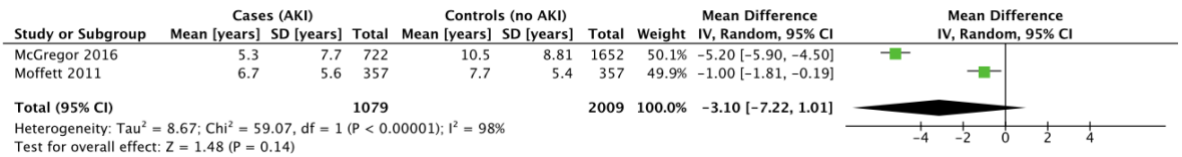
A) Overall incidence of AKI in total cohort of non-critically ill patients



B) Overall incidence of AKI in cohort of non-critically ill patients exposed to nephrotoxins



C) Mean age (years) in cases vs controls



D) Mean length of stay (days) in cases vs controls

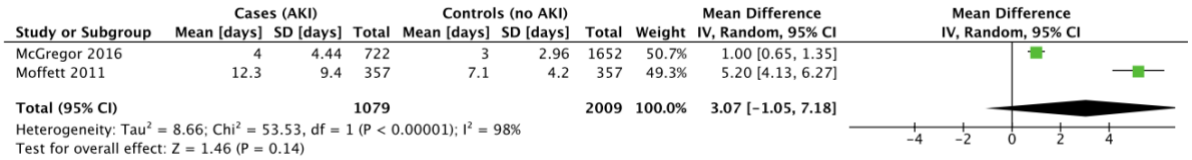


Figure 2.3: Forest plots of outcomes and risk factors in non-critically ill hospitalised children

Five studies[21, 28, 29, 44, 49] were identified as using non-critically ill, hospitalised children as the eligible population. Of these, two[21, 44] report AKI outcomes in all non-critically ill hospitalised patients (with and without nephrotoxin exposure), and three[28, 29, 49] report outcomes only in those with nephrotoxin exposure. These two groups were considered separately in the meta-analysis.

The pooled incidence of AKI in all non-critically ill, hospitalised children (i.e. both exposed and non-exposed population combined) was 32% (p<0.00001, 95% CI 29-35%, pooled data from two papers[21, 44] (n=3088 patients)) as seen in **figure 2.3A**. Separately, the papers both suggested that children with AKI were younger than those without. However this association was not statistically significant when data was combined (p=0.14, mean difference 3.10 years, 95% CI -7.22-1.01, pooled data from two papers[21, 44] (n=3088 patients)) (**figure 2.3C**).

The pooled incidence of AKI in nephrotoxin-exposed, non-critically ill, hospitalised children was 17% (p<0.00001, 95% CI 15-19%, pooled data from three papers[28, 29, 49] (n=747 patients[49] combined with n=7756 nephrotoxin exposures[28, 29])) (**figure 2.3B**).

Weight was only reported in one study[44], which concluded that patients with AKI had lower weight-for-age (z-score, −0.4 vs. 0.0; p-value <0.001; nonmissing = 2321).

All papers considered nephrotoxin exposure as a risk factor for the development of AKI, although there was insufficient homogeneity for meta-analysis. Moffett et al[21] formally tested for and demonstrated in a case-control study that the odds of exposure for at least

one nephrotoxin was significant for the development of AKI (p=0.03, odds ratio 1.7, 95% CI 1.04-2.9), and that patients with AKI had exposure to more nephrotoxins for a longer period of time than controls (no AKI). In a retrospective cohort study by McGregor et al[44], patients with and without AKI had similar numbers of nephrotoxic medication exposure (median 1 vs 1, p=0.05). However, throughout the paper the authors do refer to nephrotoxins as "exacerbating factors" and "modifiable risk factors". Schaffzin et al[49] also conducted a retrospective cohort study in relation to identifying NTMx-AKI, but not specifically testing the association. The authors recognise that "exposure to nephrotoxic medications is among the most common causes of AKI". The papers by Goldstein et al did however recognise that AKI rate decreased when nephrotoxins were reduced. In their 2016 paper[28], it was estimated that 633 exposures and 398 AKI episodes were avoided through implementation of an Electronic Health Record (EMR) screening program to flag eligible nephrotoxin-exposed patients (non-critically ill hospitalised children receiving an IV aminoglycoside for more than 3 days or 3 or more nephrotoxins simultaneously), across a 42 month period). The intervention implemented was daily SCr monitoring after appearance on the trigger report. The initial rate of AKI in this study was 2.96 episodes per 1000 patient days, which decreased to 1.06 episodes per 1000 patient days post-intervention. In their following paper in 2020[29], a 23.8% decrease in NTMx-AKI rates was observed by implementing the Nephrotoxic Injury Negated by Just-in time Action (NINJA) program (again, SCr screening and also the substitution of nephrotoxins for less nephrotoxic medications). They estimated that a total of 242 episodes of AKI were avoided over the 2-year study.

Separately, the data from each paper suggested that AKI prolongs hospital stay, but in the meta-analysis this was not statistically significant (p=0.14, mean difference 3.07 days, 95% CI -1.05-7.18, pooled data from two papers[21, 44] (n=3088 patients)) (**figure 2.3D**). A retrospective cohort study by Schaffzin et al[49] (not included in meta-analysis for length of stay due to differences in reporting of AKI episodes to the other two homogenous papers included), compared nephrotoxin-exposed children to non-exposed children, and identified an increased length of stay in those exposed than unexposed (mean 9.5 days, SD 16.64) than those unexposed (mean 4.99 days, SD 10.58), which produces a mean difference of 4.51 days, 95% CI 3.65-5.37, p<0.00001. Mortality was only reported in one paper[44]. In-hospital mortality was higher in those with AKI (0.6%, n=4/701 with data available) than

without (0.06%, n=1/1604 with data available) (total of 5 deaths in the cohort of 2305 (of 2374) with data available), and more deaths took place in those with a higher stage of AKI (stage 1-0.2%, n=1/427 with data available; stage 2-0.0%, n=0/194 with data available; stage 3-3.8%, n=3/77 with data available). Treatment modality was only reported in a single study[28] and was not compared to those without AKI. In this study, 19 patients (of 248 patients comprising 457 admissions leading to 575 AKI episodes) required RRT (13 intermittent haemodialysis; 2 continuous RRT; 4 both), with 16 of these patients initiating RRT in the intensive care unit.

2.4.4.2 Critically ill hospitalised children

A) Overall incidence of AKI in total cohort of critically ill patients

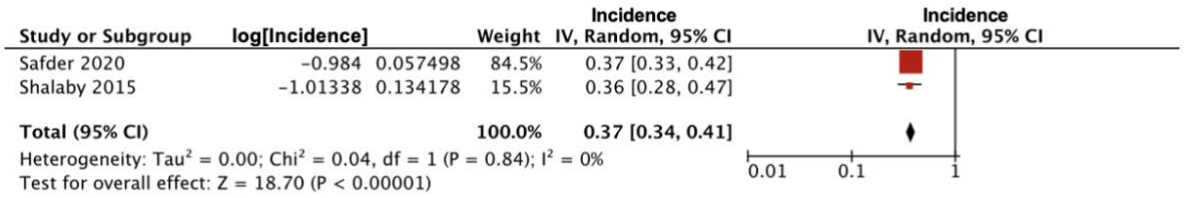


Figure 2.4: Forest plots of outcome in critically ill hospitalised children

Two eligible papers studied a population of critically ill hospitalised children[48, 50]. In both papers, critically ill children were defined as children admitted to the Paediatric Intensive Care Unit (PICU). Both studies excluded neonates (less than 28 days old) and children with a history or evidence of CKD stage 3 or above. One paper[48] also excluded patients admitted electively for central line insertion or with insufficient data, and the other[50] excluded children admitted for less than 24 hours[50].

The incidence of AKI in all critically ill, hospitalised children eligible for inclusion in selected studies was 37% (p<0.00001, 95% CI 34-41%, pooled data from two papers[48, 50] (n=1646 patients)) and is displayed in **figure 2.4A**. When data was pooled, no heterogeneity (I^2=0) was seen between these two papers, despite differences in the definition of AKI (study by Shalaby et al[50] reporting 36.3% using pRIFLE, and Safder et al[48] reporting 37.4% using KDIGO).

Other risk factors and outcomes from the two papers could not be combined, due to no control group in the study by Safder et al[48] due to the prospective study design which compared children with different stages of AKI rather than to children without AKI. However, papers are homogenous enough (in terms of population included and outcomes reported) to compare results.

In one of the studies[50], critically ill children with AKI were younger than those without AKI (mean 43.1 months, SD 50.4 vs mean 50.7 months, SD 53.4) however this association was not found to be statistically significant (p=0.2). This is difficult to compare with other studies as the oldest children in this study[50] were 60 months (5 years) old, whereas our inclusion criteria means we have eligible studies with children up to the age of 18. The other study of critically ill children[48] did not compare to children without AKI, however did report that those with more severe AKI were younger than those with less severe AKI (KDIGO stage 1 mean 47.0 months, 95% CI 40.5-53.4; stage 2 mean 45.3 months; 95% CI 37.4-53.2; stage 3 mean 38.8 moths, 95% CI 29.1-48.4). Authors also go on to discuss how the majority of children developing AKI were less than 5 years of age, implying that younger children are more prone to AKI development[48].

An association with height or weight and AKI was not statistically significant in critically ill children in the one study documenting these demographics[50], and was not reported in the other study[48].

Both studies reported the aetiologies of AKI episodes. In one study[50], 4 of 102 children (3.9%) were reported to have toxic nephropathy as the cause of AKI. Sepsis (35/102 children, 34.3%) and hypoxia (28/102 children, 27.5%) were the most common causes of AKI in this critically ill sample of children[50]. In the second eligible study of critically ill children[48], the leading cause of AKI was also sepsis (32.1% of stage 1, 32.7% of stage 2, 40.4% of stage 3), followed by post-cardiac surgery (30% of stage 1, 21.4% of stage 2, 13.1% of stage 3) then hypoxia (18.3% of stage 1, 18.5% of stage 2, 10.1% of stage 3). In this study, a toxic cause accounted for 0.4% of stage 1, 1.2% of stage 2, and 2% of stage 3 AKI[48].

One study[50] demonstrated a longer PICU length of stay in children with AKI than those without (mean 7.9 days, SD 7.3 compared to mean 5.0 days, SD 5.7, p=0.0003) in unadjusted models (which included age and gender as confounding variables). This finding was further broken down to show that the severity of AKI was significantly associated with the length of PICU stay. Those in pRIFLE category Risk had a mean length of PICU stay of 5.9 days (SD 4.8), Injury of 10.1 days (SD 9.1), Failure of 9.7 days (8.5) (p=0.03)[50]. Mean length of stay could potentially be slightly lower in the Failure group due to the highest rate of mortality in this group. In the other study of critically ill children[48], children with more severe AKI had significantly longer length of both PICU and hospital stay. Children with KDIGO stage 1 AKI had a mean length of PICU stay of 7.6 days (95% CI 6.0-9.1, p<0.001) and a hospital stay of 8.0 days (95% CI 5.3-10.7, p<0.001), stage 2 mean PICU stay 11.6 days (95% CI 9.8-13.4, p<0.001) and hospital stay 15.0 days (95% CI 11.9-18.1, p<0.001), and stage 3 PICU stay 12.2 days (95% CI 9.9-14.4, p<0.001) and hospital stay 15.5 days (95% CI 11.5-19.4) in unadjusted models.

In critically ill children[50], mortality was significantly associated with AKI, with 5.46% mortality in those without AKI, and 28.57% in those with AKI (p<0.0001). Mortality was high in this paper[50] (34.3% in the whole cohort). It is worth noting that in this particular study[50], sepsis was the most common cause of AKI (34.3%, 35 of 102 patients with AKI) which is associated with high mortality. This can be further analysed by the severity of AKI. Patients with more severe AKI had a higher mortality rate in this study[50] (19.5% of in the Risk category, 37.1% in the Injury category, and 53.9 in the Failure category, p=0.01). Mortality is notably higher in this paper[50] with a critically ill population than seen in other populations, which is to be expected. The other paper considering critically ill children[48] reported that stage 1 AKI doubled the risk of mortality (OR 2.54, 95% CI 1.39-4.62, p=0.002) compared to children without AKI with a PRISM (Paediatric Risk of Mortality) score (a factor for predicting mortality rate in PICU patients) of 7.9 (SD 6.5, 95% CI 7.0-8.6). Moreover, more severe AKI was again associated with increased risk of in-hospital mortality (stage 1 OR 2.54, 95% CI 1.39-4.62, p=0.002; stage 2 OR 6.33, 95% CI 3.65-10.96, p<0.001; stage 3 OR 23.9, 95% CI 13.4-42.4, p<0.001)[48] in unadjusted models. In multivariable analysis, hypervolemia (OR 5.3, 95% CI 2.6-10.9, p<0.001), hypocalcaemia (OR 2.02, 95% CI 1.06-3.8, p=0.03) and anaemia (OR 4.5, 95% CI 2.1-9.4, p<0.001) were identified as features of renal impairment that were

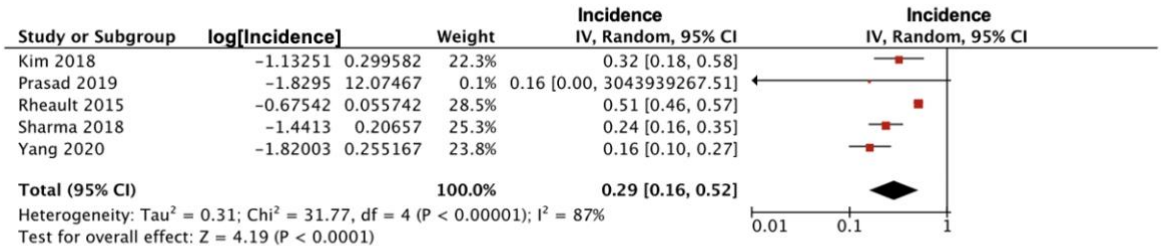
predictors of mortality in one paper[48], whilst hypovolaemia (OR 2.45, 95% CI 1.09-5.51, p<0.05), mechanical ventilation (OR 12.23, 95% CI 1.90-92.04, p<0.05), RIFLE class Failure (OR 2.88, 95% CI 1.38-6.04, p<0.05) and RRT initiation (OR 2.20, 95% CI 1.18-4.12, p<0.05) were all recognised as predictors of mortality in the other[50].

Both studies reported the need for RRT as a treatment modality. Of critically ill children from one study[50], 9 of the 102 patients (8.8%) required RRT, all of which were from the Failure group. From the other study[48], 11.4% (number of patients not reported) of the critically ill children required RRT (95% CI 8.7-14.4).

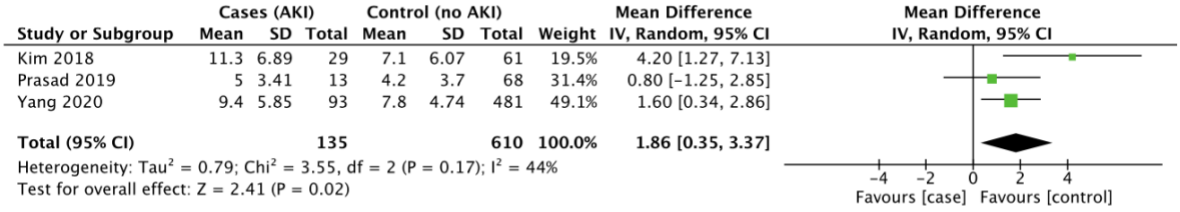
Another important finding was that after multivariable analysis, the presence of anaemia is associated with poor outcome (a predictor of mortality) in this population of children with AKI (OR 4.5, 95% CI 2.1-9.4, p<0.001)[48]. Acidosis, hypervolaemia and hypocalcaemia were also statistically significant predictors of mortality (OR 1.8, 95% CI 1.0-3.4, p=0.05) (OR 5.3, 95% CI 2.6-10.9, p<0.001) (OR 2.02, 95% CI 1.06-3.8, p=0.03) respectively[48]. Hypervolaemia was a predictor of mortality seen in the other study of critically ill children, too (adjusted risk ratio (ARR) 2.45, 95% CI 1.09-5.51)[50].

2.4.4.3 Children with Nephrotic Syndrome

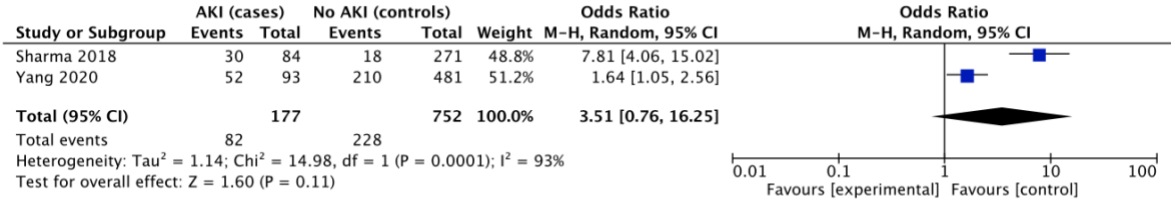
A) Overall incidence of AKI in total cohort of children with nephrotic syndrome



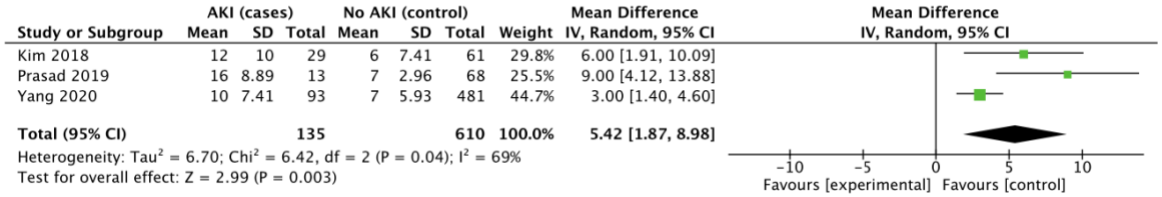
B) Mean age (years) in cases vs controls



C) NTMx exposure in cases vs controls



D) Mean length of stay (days) in cases vs controls



E) Mortality in cases vs controls

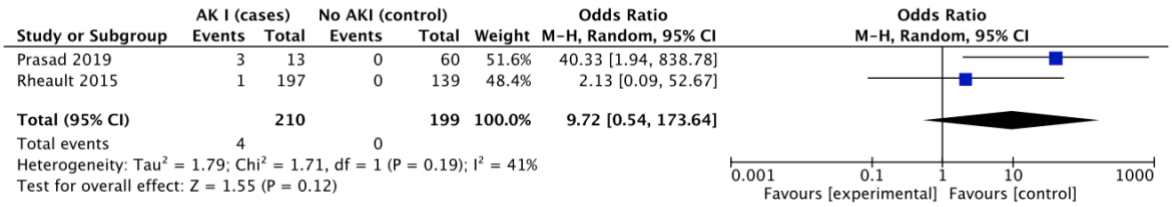


Figure 2.5: Forest plots of outcomes and risk factors in hospitalised children with Nephrotic Syndrome

Six[42, 45, 46, 51, 56, 57] of the papers meeting the eligibility criteria for the systematic review were conducted in a population of children with nephrotic syndrome. Five[42, 45, 46, 51, 56] of these

papers were able to be included in the meta-analysis. The paper[57] that could not be included in the meta-analysis was a prospective observational study of children with NS and AKI, therefore did not display data in the format suitable for meta-analysis (i.e. did not report incidence of AKI or comparisons of outcomes as only enrolled patients with AKI).

The five papers homogenous enough for meta-analysis (reported incidence of AKI (despite differences in AKI definitions) in the population of children with nephrotic syndrome) reported a range of incidence of AKI from 16%[45, 56] to 51%[46].The pooled incidence of AKI in children with NS was 29% of all hospitalisations (p<0.0001, 95% CI 16-52%, pooled data from five papers[42, 45, 46, 51, 56] (n=1715 hospitalisations)) (**figure 2.5A**). However, results may be affected depending on whether the KDIGO or pRIFLE criteria was used to define AKI, and whether AKI at admission or also during the stay was counted, as considered in the discussion section of this chapter. These differences could provide potential explanations for the high heterogeneity (high I-squared) in figures 2.4 A-E.

Children with AKI were older than those without (p=0.02, mean difference 1.86 years, 95% CI 0.35-3.37, pooled data from three papers[42, 45, 56] (n=745 hospitalisations)) (**figure 2.5B**). This supports the finding described in one of these three papers (retrospective cohort study by Yang et al[56]) that longer duration of nephrotic syndrome was a risk factor for developing AKI.

All papers demonstrated nephrotoxin exposure as a risk factor for the development of AKI, although the pooled data did not reach statistical significance (P=0.11, odds ratio 3.51, 95% CI 0.76-16.25, pooled data from two papers[51, 56] (n=929 hospitalisations)) (**figure 2.5C**).

Both Sharma[51] (n=355) and Yang[56] (n=363 accounting for 574 hospitalisations) reported that lower albumin level was also a risk factor for development of AKI, however this was not a significant risk factor seen in smaller studies[42, 45, 46]. In the prospective study by Yaseen et al[57], 92 of 119 (77.3%) of the cohort with AKI had hypoalbuminemia.

A retrospective cohort study by Rheault et al[46] did not have data suitable for meta-analysis. However, it supports the finding that nephrotoxin exposure is a risk factor for AKI, by

concluding that nephrotoxic medication exposure (p=0.002, odds ratio 1.35, 95% CI 1.11-1.64), days of nephrotoxic medication exposure (p=<0.001, odds ratio 1.10, 95% CI 1.05-1.15) and medication exposure intensity (p=0.01, odds ratio 1.34, 95% CI 1.09-1.65) were significantly associated with the development of AKI.

Calcineurin inhibitors (CNI) and methylprednisolone pulse therapy in particular showed statistical significance in being associated with the development of AKI (p=0.027 and p=0.018 respectively) in the study by Yang et al[56] (n=363 accounting for 574 hospitalisations).

In a smaller observational study by Prasad[45], CNI use was not statistically significant (p=0.13), ACEI, vancomycin, and furosemide infusions were found to be associated with the development of AKI (p=0.04, p=0.003, p<0.001 respectively). Associations with other nephrotoxins considered (oral/intermittent IV bolus furosemide, CNI, and amikacin) were not statistically significant.

The only statistically significant finding in relation to nephrotoxins in a small retrospective cohort study by Kim et al[42] was cyclosporin A (CyA) in combination with Renin-Angiotensin System Inhibitor (RASi) (p=0.018, odds ratio 3.440, 95% CI 1.235-9.578) as a risk factor for AKI. Other nephrotoxins reported in this study (CyA alone, tacrolimus, RASi, and methylprednisolone) were not shown to be statistically significant.

Findings from these studies in relation to specific nephrotoxins or combinations are displayed in **table 2.4.**

Table 2.4: Nephrotoxins identified in studies of children with NS

Drug	Significant or non-significant findings
ACEi	Significant in Prasad 2019[45]
CNI (cyclosporin, tacrolimus)	CNI significant in Yang 2020[56] CNI not significant in Prasad 2019[45] Tacrolimus not significant in Kim 2018[42] Cyclosporin A not significant in Kim 2018[42]
CyA and RASi combination	Significant in Kim 2018[42]
Furosemide	Significant in Prasad 2019[45]
Methylprednisolone pulse therapy	Significant in Yang 2020[56] Not significant in Kim 2018[42]
Vancomycin	Significant in Prasad 2019[45]

One paper[51] showed a significant association between a higher incidence of hypertensive children with NS developing an AKI (69.04% of cases (AKI) had hypertension, 32.84% of controls (no AKI) had hypertension, $p<0.0001$).

Proteinuria was associated with the development of AKI in children with nephrotic syndrome, with one paper[51] showing mean urinary protein as 11.89 g/day (SD 2.7) in the cohort with AKI, compared to 10.17 g/day (SD 1.82) in those without ($p<0.0001$). The urinary protein levels not differ significantly between cases and controls in one study[56].

One study[56] showed cholesterol levels to be significantly higher in children with nephrotic syndrome and AKI (median 446 mg/dL), than those without AKI (median 382 mg/dL) ($p=0.004$).

Data from a prospective study by Yaseen et al[57] (n=119) could not be included as part of the meta-analysis due to the difference in study type (a prospective observational study of children with NS and AKI), however the findings are supported by this study that showed drug toxicity to be the second most common cause of AKI in 52 of 119 the cases (second to infection) of children with nephrotic syndrome. Interestingly, drug toxicity was also identified as a predictor of AKI in idiopathic nephrotic syndrome progressing to CKD ($p=0.029$, odds ratio 2.3, 95% CI 1.08-4.87).

In the study by Rheault et al[46], age was displayed in groups rather than as a mean with a standard deviation, or a median and interquartile range (which could have been used to estimate mean and SD), meaning it could not be included in the meta-analysis with the other studies. AKI was significantly associated with length of stay (mean duration 1.73 days, SD 0.63 [log]days compared with mean duration 1.26 days, SD 0.49 [log]days in hospitalisations without AKI, p<0.001), however age had no effect on the risk of AKI in this study.

The different clinical patterns of nephrotic syndrome were relevant in relation to the incidence of AKI. One study[51] showed children with Steroid-Dependent Nephrotic Syndrome (SDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS) were more likely to develop AKI compared to children with Steroid-Sensitive Nephrotic Syndrome (SSNS) (p<0.0001)[51] (odds ratio 2.06, 95% CI 1.33-3.19)[46]. Two studies[45, 56] showed steroid resistance to be more common in cases than controls after univariate logistic regression analysis (odds ratio 1.95, 95% CI 1.23-3.09, p=0.004)[56] however after multivariate logistic regression analysis this was not a significant risk factor in either. Another study showed there was no statistically significant differences between AKI and non-AKI groups in terms of sensitivity to initial steroid therapy (SSNS vs SRNS)[42]. Two studies[42, 46] reported that children with SDNS/frequently relapsing NS did not have a higher risk of AKI than children with infrequently relapsing NS[42, 46] (odds ratio 0.87, 95% CI 0.57-1.34, p=0.53)[46], (p=0.403)[42].

AKI was associated with prolonged hospital stay (p=0.003, mean difference 5.42 days, 95% CI 1.87-8.98, pooled data from three papers[42, 45, 56] (n=745 hospitalisations)) (**figure 2.5D**), but an association with mortality did not reach statistical significance (p=0.12, odds ratio 9.72, 95% CI 0.54-173.64, pooled data from two papers[45, 46] (n=409 patients, 4 deaths)) (f**igure 2.5E**). Mortality was reported in a prospective study[57] in children with nephrotic syndrome, which observed death in 5 of 119 children with AKI. This was not included in the meta-analysis as there was no control group. Furthermore, children with stage 3 AKI had longer length of stays (median 15 days) than children with stage 1 or 2 AKI (median 8 days (p=0.001) and median 8 days (p=0.003) respectively) in one study[56].

More long-term outcomes were reported in some studies. One study[56] reported that 93.5% (n=87/93) of AKI episodes recovered without a deterioration in kidney function. The remaining 6 (6.5%) episodes (all with stage 3 AKI) progressed to varying degrees of CKD[56]. Two children (2.15%) (both with Focal Segmental Glomerulosclerosis (FSGS)) became dialysis dependent following AKI (2/93)[56]. No cases of mortality were documented[56]. In another study[57], 54.6% (65/119) children recovered from AKI, with 41.2% (49/119) developing various degrees of CKD (did not report RRT as an outcome), and also mortality 4.2% (5/119). Of these 5 deaths, 2 patients were classified in the Risk (pRIFLE) category, and 3 in the Failure category at the time of presentation[57]. One study[45] with a small cases group (13 episodes of AKI in 13 children) reported complete renal recovery in all five children with stage 1 AKI, one complete recovery and one partial renal recovery in the two with stage 2 AKI, and of the 6 children with stage 3 AKI, one complete recovery, two partial recoveries, and three deaths (23.1%) (3/13). One child required RRT (Peritoneal Dialysis (PD)) (7.7%) (1/13), who was from the stage 3 group[45]. 12 patients (6.09%) (of 313 hospitalisations in 197 children) required RRT in another study[46], and one case of mortality was reported in a child with stage Failure AKI (0.51%) (1/197).

Long term outcomes were not documented in detail in two studies[42, 51], however both reported that no children went on to require RRT after AKI, and no children died in one study[42] (mortality not documented in the other[51]).

2.4.4.4 Children having undergone congenital heart surgery

One eligible paper[54] studied children admitted following Congenital Heart Surgery (CHS) and their exposure to nephrotoxins. Cases (n=32) and controls (n=122) were high vs low exposure, as opposed to AKI vs no AKI. High exposure was defined as receipt of $\geq$3 nephrotoxins concurrently (as per the NINJA collaborative). Nephrotoxin exposure was common in this population, with 131 of 154 children (85.1%) being exposed to at least one nephrotoxin. High exposure was seen in 32 of 154 patients (20.8%). The incidence of AKI was more common in children with high nephrotoxin exposure (62.5%) than no high exposure (50.8%) however authors concluded this was not significant after adjusting for confounders (p=0.24). Multivariable analysis was carried out which demonstrated that nephrotoxin exposure was not associated with the development of AKI (adjusted RR 1.2,

95% CI 0.8-1.8), nor the development of severe (stage 2 or 3) AKI (adjusted RR 1.1, 95% CI 0.5-2.3).

The median age of the entire cohort was 1.7 years (IQR 0.18-4.95) and mean age was 3.2 years (SD 4.36). This is lower than the average ages seen across many of the other studies due to the cohort studied and that congenital heart surgery is typically in young children. In this study, children with high exposure were older than those without (mean 5.0 years, SD 5.56 vs mean 3.2 years, SD 4.36). Age in children with AKI and without AKI was not reported.

Statistically significant findings in this study included increased cardiopulmonary bypass (CPB) time in those with high nephrotoxin exposure (mean 171.2 minutes, SD 92.2) compared to those without high exposure (mean 131.3 minutes, SD 96.4) (p=0.04) and increased length of stay in the high exposure group (mean 16.9 days, SD 18.1) compared to the group without high exposure (mean 12.8 days, SD 18.7) (p=0.01).

At follow-up (3 months after AKI), the rate of renal recovery was similar in both cases (80.0%) and controls (69.4%) (p=0.36) and the difference was not significant. However, renal recovery was less common at follow-up in children who had severe AKI (KDIGO stage 2 or 3) (51.6% vs 84.3%, p=0.001) however this was independent of nephrotoxin exposure.

2.4.4.5 Very low birth weight infants

One paper[47] studied nephrotoxin exposure in Very Low Birth Weight (VLBW) infants (birth weight $\leq$1500g) with the aim of determining any association between nephrotoxin exposure and AKI in this cohort.

AKI was seen in 28 (26.2%) of the cohort (n=107), who together had 41 episodes of AKI. In this cohort, the majority of infants (21) (75%) with AKI were classified as KDIGO stage 1 AKI, 6 (21.4%) stage 2, and only 1 patient (3.6%) had stage 3 AKI.

86.9% (93 of 107) of this vulnerable population had exposure to at least 1 nephrotoxin across the 12-month study period. Infants were excluded if they were admitted at more than 2 days of age due to data and records being inaccessible or incomplete, or if they did

not survive to discharge. Incidence may have been higher if these patients were included, who had a good chance of having been exposed to nephrotoxins. The mean number of nephrotoxins received was 1.64 (SD 1.08) and the median was 2 (no IQR reported).

The authors reported outcomes as total nephrotoxic medication days (sum of the number of treatment days for all nephrotoxins received), and mean nephrotoxic medications per day (total nephrotoxic medication days divided by length of stay in days).

Patients developing AKI had greater nephrotoxic medication days than those without AKI (mean 23.9 days vs 9.9 days, $p<0.001$). In logistic regression models, total nephrotoxic medication days were significantly associated with AKI development ($p<0.001$). However, in multivariate models (adjusting for birth weight or gestational age), the association was not statistically significant. A linear association with total nephrotoxic medication days and peak creatinine levels was significant even after accounting for birth weight and gestational age.

The group with AKI had higher mean nephrotoxic medications per day, than those without AKI (0.24 vs 0.15, $p=0.003$). Birth weight and mean nephrotoxin exposure per day had an inverse linear relationship, with smaller infants receiving more nephrotoxins per day on average ($R^2=0.169$, $p<0.001$). AKI was associated with nephrotoxins received per day in logistic regression models, however the association was non-significant in multivariate models (adjusting for birth weight and gestational age). There was a linear association with mean nephrotoxic medications per day and peak creatinine in infants who developed AKI, which persisted after adjusting for birth weight and gestational age ($R^2=0.378$, $p=0.003$).

Furthermore, this study analysed the timing of AKI in relation to the exposure to nephrotoxic medications. 47% of the nephrotoxins were administered prior to AKI episodes (the remaining 53% of the exposures occurred after creatinine had peaked).

No infant in this study received dialysis.

The smallest, most immature infants, and those who developed AKI had the most nephrotoxin exposure in this study.

2.4.4.6 Critically ill neonates/infants

One eligible study had a population of neonates (<28 days old) and infants (≥28 days old), all exposed to nephrotoxins[52].

This was an interventional study, incorporating NINJA (termed Baby NINJA) into patients in a neonatal intensive care unit, to test if AKI was preventable in this population. As in previous studies incorporating NINJA[28, 29], infants were screened for high-risk nephrotoxic medication exposure (≥3 nephrotoxic medications within 24 hours, or ≥4 calendar days of IV aminoglycoside) and began daily SCr monitoring if flagged, until 2 days after the end of exposure or AKI (whichever was last). Discussions then took place regarding alternative medications, drug dosages, timing of drug levels, and hydration status.

Across the study period (30 months), the incidence of AKI was 19.7% (94 of 476) of infants classed as having high nephrotoxin exposure. The incidence of AKI before intervention was 25.2% (p=0.339), which decreased to 11.0% (p<0.001) in the sustainability era (the study period in which the intervention was occurring), suggesting an association between nephrotoxin exposure and AKI. AKI prevalence was reported per 1000 patient days and was 3.1 pre-NINJA era (p=0.055), 5.1 in the initiation era (p<0.001), dropping to 1.1 In the sustainability era (p<0.001).

The rate of high nephrotoxic medication exposure also decreased pre- and postintervention. The rate in the pre-NINJA era was 12.4% (p=0.034), in the initiation era 16.4% (p<0.001), and 9.6% in the sustainability era (p=0.030).

Authors estimated that approximately 100 AKI episodes were prevented alongside 157 days of AKI in the NICU throughout the 18-month sustainability era.

2.4.4.7 Infants with a diagnosis of neonatal encephalopathy

Infants (≥ 34 weeks gestational age) with a diagnosis of Neonatal Encephalopathy (NE) were the study population in one retrospective analysis[43]. This multicentre study was performed

by identifying infants with a diagnosis of NE from the Analysis of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) database.

113 infants with NE were included, of whom 47 developed AKI – resulting in an AKI incidence of 41.6% in this cohort.

Infants with NE who were exposed to nephrotoxins (defined as exposure to gentamicin, vancomycin, furosemide, indomethacin within first 7 days) were more likely to develop AKI than those not exposed to nephrotoxic drugs (p=0.10) – with 74.2% (49 of 66) with no AKI being exposed to nephrotoxins, and 87.2% (41 of 47) with AKI being nephrotoxin exposed. Nephrotoxin exposure was included as part of multivariate logistic regression to determine associations between other risk factors and AKI (outborn, Intrauterine Growth Restriction (IUGR), Meconium-Stained Amniotic Fluid (MSAF)) however adjusted values for nephrotoxin exposure were not reported.

This study showed no significant differences between infants with NE and AKI compared to infants with NE without AKI in terms of gestational age at delivery (p=0.64), ethnicity nor race (p=1.00 and p=0.50 respectively), or birth weight (p=0.55).

Other risk factors identified to increase odds of AKI in this study, that were not reported in other populations, were being outborn (outside the admitting institution) (OR 4.3, 95% CI 1.2-14.8, p=002), IUGR (OR 10.3, 95% CI 1.1-100.5, p=0.04) and MSAF at delivery (OR 2.8, 95% CI 1.04-7.7, p=0.04) which were all significant after multivariate logistic regression.

Infants with NE and AKI had longer lengths of hospital stays, than infants with NE and no AKI (adjusted parameter estimates: mean difference 8.48 days, 95% CI 0.79-16.2 days, p=0.03). In this study, mortality was not significantly different in infants with or without AKI (unadjusted p value p=1.00).

2.4.4.8 Children having undergone stem cell transplant

Benoit et al[41] conducted a prospective cohort analysis in inpatient paediatric stem cell transplantation (SCT) across a 4 year period – 2 years pre-, and 2 years post-intervention. Outcomes were reported similarly to those seen in previous NINJA projects[28, 29, 52].

The intervention implemented was a change in the antimicrobial algorithm (for 1st line fever coverage from Piperacillin-Tazobactam (PTZ) to Cefepime, and altered guidance on duration of therapy and also vancomycin double coverage). Nephrotoxins were defined by the NINJA system[28] and data on nephrotoxin exposure in general (not specific to PTZ and cefepime) was collected, hence this paper met inclusion criteria.

The intervention resulted in a decrease in nephrotoxin exposure and NTMx-AKI. Nephrotoxin exposure decreased from 143 to 96 per 1000 patient days (33% decrease), and NTMx-AKI decreased from 24.1 to 6.2 days per 1000 patient days (74% decrease). Mean rates of KDIGO stages 1, 2 and 3 NTMx-AKI also decreased by more than half following the intervention (days of stage 1 NTMx-AKI decreased from 12.8 to 3.1 per 1000 patient days, stage 2 from 8.9 to 3.9, and stage 3 from 3.0 to 0.5). Authors report that there was no increase in treatment failures seen post-intervention (no increase in the frequency of enterococcal infections).

Although incidence was not directly reported in this study, authors refer to Goldstein et al 2016 study[28], where the incidence of AKI seen in SCT patients who were exposed to nephrotoxins was 39%. The study[28] also demonstrated that patients admitted for bone marrow transplant services was one of the populations most commonly exposed to nephrotoxins (accounting for 24% of the cohort studied).

2.4.4.9 Hospitalised children with cancer

Two studies of different designs (one retrospective cohort study[55], another prospective interventional study[58]) reported outcomes in children under oncology services. The data from these two studies were not meta-analysed due to differences in the population that outcomes were reported in. The retrospective cohort study[55] included children with cancer,

both exposed and not exposed to nephrotoxins, whilst the interventional study[58] reported outcomes in nephrotoxin-exposed children with cancer.

Xiong et al[55] conducted a retrospective cohort study in hospitalised children with cancer across a two year period. A large proportion (55.7%) of the cohort studied was children with leukaemia[55]. Other cancers in the study population were cancer of the nervous system (11.2%), lymphoma (9.7%), urinary system cancer, hepatic cancer, and retroperitoneal malignancies[55]. Of the 9828 children with cancer meeting inclusion criteria, 1657 developed AKI (16.9%)[55]. 549 (5.6%) of these were identified as community-acquired AKI (CA-AKI), and 1108 (11.3%) were hospital-acquired AKI (HA-AKI)[55].

Risk factors identified for AKI in this cohort varied between CA- and HA-AKI. Younger age was shown to be associated with a higher incidence of AKI in both CA- and HA-AKI ($p<0.001$)[55]. Those without AKI had a mean age of 7.2 years (SD 4.9) compared to those with CA-AKI having a mean age of 6.2 years (SD 4.4) and HA-AKI 5.8 years (SD 4.5)[55].

A large proportion of patients were exposed to nephrotoxins which was significantly associated with the development of HA-AKI[55]. The highest hazard ratios seen were in children with HA-AKI exposed to contrast media (Hazard Ratio (HR) 3.96, 95% CI 1.55-6.15) and diuretics (HR 1.68, 95% CI 1.35-2.09), compared to the total cohort of patients[55]. The use of chemotherapy drugs also increased the risk of HA-AKI (HR 1.10, 95% CI 0.89-1.36) [55]. Exposure to different chemotherapy drugs were reported in the children who did and did not develop AKI. Children treated with purine analogues had a greater incidence of AKI (15.99%) than children treated with other classes of chemotherapy drugs ($p<0.05$)[55].

Differences in AKI rates were seen in children with different types of cancer. The highest incidence of AKI was seen in those with urinary system cancer (25.8%), hepatic cancer (19.4%) and retroperitoneal malignancies (19.1%)[55]. Furthermore, patients with cancer who developed shock during their hospital stay had a higher incidence of AKI than those who did not develop shock (hazard ratio 6.30, 95% CI 3.98-9.98)[55].

Children with AKI had longer length of hospital stays than children without AKI (p<0.001)[55]. Children with no AKI had a median length of stay of 26 days (IQR 15-47), whilst those with CA-AKI had a median of 38 days (IQR 22-62), and HA-AKI 33 days (IQR 17-57)[55].

The incidence of kidney recovery was reported in 992 patients with HA-AKI who had one or more SCr results following AKI[55]. Recovery of kidney function before discharge was seen in 609 (66.1%) children[55]. Patients with stage 3 AKI had a longer recovery time (median 13.0 days, 95% CI 11.0-19.3) than those with stage 1 (10.0 days, 95% CI 8.9-11.9 days) or 2 (10.5 days, 95% CI 8.9-14.9) AKI[55].

Mortality was higher in hospitalised children with cancer who had AKI (90 of 1657) than without (74 of 8171) (5.4% vs 0.9% respectively)[55]. The rate of mortality was also higher in those with HA-AKI than those with CA-AKI (6.6% vs 3.1%, p<0.001)[55].

Outcomes were also reported in those who died compared to those who did not. The incidence of AKI in children who died were higher than those who survived (54.9% vs 16.2%, p<0.001)[55]. More patients who died spent time in ICU than those who did not (34.2% vs 9.6%, p<0.001)[55]. Furthermore, AKI stage was significantly associated with the rate of mortality (p<0.001)[55]. In the children who died (both with and without AKI), AKI stage 3 was most common (26.8%, 44 of the 164 who died, compared to 11.6% with stage 1, and 16.5% with stage 2), whereas AKI stage 1 was most common in children who did not die (7.9%, 766 of 9664 who did not die, compared to 4.3% with stage 2, and 4.0% with stage 3)[55].

Young et al[58] conducted an interventional study targeting nephrotoxin exposure, with the aim of reducing AKI in children with cancer. This study implemented similar interventions (cefepime replaced PTZ for febrile neutropenia, vancomycin exposure reduced, and nephroprotection for patients receiving IV contrast) seen in Benoit et al[41] SCT interventional study, also part of the Cincinnati group. Again, outcomes were reported similarly to those seen in previous NINJA projects[28, 29, 52].

The incidence of AKI in this cohort of children with cancer who were all exposed to nephrotoxins was 21.60% (111/514) of all exposure episodes (111 AKI episodes (defined as

any exposed patient who went on to develop AKI), in 273 unique patients with 514 exposure episodes)[58].

The rate of nephrotoxin exposure decreased by 49% following the intervention (from 16.08 to 8.17 per 1000 patient days)[58].

NTMx-AKI episodes also decreased, by 45% (from 3.48 to 1.92 per 1000 patient days)[58].

The study[58] evaluated rates of repeat positive cultures, to screen for any negative consequences of the interventions implemented. The findings from pre- and post-exposure were found not to be significant, and therefore no negative consequences were noted from this evaluation.

In this study[58], rates (number of episodes) of AKI did not change with the implementation of nephroprotection in patients receiving IV contrast.

2.4.4.10 Renal patients

One study[53] of the eligible papers was a prospective observational study with the primary focus of determining short-term outcome specifically in patients admitted to a tertiary paediatric nephrology centre.

Across the 12-month study period, 116 patients were identified and diagnosed with AKI, who were followed up at 3 months and then reported as recovered, CKD, ESRD, death, or lost to follow-up[53].

Of the cohort included, the mean age was 7.5 years (SD 4.4), and a larger proportion were male than female (60.3%)[53]. A large proportion of the cohort were in AKI pRIFLE stage Failure at presentation (89/116, 76.7%)[53]. 16 patients (13.8%) were in Injury and 11 (9.5%) patients were in Risk[53].

The main causes of AKI seen in this cohort of renal patients were glomerulonephritides (Post-infectious Glomerulonephritis (PIGN) (n=26, 35.1% of renal cases) and crescentic (n=20, 26% of renal cases)) and obstructive urolithiasis (n=24, 85.7% of post-renal cases)[53].

Toxin-induced AKI was seen in 2 (2.7%) of the 74 renal cases of AKI in this study (63.8% total cohort)[53].

In terms of outcomes, 68 (58.5%) patients recovered, 18 (15.5%) developed CKD, 22 (19%) developed ESRD, and there was 6 (5.2%) cases of mortality[53]. 2 patients were lost to follow up. Of the 2 patients with AKI caused by drugs, 1 recovered, and 1 went on to develop CKD[53]. The severity of AKI was significant in terms of the outcome. All patients with stage Risk AKI (n=11) recovered (100%), and 12 of 16 patients in Injury category recovered (75%) and 4 developed CKD (25%)[53]. However of those in Failure category (n=89), 45 patients recovered (15.7%), 14 developed CKD (15.7%), 22 developed ESRD (24.7%), 6 died (6.7%) and 2 (2.2%) were lost to follow-up[53].

Authors compared variables in recovered vs unrecovered patients following an episode of AKI (rather than a case and control group of AKI vs no AKI). A larger proportion of patients less than 5 years old were seen in recovered patients (27 of 69, 39.7%) than unrecovered (12 of 47, 40.5%) however this was not found to be statistically significant (p=0.09)[53] (for the values of recovered and unrecovered patients here we assume that one from the two patients lost to follow up fitted in each group, although this is not clearly explained in the paper). Variables that had a statistically significant association with non-recovery were hypertension, severe anaemia, oedema, volume overload, requirement for mechanical ventilation, initiation of dialysis and the need for more than 5 dialysis sessions ($p<0.05$ in all variables)[53].

2.4.5 Secondary outcomes

2.4.5.1 Describe outcome measures to report AKI epidemiology in children

Outcome measures used to report AKI in hospitalised children varied across studies. These are summarised in **table 2.2**.

2.4.5.2 Describe identified risk factors for the development of AKI in children

Many of the included studies reported or described known risk factors for AKI in children. The most commonly reported risk factors are described below, whilst risk factors more specific to individual patient populations (for example those with nephrotic syndrome) are described in the relevant subsections above in **section 2.4.4**.

2.4.5.2.1 Age

Of the two studies reporting outcomes in nephrotoxin-exposed and unexposed non-critically ill children, both reported younger age as a risk factor for the developing AKI[21, 44]. Of the four papers[42, 45, 46, 51, 56] reporting age as a variable in children with nephrotic syndrome, three found that children developing AKI were of an older age[42, 45, 56]. In one paper reporting risk factors in critically ill children[50] an association with age was not statistically significant, although children with AKI were younger than those without. In the other study of critically ill children[48], the majority of patients developing AKI were less than five years of age, and those with more severe AKI were younger than those with less severe AKI. Age was not formally analysed as a risk factor for AKI development in VLBW infants[47], however infants with a lower gestational age were more likely to receive nephrotoxic medications than those with a higher gestational age. Gestational age at delivery was not a significant finding in infants with NE and AKI compared to without AKI[43]. In hospitalised children with cancer, younger age was associated with a higher incidence of AKI (both community- and hospital-acquired)[55].

2.4.5.2.2 Nephrotoxin exposure

All five studies concerning non-critically ill children considered nephrotoxin exposure as a risk factor for the development of AKI[21, 28, 29, 44, 49]. Of the 6 papers studying children with nephrotic syndrome, all addressed nephrotoxins as a cause of risk factor of AKI[42, 45, 46, 51, 56, 57]. No association was seen between exposure to nephrotoxins and the development of AKI in children having undergone CHS[54], however authors suggest nephrotoxin use is a modifiable risk factor for the development of AKI. Both studies of critically ill children[48, 50] reported toxic nephropathy as being the cause for some of the AKI cases. However, they did

not directly discuss the association of nephrotoxin exposure with the development of AKI. In very low birth weight infants[47], an association with total nephrotoxin medication days and mean nephrotoxins per day with AKI was not significant after multivariate models. However, in this population[47] an association with both total nephrotoxic medication days and mean nephrotoxic medications per day with peak creatinine levels was significant. In infants with NE[43], those exposed to nephrotoxic drugs in the first 7 days were more likely to develop AKI than those unexposed. One interventional study in SCT patients[41] demonstrated a reduction in NTMx-AKI rates after reducing nephrotoxin exposure, implying nephrotoxins are a risk factor for AKI development in this population. In hospitalised children with cancer, one study[55] showed exposure to nephrotoxins was associated with the development of AKI and in particular HA-AKI, whilst the other[58] demonstrated reduction in NTMx-AKI rates alongside reducing nephrotoxin exposure.

2.4.5.2.3 Ethnicity

Race was significant in some studies for the risk of AKI. One study[46] showed non-white children with nephrotic syndrome had a higher risk for AKI (OR 1.70, 95% CI 1.17-2.48, p=0.01)[46] than other children with nephrotic syndrome. Race nor ethnicity was not reported in the other papers of children with nephrotic syndrome[42, 45, 51, 56, 57]. Race was only reported as part of the demographics in an AKI cohort vs a no AKI cohort in one paper[44] of non-critically ill children which showed no statistical significance between race and AKI between cases and controls (p=0.7). No significant differences in race nor ethnicity were seen in the cohort of infants with neonatal encephalopathy and AKI compared to those without AKI (p=1.00 and p=0.50 respectively)[43].

2.4.5.2.4 Weight

Weight was only reported in one study of non-critically ill chidlren[44], which concluded that patients with AKI had lower weight-for-age (z-score, −0.4 vs. 0.0; p-value <0.001; nonmissing = 2321). In critically ill children, an association with neither weight nor height was statistically significant in one paper[50], and not reported in the other[48]. In VLBW infants[47], birth weight had an inverse linear relationship with mean nephrotoxic medication exposure

per day – with smaller infants receiving more nephrotoxins on average. Birth weight in infants with NE was not significant for the development of AKI (p=0.55)[43].

2.4.5.3 Describe strategies that have demonstrated improvements/have been shown to mitigate AKI

Several interventional studies were included in the systematic review, which are described by the intervention and outcome measures both pre- and post-intervention in **table 2.5**.

Table 2.5: Table of interventional studies included in the systematic review

Study	Authors	Intervention	Outcome measure	Pre-intervention measures	Post-intervention measures
A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury	Goldstein et al 2016[28]	Health Electronic Record (HER) screening for nephrotoxin exposure* and decision to support process. Recommended daily SCr monitoring in exposed patients. Substitution of a non-nephrotoxic or less nephrotoxic medication and/or pharmacokinetic drug concentration monitoring if appropriate.	AKI prevalence rate (per 1000 patient-days)	2.96	1.06
			High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	11.63	7.24
			Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	23.3	15.4
			AKI intensity rate (per 100 exposed patient-days)	27.7	19.1
A prospective multi-center quality		HER screening for nephrotoxin exposure† and decision to support process.	AKI prevalence rate (per 1000 patient-days)	1.7	1.3

improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children	Goldstein et al 2020[29]	Recommended daily SCr monitoring in exposed patients - for the duration of, and two days after, exposure ending. Substitution of a non-nephrotoxic or less nephrotoxic medication and/or pharmacokinetic drug concentration.	High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	7.0	6.9
			Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	23.6	15
			AKI intensity rate (per 100 exposed patient-days)	11.2	11.2
Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in the Neonatal Intensive Care Unit	Stoops et al 2019[52]	HER screening for nephrotoxin exposure‡, manually verified by pharmacists on weekdays. Performed at weekends by clinical team without automated report. Recommended daily SCr monitoring in exposed patients - for the duration of, and two days after, exposure ending or post-AKI resolution (whichever occurred last). No specific recommendation to adjust medications or alter length of therapy,	SCr compliance (%)	56.6	86.1
			AKI prevalence rate (per 1000 patient-days)	3.1	1.1
			High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	12.4	9.6
			Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	25.5	11.0
			AKI intensity rate (per 100 susceptible patient-days)	6.0	2.9

		instead the team would discuss possible alternative medications, drug doses, timing of drug levels, and hydration status based on patient-specific needs.			
Reduction in Nephrotoxic Antimicrobial Exposure Decreases Associated Acute Kidney Injury in Pediatric Hematopoietic Stem Cell Transplant Patients	Benoit et al 2019[41]	EMR screening for exposed§ patients. First line fever coverage changed from PTZ to cefepime. Limiting duration of antimicrobial exposures, specifically vancomycin.	Rate of PTZ usage (per 1000 patient-days)	196	33
			Rate of cefepime usage (per 1000 patient-days)	62	290
			Rate of vancomycin usage (per 1000 patient days)	62	41
			Rate of nephrotoxin exposure per 1000 patient-days)	143	96
			Rate of nephrotoxin associated AKI (per 1000 patient-days)	24	6
Reducing acute kidney injury in pediatric oncology patients: An improvement project targeting nephrotoxic medications	Young et al 2020[58]	EMR screening for exposed¶ patients. Cefepime replaced PTZ for febrile neutropenia.	Rate of nephrotoxic medication exposure (per 1000 patient-days)	16.08	8.17
			Rate of AKI episodes associated with nephrotoxic	3.48	1.92

		Vancomycin stewardship limited empiric courses to 72 hours (automatic stop date on electronic health record). Nephroprotection for IV contrast administered for high-risk patients.	medication exposure (per 1000 patient-days)		

*Exposure is defined as exposure to ≥3 nephrotoxins or an IV AG. Exposure started to be counted on the third day of AG. Considered exposed for 48hrs after stopping IV AG or reducing to <3 nephrotoxins.

†Exposure is defined as exposure to ≥3 nephrotoxins on the same calendar day or an IV aminoglycoside (AG) on ≥3 consecutive days. Considered exposed for 2 days after exposure ended.

‡Exposure is defined as exposure to ≥3 nephrotoxins within 24 hours or ≥4 calendar days of an IV AG.

§Exposure is defined as exposure to ≥3 nephrotoxins on the same calendar day, ≥3 days of IV AG, or ≥3 days of IV vancomycin. Considered exposed for 48 hours after exposure ended.

¶Exposure is defined as exposure to ≥3 nephrotoxins, ≥3 consecutive days of AG or ≥3 consecutive days of vancomycin

There were two interventional studies by Goldstein et al[28, 29] included in the meta-analysis of non-critically ill hospitalised children, which displayed a reduction in AKI rates after interventions were put in place. The interventions used in each study included daily SCr monitoring and substitution of nephrotoxic meds for less nephrotoxic medications. In their 2016 paper[28], 633 exposures and 398 AKI episodes were estimated to have been prevented across the 42 month study period – with AKI rate decreasing from 2.96 episodes per 1000 patient days, to 1.06 episodes per 1000 patient days. This particular intervention was screening the EMR to flag eligible (non-critically ill, hospitalised) nephrotoxin exposed patients who were receiving an IV aminoglycoside for 3 days or more, or 3 or more nephrotoxins simultaneously, followed by daily SCr monitoring in patients appearing on the trigger report and considering substitution for less nephrotoxic medications. A subsequent paper in 2020[29] estimated a total of 242 avoided AKI episodes across the 2-year study – with a 23.8% decrease in NTMx-AKI. This intervention was implementation of the NINJA program – SCr screening followed by substitution of nephrotoxins.

Similar findings were seen in critically ill children (neonates and infants were the study population) in a study by Stoops et al[52]. Interventions adapted for use in this population from those seen in the two Goldstein papers[28, 29] resulted in improved outcomes, including a reduction in high nephrotoxin exposure of 42% and a reduction in AKI rate of 78% - preventing approximately 100 AKI episodes.

Another interventional study[41] from the Cincinnati group demonstrated findings of the same nature. After substitution of a nephrotoxin (PTZ) for a less nephrotoxic drug (cefepime) alongside limiting vancomycin exposure, NTMx-AKI rates reduced by 74%[41].

In oncology patients, similar intervention (cefepime replacing PTZ) was seen to reduce NTMx-AKI episodes by 45%[58].

The improvements seen emphasise how recognising those with high nephrotoxin exposure and increased surveillance of these patients can mitigate AKI.

Nephroprotection was studied in hospitalised children with cancer[58], however rates (number of episodes) of AKI did not change with the implementation of nephroprotection in patients receiving IV contrast.

2.5 Discussion

2.5.1 Summary of evidence

AKI was common in children with a reported incidence between 16.9% and 62.5% in studies included in our review. The papers included had varying inclusion criteria and defined outcomes in different ways, which could have led to differences seen in significance of risk factors and outcomes, incidence rates, and exposure rates. Risk factors including but not limited to age, weight and nephrotoxin exposure were identified and outcomes such as length of hospital stay and mortality were described where possible.

2.5.1.1 Incidence of AKI

2.5.1.1.1 Non-critically ill children

The pooled incidence of AKI in non-critically ill hospitalised children was 32%, in comparison to 17% in non-critically ill, hospitalised, nephrotoxin-exposed patients. There are several explanations for the possible reasons for this that should be considered. Firstly, the two papers making up the meta-analysis for the incidence in noncritically ill children (32%) should be considered.

In the study by McGregor et al[44], the incidence reported was of all evaluated patients (n=2374). This is a different total number of children to the eligible patients (n=13,914) which if used, would produce a lower AKI incidence rate. Patients were eligible if they had at least 2 SCr measurements. The same requirement for 2 SCr measurements was observed in the other study by Moffett et al[21], which identified a total of 5437 patients with only 1160 meeting eligibility criteria. We can speculate that patients with sufficient SCr measurements (and therefore eligible for inclusion in these two studies) may have been more likely to have had risk factors for AKI (such as nephrotoxin exposure), or a diagnosis of AKI and therefore would have had more frequent renal function monitoring.

Two[28, 29] of the three[28, 29, 49] papers contributing to the pooled data for incidence in the nephrotoxin exposed cohort were interventional studies that had been shown to successfully reduce AKI rates. Therefore, AKI rates seen here are likely to be accurate in these centres implementing interventions, but could be lower than rates in other centres without such an approach. There was also variation in the way each study defined AKI. Some studies used pRIFLE which is more sensitive due to the lower boundary for classification of AKI, whilst others used the KDIGO criteria. The incidences (considered as separate meta-analyses for both nephrotoxin exposed and non-exposed non-critically ill children and also nephrotoxin exposed non-critically ill children as seen in **figure 2.2A-B**) in this cohort did not have a large range, and so this did not seem to affect these particular results. All papers meeting inclusion criteria in non-critically ill hospitalised children excluded children with pre-existing renal pathology, however this is defined slightly differently in each paper. For example, Schaffzin et al[49] and McGregor et al[44] excluded those with CKD. Moffett et al[21] excluded patients admitted to renal services, with CKD, with ESRD, renal transplant, UTI or pyelonephritis. Goldstein et al 2016[28] excluded patients with CKD, real transplants, or UTI, whilst Goldstein et al 2020[29] excluded those with UTI.

2.5.1.1.2 Children with Nephrotic Syndrome

The pooled incidence of AKI in hospitalised children with nephrotic syndrome was 29%. This is slightly lower than the 32% incidence in non-critically ill children. One of the reasons for this small difference could be that children with nephrotic syndrome i.e., known kidney pathology, are most likely under the care of specialist healthcare professionals. For this reason, these children may be more likely to have kidney function monitoring and potentially an earlier awareness of the development of AKI, and to be treated at an earlier stage than non-critically ill children, cared for by a non-specialist team with the focus on another pathology. As discussed above, an alternative explanation could be that the incidence in non-critically ill children could be higher due to the inclusion and exclusion criteria discussed. The five papers homogenous enough for meta-analysis reported a range of incidence of AKI in children with nephrotic syndrome, from 16%[45, 56] to 51%[46]. There are several reasons that this wide range could be attributed to. Firstly, as discussed above, pRIFLE (used in two papers[46, 51] included in meta-analysis) can potentially overestimate the incidence of AKI due to having a higher sensitivity than the KDIGO criteria (used in three

papers[42, 45, 56]). The rates seen in papers defining AKI by pRIFLE were 24%[29] and 51%[36], whilst rates in papers using the KDIGO criteria were 16%[30, 31] and 32%[34]. Moreover, papers varied in terms of their inclusion criteria for a diagnosis of AKI. The lowest incidence seen (16%) was in a paper[56] only including patients who had AKI at the time of admission, rather than including those who developed it during their stay too – hence a lower incidence is to be expected. This same method of identifying AKI at admission was used in another study[51] included in the meta-analysis with an incidence reported as 23.66% at admission.

2.5.1.1.3 Children following congenital heart surgery

The incidence of AKI in children having undergone CHS was high (62.5%)[54]. The authors recognise that this could be an underestimation due to using SCr only to define AKI, without UO criteria in the paediatric population. Therefore, the true incidence of AKI in this population could be higher.

2.5.1.1.4 Critically ill children

Meta-analysis of the two studies conducted in critically ill children displayed that the incidence of AKI was 37%. Although different definitions were used (study by Shalaby et al[50] using pRIFLE, and Safder et al[48] using KDIGO) the incidence was similar before pooling data, and still significant once combined. As expected, this is higher than the incidence seen in non-critically ill children (32%). It could be suggested that the difference in AKI rates would be larger, if the non-critically ill data was not extracted from interventional studies. Both of these studies excluded critically ill neonates (<28 days old), which we know from other studies[52] is a cohort at risk of AKI. Both studies also excluded children with evidence of CKD stage 3 or higher, which could potentially have excluded a group of children that would have increased the incidence of AKI.

2.5.1.1.5 Very low birth weight infants

The incidence of AKI in VLBW infants was 26.3% of the cohort included in the one eligible study[47] of this population. Exclusion criteria included infants admitted at age 2 days and older, or if they did not survive to discharge. This could potentially have excluded patients at a high risk of exposure to nephrotoxins, and potentially developing AKI.

2.5.1.1.6 Critically ill neonates and infants

The incidence of AKI in neonates and infants with high nephrotoxin exposure was 19.7%[52]. As described in **table 2.5**, interventions (involving screening for nephrotoxin exposure, increased SCr monitoring, and discussion of medication) were implemented, which resulted in decreasing rates of nephrotoxin exposure and AKI episodes. For this reason, the incidence of 19.7% may be lower than the incidence we could expect to see for this same population in other centres without these interventions. As discussed in the results section (**2.4.5.6**), rates of the outcomes measured (AKI prevalence rate, high nephrotoxin exposure prevalence rate, rate of patients with high nephrotoxin exposure who develop AKI, and AKI intensity rate) increase on implementation of the intervention, followed by decreasing over the remaining time course of the study (to lower rates than pre-intervention). The increase of each outcome during the initiation period could be attributed to the intervention. The SCr compliance rate increased (from 56.5% pre-intervention ($p<0.001$) to 90.7% during initiation ($p=0.950$), which in turn could increase AKI prevalence and intensity rate (as more cases of AKI are picked up). The authors offer possible explanations for the increase in high nephrotoxic medication exposure rate following initiation of the interventions, including seasonal variation, increasing patient complexity, change in practice patterns, and ascertainment bias.

2.5.1.1.7 Infants with neonatal encephalopathy

One study of infants with NE and AKI[43] breaks down patients identified as having AKI (incidence 41.6%) into which KDIGO diagnostic criteria they met. 13 of the 47 infants with AKI (27.7%) had creatinine-defined AKI, 22 (46.8%) had UO defined AKI, 12 (25.5%) met both SCr and UO criteria. Many studies included in this review define AKI using only the SCr measurement criteria, due to inconsistent UO recordings. This may mean that the true incidence of AKI in other studies is higher and could account for why the incidence is so high in this population. However, these findings are important and this vulnerable population should be carefully monitored in clinical practice due to the high rates of AKI seen in this cohort.

2.5.1.1.8 Children following stem cell transplant

The incidence of AKI in SCT patients exposed to nephrotoxins was 39%[28, 41]. Goldstein et al 2016[28] demonstrated that this population of patients is among the most commonly exposed to nephrotoxins, with patients admitted for bone marrow transplant services accounting for 24% of admissions[28]. The interventional study[44] involved a change of first line fever coverage from PTZ to cefepime, limiting duration of antimicrobial exposures (with a focus on vancomycin), and EMR screening for nephrotoxin exposed patients. As expected, rates of PTZ and vancomycin usage decreased, whilst rates of cefepime usage increased. No increase in frequency of enterococcal infections was observed. Rates of nephrotoxin medication exposure and rate of nephrotoxin associated AKI both decreased after interventions, demonstrating that treatment outcomes in SCT can be maintained, alongside reducing nephrotoxin exposure and hence decreasing NTMx-AKI rates and severity.

2.5.1.1.9 Oncology patients

In children admitted under oncology services, the incidence of AKI was 16.9%[55]. Another study[58] reported 111 AKI episodes (defined as any exposed patient who went on to develop AKI), in 273 unique patients with 514 exposures – an incidence of 21.60%. Authors note that in this study[58], a limitation was the definition of baseline SCr (lowest documented SCr within the past 6 months). They describe how oncology patients often receive aggressive hyperhydration along with chemotherapy drugs or for renal protection, which can result in a transient decrease in SCr. For this reason, AKI episodes in this cohort could have been overestimated due to a lower baseline SCr.

2.5.1.2 Risk factors for the development of AKI

2.5.1.2.1 Age

In non-critically ill hospitalised children, those with AKI were younger than those without AKI, seen in the two separate papers[21, 44]. When data was pooled for meta-analysis, the association was not significant. One reason for this could be due to the difference in study types. One of these studies[21] was a case-control study in which patients were matched in a pairwise fashion. The authors recognise that the case-control data set was significantly different from the entire population (i.e., those not paired and therefore not evaluated)

with regard to mean age (mean age 7.2 years, SD 5.5 vs 8.8 years, SD 6.0, $p<0.05$). Therefore, the mean age of the cohort evaluated (7.2 years) could have been higher if pairings were available for more patients to be evaluated. The median age in the other study[44] used for the meta-analysis was 8.8 years, which is a notably higher average than the study that data was combined with. The inclusion criteria for age was slightly different in each of these two studies. Whilst Moffett et al[21] included patients aged 1 day up to $\leq$18 years old, McGregor[44] included patients aged 28 days to 21 years old – excluding the neonatal cohort, and capturing patients of a slightly older age and potentially explaining the higher average age.

Interestingly, in children with nephrotic syndrome, those with AKI were older than those without. This was a significant finding after pooling data from three papers[42, 45, 56] in our meta-analysis. One potential reason for this could be that children with nephrotic syndrome are exposed to nephrotoxins for a longer time period, throughout their disease duration. This could possibly mean that an acute change that may not affect a younger child, could affect older children's renal function more easily (i.e. less of an acute change is required to affect a kidney with already reduced renal function, or exposed to nephrotoxins for a longer time period). This is recognised in one of the studies[56] which identifies that longer duration of nephrotic syndrome was a risk factor for developing AKI. Age did not have an effect on the risk of AKI in two studies[46, 51], however age was displayed in groups (e.g. 1-5 years old) which may not provide as accurate results as a comparison of mean ages in cases compared to controls, as other studies did.

In studies of critically ill children[48, 50], it also appears that younger children are more prone to developing AKI, and are also more likely to develop a severe AKI. In one paper observing critically ill children[50], children with AKI were younger than those without, however the association was not found to be statistically significant. The oldest children included in this study were 60 months (5 years) old, making comparison to other populations (including children up to 18 years of age) difficult. The other paper studying critically ill children[48] compared children with and without AKI, concluding that those with more severe AKI were younger than those with less severe AKI. Another finding was that the majority of children

developing AKI were less than 5 years of age – implying that younger children are potentially more prone to AKI development.

Gestational age was not assessed as a potential risk factor for the development of AKI in VLBW infants[47], and was also not significant in infants with NE and AKI compared to without AKI[43].

In children with various types of cancer[55], younger age was associated with the development of both CA- and HA-AKI.

Patients with renal pathology were studied in one prospective observational study[53] to determine short-term outcomes. Of the cohort included, the mean age was 7.5 years (SD 4.4), however the authors recognise the underrepresentation of younger patients in this study, due to the study setting managing patients between 1.5 months and 15 years of age[53]. There were only 39 patients (33.6%) included in the study that were less than 5 years old[53].

2.5.1.2.2 Exposure to nephrotoxins

In the non-critically ill, hospitalised population, exposure to nephrotoxins was considered as a risk factor in all included papers[21, 28, 29, 44, 49]. This was not formally tested for in each paper, but the association is well recognised and clinically important. Importantly, in the two interventional papers[28, 29] included in the review, the rates of AKI decreased after implementing a change with the aim of monitoring and reducing nephrotoxin exposure.

Nephrotoxin exposure was also recognised in each paper as a risk factor for the development of AKI in children with nephrotic syndrome[42, 45, 46, 51, 56, 57] however pooled data did not reach statistical significance (when considered separately the association was statistically significant). Although both studies showed increased odds of developing AKI after exposure to nephrotoxins, the difference between the two was notable. One study noted an odds ratio of 7.8 ($p<0.0001$, 95% CI 4.06-15.01)[51], with the other reporting an odds ratio of 1.64 ($p=0.003$, 95% CI 1.05-2.56)[56]. Sharma et al[51] had a much smaller number of controls (no AKI) who were exposed to nephrotoxins, therefore making the odds ratio much

higher on data analysis. The populations observed were both similar, for example both including patients with AKI at admission, not counting those developing it during their stay. One difference was that the study by Sharma et al[51] implies that one child is equal to one hospitalisation, in comparison to one patient accounting for several hospitalisations in the study by Yang et al[56]. A possible reason for the lower odds of developing AKI when exposed to nephrotoxins in the study by Yang et al[56] could be that if the same patient is readmitted to hospital and has previously had an AKI, clinicians may be more aware of the possibility of developing an AKI and therefore monitor and treat this sooner. Although not included in meta-analysis, one study[57] showed that drug toxicity was the second (second to infection) most common cause of AKI in children with nephrotic syndrome, found in 43.7% of cases, with 31.9% being due to cyclosporine. Another concluded that nephrotoxic medication exposure, days of exposure, and exposure intensity were all significantly associated with the development of AKI in children with nephrotic syndrome[46].

The rate of nephrotoxin exposure was common in post-operative CHS patients[54], with 131 of 154 children (85.1%) being exposed to at least one nephrotoxin and 32 patients (20.8%) having high exposure (defined as $\geq$3 nephrotoxins concurrently). After adjusting for confounders, there was no significant association between nephrotoxin exposure and the rate of AKI seen in this study. The authors note that a reason for this could be because AKI can be multifactorial in this population, and that nephrotoxin exposure may be a modifiable risk factor for AKI. Furthermore, the small sample size and high rate of AKI may contribute to the lack of significant association seen between nephrotoxin exposure and AKI rates in this study. Although no significant association was seen between nephrotoxin exposure and the development of AKI, this study importantly shows that nephrotoxins are commonly prescribed in this population (85.1% cohort having exposure to at least one nephrotoxin) and that the rate of AKI is high (62.5%). Whether associated or not, it is important to be aware of the high rates of exposure and AKI in children following CHS and consider careful monitoring of kidney function and substitution for less nephrotoxic drugs.

Nephrotoxin exposure was not formally reported as a risk factor in studies of critically ill children[48, 50], however toxic nephropathy was documented as a cause for AKI in both

studies. Further research into the rates of nephrotoxin exposure and the association with AKI in the critically ill population would be valuable.

In VLBW infants[47], nephrotoxin exposure (both total medication days, and total medications per day) had non-significant associations after adjusting for birth weight and gestational age in multivariate models. There was however a significant association with mean nephrotoxic medications per day and peak creatinine in infants with AKI after adjusting for birth weight and gestational age. The small sample size (107) and single centre design could limit the findings, and so larger cohort studies could provide useful data.

In critically ill neonates and infants exposed to nephrotoxic medication[52], a reduction in nephrotoxin exposure was accompanied by a reduction in AKI rates, described by the authors as a reduction in nephrotoxic medication-AKI rates. The authors also discuss how the intervention (increased surveillance of highly exposed critically ill neonates/infants) prevented approximately 100 AKI episodes during the 18-month sustainability era.

These outcomes in critically ill neonates/infants can be compared to the outcomes reported by Goldstein et al 2016[28] due to similar interventions (although, due to the different age range of the population, this should be interpreted with caution). For discussion, critically ill neonates and infants are referred to as ICU patients, whilst non-critically ill children are referred to as non-ICU patients. In ICU patients, a 42% reduction in nephrotoxic medication exposure, compared to a 38% reduction in the non-ICU population. AKI exposure rate reduced by 78% in ICU patients, compared to 64% in non-ICU patients. Lastly, nephrotoxic-AKI rate was reduced by 64% in ICU patients, compared with 34% in non-ICU patients. Stoops et al[52] recognise that due to less mature renal physiology and a higher acuity of the population, nephrotoxin exposure and AKI rates are likely higher in the ICU population (19.7%) compared to the non-ICU studies (17.7% from the comparable study[28], or 17% from our meta-analysis ($p<0.00001$, 95% CI 15-19% pooled data from three papers[28, 29, 49] (n=747 patients[49] combined with n=7756 nephrotoxin exposures[28, 29])).

Nephrotoxic drug exposure was also common in infants with NE[43], with 90 of the 113 children (79.6%) being exposed to nephrotoxins. The incidence of AKI was high in this cohort

(41.6%) and for this reason, careful monitoring and cautious prescribing of nephrotoxins would be valuable in this vulnerable population.

Benoit et al[41] conducted a study in SCT patients, who were previously identified as being commonly exposed to nephrotoxins by Goldstein et al 2016[28]. Of patients studied, 24% of the nephrotoxin-exposed patients were made up of SCT patients[28] – accounting for a large proportion of the cohort. The incidence of AKI in nephrotoxin exposed SCT patients was 39%[28, 41], and as expected, rates decreased on intervention (reducing nephrotoxin exposure).

In hospitalised children with cancer[55, 58], patients were commonly exposed to nephrotoxins. Nephrotoxic drug exposure was significantly associated with HA-AKI, with the highest hazard ratios seen in those exposed to contrast media, diuretics and also chemotherapy agents.

2.5.1.2.3 Albumin level

Two studies[51, 56] described lower albumin level as a risk factor for children with nephrotic syndrome developing AKI, and a large percentage (77.3%) of the total cohort of a prospective study[57] following children with nephrotic syndrome and AKI, had hypoalbuminaemia reported in their baseline characteristics. Hypoalbuminaemia is a well recognised risk factor for the development of AKI, and also as a predictor of death following AKI development in adult populations[59]. None of the papers with the population of non-critically ill children[42, 45, 46, 51, 56, 57] documented albumin levels, however we would not expect to see hypoalbuminaemia in non-critically ill children so these children may not have had a baseline level and documented measurements throughout their stay.

2.5.1.3 Outcomes in children with AKI

2.5.1.3.1 Length of stay

AKI has been shown to prolong the length of hospital stay. In our meta-analysis in non-critically ill children, this association was not statistically significant. However, when the two papers were considered separately, the association was significant. In a case-control study[21]

the mean difference was 5.20 days, compared to 1.00 days in a retrospective cohort study[44]. This large difference could be attributed to several reasons. Firstly, in order to include the data from the retrospective cohort study[44], the mean and SD had to be estimated from the median and IQR given. This is often recommended against, however we used the Cochrane handbook[40] advice in order to be able to include this study in the meta-analysis. As previously discussed, the inclusion criteria was slightly different in each of these two studies in terms of age – with McGregor et al[44] capturing a cohort of older children than Moffett et al[21]. Furthermore, Moffett et al[21] defined AKI using the pRIFLE criteria and therefore possibly overestimating AKI due to a higher sensitivity than the KDIGO criteria used in the paper by McGregor et al[44], meaning patients with a lower level of renal dysfunction (and hence potentially less ill) could have been included in the AKI cases group. This however does not provide an explanation for the longer length of hospital stay seen in Moffett et al's[21] paper using the pRIFLE criteria, and allows for further speculation. The association between AKI increasing length of stay in non-critically ill hospitalised children was supported by findings from another study[49], which identified that patients exposed to nephrotoxins had a longer length of stay than those unexposed, with a mean difference of 4.51 days. This data could not be included in the meta-analysis because the cases and controls were different, although the findings align with those seen in the other studies included[21, 44].

In children with nephrotic syndrome, AKI was associated with prolonged hospital stay when data from three papers was combined[42, 45, 56]. Length of stay had a mean difference of 5.42 days more than children without AKI. This is pertinent as increased length of stay ultimately correlates to possible longer treatment duration (and hence longer exposure to nephrotoxins), increased costs, and possibly most importantly less time spent in school. These children with nephrotic syndrome may already be more likely to spend less time in school than children without renal pathology, and so any increased length of stay in hospital contributes to this issue.

Increased length of stay was reported in children post-operatively from CHS[54] who had high exposure to nephrotoxins, than those not highly exposed (mean 16.9 days, SD 18.1 compared to mean 12.8 days, SD 18.7, p=0.01). This study did not report length of stay in patients with AKI compared to no AKI, and there was no significant association between

nephrotoxin exposure and AKI development. However, it is important for clinicians to take these findings into consideration when prescribing nephrotoxins, to avoid any unnecessary nephrotoxin exposure which could potentially contribute to longer lengths of hospital stay.

Critically ill children with AKI had longer PICU stays than those without, in one study[50]. Length of stay as an outcome was further analysed to also prove that the severity of AKI was significantly associated with the length of PICU stay – with those in pRIFLE category Risk having a mean length of PICU stay of 5.9 days, Injury of 10.1 days, and Failure of 9.7 days[50]. Mean length of stay could potentially be slightly lower in the Failure group due to the highest rate of mortality also seen in this group. This finding was supported in the other study of critically ill children[48], which reported longer stays in both PICU and hospital in general, and also in infants with NE and AKI[43] – who on average spent 8.48 more days in NICU than infants with NE without AKI.

As seen in other studies, oncology patients with AKI had longer hospital stays than those without AKI[55]. Compared to other studies, this population had longer length of stays in general, possibly due to the nature of their treatment and the likelihood of being treated with chemotherapy agents during their admission.

2.5.1.3.2 Mortality

Although only reported in one study[44], mortality was low in the non-critically ill hospitalised children cohort. This was an expected finding due to the non-critically ill population being studied. Even so, data was sufficient and showed a statistically significant association, within-hospital mortality being higher in those with AKI than those without and that more deaths occurred in those with a higher stage of AKI.

In children with nephrotic syndrome, an association with age and the development of AKI did not reach statistical significance when data was combined from two papers[45, 46]. Mortality was only reported in a small sample size even with data combined (n=409), with a total of 4 patient deaths. All four of these deaths were reported in patients with AKI (n=210), whilst zero deaths were reported in patients without AKI (n=199). One of the papers included[45] was only a small study, with a total of 73 patients. 3 of the 4 deaths were

reported in this paper, meaning 3 of the 13 cases (AKI) died, compared to 1 of 197 cases dying in the other study[46]. The authors comment that the high rate of mortality could be due to 46% (n=6) of cases progressing to KDIGO AKI stage 3. This could serve as a reasonable explanation for the difference between the two papers, considering only 19.8% (n=39) of cases reached pRIFLE stage Failure (the equivalent to stage 3 AKI) in the other study[46]. Mortality from a prospective study[57] in children with nephrotic syndrome was not included in the meta-analysis due to the study design. However, death was observed in 5 of 119 children with AKI, which was the entire cohort in this study (no control group without AKI was considered).

As could be expected, the rate of mortality was high in the critically ill population (34.3% in the whole cohort before exclusion, 28.57% in those with AKI)[50]. It is worth noting that in one particular study[50], sepsis was the most common cause of AKI which is itself associated with a high mortality rate. Patients with more severe AKI had a higher mortality rate in both studies of critically ill children[48, 50].

In infants with NE[43], Kirkley et al. did not detect a significant difference in mortality between infants with AKI and without, however, small sample size may have limited this data analysis. Authors also comment that the lower threshold for meeting AKI diagnostic criteria could be a possible reason for failing to detect a difference in mortality between cases and controls. Furthermore, they recognise that the low mortality seen in the study could have been due to the interval improvement in the care of asphyxiated infants – especially in the high-resource tertiary and quaternary centres included in the AWAKEN database.

Xiong et al[55] reported higher mortality in hospitalised children with cancer with AKI than without AKI. Mortality was higher in children with HA-AKI than CA-AKI. A possible explanation for this finding could be the difference in aetiology of AKI in hospital and community-acquired AKI, and that community-acquired cases may be easier to manage. Furthermore, those with AKI recognised at admission could have treatment to improve or reduce further decline in renal function at an earlier stage.

Tresa et al[53] did not compare outcomes of patients with AKI to those without AKI, instead conducting a prospective observational study of hospitalised children with AKI. However, authors did report that the severity of AKI was associated with mortality. However, it should be noted that as potentially expected in a cohort of patients with renal pathology, a large proportion of the cohort had severe AKI on presentation and so made up the largest proportion of the children included[53].

2.5.1.3.3 Requirement for RRT

Renal replacement therapy was reported as an outcome mainly in papers considering children with nephrotic syndrome. The percentage of children with AKI going on to require RRT was varied across studies. It is difficult to conclude which children go on to require RRT and further research would be valuable. The studies included consider children with varying severities of AKI and therefore a range of different percentages of children going on to require RRT. One paper reported 2 of 93 children (2.15%)[56] with AKI became dialysis-dependent, another with 1 of 13 children (7.7%)[45], and a final paper reported 12 of 197 (6.09%)[46] children required RRT. Two papers in children with nephrotic syndrome had no patients go on to require RRT[42, 51], and another did not report RRT as an outcome[57].

The requirement for RRT was only reported in one included paper[28] of the non-critically ill population, which was an interventional study and was not compared to a control group without AKI. It is worth noting that this entire population had been exposed to nephrotoxins. 19 of 248 patients (accounting for 457 admissions with 575 episodes of AKI) required varying types of RRT (13 intermittent haemodialysis; 2 continuous RRT; 4 both) (7.66%). However, a large proportion of these were intermittent haemodialysis which may account for the high percentage seen in the non-critically ill population with no pre-existing renal pathology. This percentage may have been higher in a study without an intervention with the aim to reduce nephrotoxin exposure (and in turn, AKI rates), as AKI episodes may have been prevented or treated sooner due to flagging patients exposed to certain nephrotoxins.

Both of the two included studies of critically ill children reported the percentages of children requiring RRT. In one paper[50], 9 of the 102 patients (8.8%) required RRT (all of which were

from the Failure group), and from the other study[48], 11.4% of the critically ill children required RRT. The rate of RRT requirement in critically ill children could possibly be higher than has been seen in other populations because these children are more likely to have more severe AKI and longer length of hospital stays than other cohorts of children.

No VLBW infants (one study[47]) required RRT although the incidence of AKI (26.3%) was high (albeit in a small cohort of 107 infants). One possible explanation for this could be that the majority of AKI episodes were KDIGO stage 1 AKI (75%), with fewer children experiencing severe AKI (stages 2 and 3). Furthermore, the lack of RRT modalities for very low birth weight infants could contribute to this.

2.5.1.3.4 Progression to CKD

Similarly, to considering RRT, progression to CKD was difficult to compare between studies due to the differing populations, varying degrees of AKI, different classification systems, and different working to describe the deterioration in kidney function (for example the small study by Prasad et al. uses the phrase 'partial renal recovery' and does not define CKD). Two papers[56, 57] in children with nephrotic syndrome clearly reported progression to CKD as an outcome. The range was varied, with one paper reporting 6.5%[56], and the other 41.2%[57].

The authors of the study reporting 6.5% progression to CKD[56] consider the paper by Yaseen et al. which reported 41.2% children progressing to CKD[57]. They note that a possible reason for this could be that their follow-up was short due to the retrospective nature of their study, where a longer follow-up may have revealed a higher incidence of CKD. One difference in the exclusion criteria was that Yaseen et al[57] excluded children with a baseline eGFR <90 ml/min/1.73m^2, compared to Yang et al[56] excluding those with an eGFR <60 ml/min/1.73m^2 for more than 3 months before admission. The difference in defining AKI in these two studies does not provide an explanation for the difference in rates of CKD development, which was similar in both studies (persistent deterioration of eGFR / <60 ml/min/1.73m^2 for more than 3 months[56], compared to persistent deterioration in renal function for more than 3 months[57]). Yang et al[56] defines AKI using the KDIGO criteria, whereas Yaseen et al[57] uses the pRIFLE criteria. As discussed earlier, pRIFLE can overestimate meaning that the study by Yaseen et al[57] may have included children with less

severe AKI, and therefore potentially less likely to develop CKD – the opposite of what is seen here comparing these two studies. The difficulty in drawing conclusions when comparing these two studies highlights the need for additional research to understand rates of longer-term outcomes, and identify children at risk of these.

Progression to CKD was not an outcome reported in any of the studies of non-critically ill children. This is an important consideration in children with AKI, and further research could provide useful insight into the proportion of non-critically ill going on to develop CKD. However, part of the inclusion criteria for this systematic review was exposure to nephrotoxins which may have resulted in studies of this theme not being included if nephrotoxin exposure was not documented.

At follow-up (3 months after AKI) of children having undergone CHS[54], the rate of renal recovery was similar in both those with high nephrotoxin exposure (80.0%) and those without high exposure (69.4%) (p=0.36) and the association was not significant. However, renal recovery was less common at follow-up in children who had severe AKI (KDIGO stage 2 or 3) (51.6% vs 84.3%, p=0.001) although this was independent of nephrotoxin exposure (which was also not associated with the severity of AKI (adjusted RR 1.1, 95% CI 0.5-2.3)). Progression to CKD is an important consideration in this population, who have both a high incidence of AKI and a high rate of nephrotoxin exposure. Prevention of AKI or nephrotoxin exposure is most important, however, if this is unavoidable then follow-up and close monitoring of this population could be valuable in improving outcomes.

In hospitalised children with cancer, 66.1% of children had a recovery of kidney function before discharge[55]. Patients with more severe AKI (stage 3) had longer recovery times than those with less severe AKI (stage 1 and 2)[55]. Progression to CKD was not formally reported in this study[55].

Tresa et al[53] reported that in patients with renal pathology, the majority of patients developing CKD (n=18) had presented with severe AKI (pRIFLE category Failure) (n=14, 77.8%). However, these patients in the Failure category did make up a large proportion of

the cohort (76.7%)[53]. The other 4 patients (22.2%) progressing to CKD were from the Injury category[53].

2.5.1.4 Mitigating factors and improving patient outcomes

There is good evidence that suggests monitoring nephrotoxin exposures in non-critically ill hospitalised children can have a positive effect on patient outcomes. In the two interventional studies by the Goldstein Cincinnati group[28, 29], a large proportion of AKI episodes were estimated to have been prevented. Interventions in these studies included EMR screening to flag nephrotoxin-exposed patients followed by daily SCr measurements in these patients[28], and medication reviews with substitution for less nephrotoxic medications[29].

The study by Stoops et al[52] also demonstrated improvements including reduction in nephrotoxic drug exposure and nephrotoxic AKI, and also the prevention of AKI episodes across the study period with the implementation of NINJA. The intervention in this study was adapted (from NINJA) slightly in order to suit the population (critically ill neonates/infants), by extending the time period of IV aminoglycoside exposure from 3 to 4 days to meet inclusion criteria, and also the baseline definition of SCr. Authors explained that the definition was adapted since initial SCr values in neonates often reflect maternal SCr values. For this reason, infants exposed during the first 14 days of life had their SCr value compared with the lowest previous value, whilst those more than 14 days of life had the lowest previous SCr prior to exposure compared to all subsequent values.

These findings were transferrable to SCT patients who were studied in more detail by Benoit et al[41]. As rates of nephrotoxin exposure were reduced following intervention, rates of NTMx-AKI decreased.

Nephroprotection was considered in one study[58] of hospitalised children with cancer, although rates (number of episodes) of AKI did not change with the implementation of nephroprotection (with N-acetylcysteine and alkalinized IV fluids) in patients receiving IV contrast. However, number of AKI days was lower in those receiving nephroprotection. This in turn meant that the calculation for average AKI days per episode was lower in the group

with nephroprotection than those without. This was calculated with the denominator using the number of AKI episodes in each group (which were different sizes) rather than the percentage of AKI episodes so should be interpreted with caution.

Increased surveillance of high-risk patients (high exposure to nephrotoxins) could be considered in different populations of children to improve their outcomes.

2.5.2 Limitations

We were not able to include all papers in the meta-analysis for various outcomes due to widely differing populations and eligibility criteria for populations in each paper. This however did allow us to analyse subgroups of patients including non-critically ill children, and those with nephrotic syndrome. Although these two cohorts represent a large proportion of children who develop AKI, it is important to look at the association in other groups of children where different causes, risk factors and outcomes may be seen, such as critically ill children.

One limitation of the current literature is the use of different AKI definitions used in different studies. Some papers used the widely accepted KDIGO criteria, whilst others used pRIFLE. pRIFLE can overestimate due to its lower cut off, meaning a patient may be included in the case (AKI) groups, who may have not met AKI criteria in another study using KDIGO and therefore would have been in the control (no AKI) group.

Some papers also set an inclusion criterion in relation to the number and timing of SCr measurements, meaning that the incidence of AKI could have been underestimated in certain studies. Children recognised by clinicians as being at risk, or likely to develop AKI could have been more likely to have sufficient SCr measurements, than those not predicted to develop AKI. This could have meant that children with underlying pathology or cared for by renal specialists were more often included than those without.

Several papers reported a number of patients in cases (AKI) and controls (no AKI) which was favourable for meta-analysis. We came across difficulty when some papers referred to

'number of children', and others referred to 'hospitalisations' – meaning we had to analyse the papers to gauge the homogeneity and whether meta-analysis was suitable.

Other papers reported incidence terms of 'patient days'[28, 29, 41, 52, 58]. This is a useful measure to use in interventional studies to be able to see the impact and improvement post-intervention. These studies also displayed information as a percentage increase or decrease, along with the estimated number of AKI episodes prevented[28, 29, 52].

The difference in outcome measures used to report AKI has been a challenge in order to compare papers, however this has been important to serve as a guide for the planning of our data analysis project (Chapter 3) and defining our own outcome measures. The differences in outcome measures reported contributed to the difficulty seen when grouping studies for meta-analysis. The development of a core outcome set would ensure consistent methods of reporting outcome measures, allowing for further comparison and data analysis. This idea is discussed in more detail and a potential core outcome set described, in Chapter 4, in **section 4.5**.

2.6 Conclusion

As seen in the papers included in this review, across a variety of paediatric populations, the risk of AKI is high – and higher in those exposed to nephrotoxic medications. Importantly, research to date has shown that NTMx-AKI is one of the biggest avoidable causes of AKI, which impacts patient's short- and long-term outcomes such as increased length of hospital stay, progression to CKD, and mortality. Interventional studies have been shown to successfully decrease AKI rates by implementing measures such as screening for nephrotoxin exposed patients, medication reviews and increased SCr monitoring without compromising other areas of patients' treatment. For these reasons, it is important to identify at-risk patients early, and consider enhanced surveillance and early intervention to improve patient outcomes.

2.7 Additional work

An abstract for a sub-review of the literature and meta-analysis in non-critically ill children was submitted to the Royal College of Paediatrics and Child's Health (RCPCH) Conference 2021, and successfully accepted for presentation as an E-poster. The abstract submitted and corresponding E-poster can be seen in Appendix 6.

An additional abstract for a sub-review of the literature and meta-analysis in children with nephrotic syndrome was submitted and accepted to the British Association of Paediatric Nephrology (BAPN) Winter Meeting 2021, for which both the abstract and E-poster and can be seen in Appendix 7.

Chapter 3 Nephrotoxin exposure and Acute Kidney Injury in non-critically ill children: An Audit at Alder Hey Children's Hospital

3.1 Introduction

The systematic review and meta-analysis in Chapter 2 provided an overview of NTMx-AKI in children, providing us with a good starting point to be able to design an audit to contribute to available research, and begin to answer the questions our review raised. The findings (primarily AKI rates) of the meta-analysis helped us to initially design this audit, make decisions regarding outcome measures, and guide our data analysis, followed by ultimately providing data for us to compare our findings to. In this chapter, we looked at data for all non-critically ill inpatients during one week at AHCH. This audit was registered with the Clinical Audit Team at Alder Hey and assigned the unique reference number 6357.

3.1.1 Objective

Through our sub-review of nephrotoxic AKI in non-critically ill children (discussed in Chapter 2), we studied papers both in a non-critically ill population and in non-critically ill children exposed to nephrotoxins. This review highlighted the differences in reporting of outcome measures between studies, making comparison and meta-analysis difficult. These findings therefore helped guide the data analysis in this chapter in terms of determining what data we needed to capture and how to define our outcomes – in a way which allowed us to best analyse the available data.

There is good evidence currently that suggests monitoring nephrotoxin exposures in hospitalised children can have a positive effect on reducing AKI rates. Our previous review demonstrated that interventions including more frequent SCr monitoring, reducing nephrotoxin exposures, and considering medication reviews reduced AKI rates. Therefore, in our audit we aimed to analyse the exposures and AKI rates in children at AHCH, laying good foundations to able to build on with future research and to prompt consideration of interventions to reduce rates at our trust.

3.1.2 Question

Our research question of interest was "What is the epidemiology of Acute Kidney Injury in non-critically ill children at Alder Hey Children's Hospital (AHCH)?". To answer this question, we addressed the following objectives:

Primary objectives:

- Describe the prevalence of AKI in non-critically ill children at AHCH
- Describe the prevalence of AKI in nephrotoxin-exposed non-critically ill children at AHCH

Secondary objectives:

- Test for association between potential risk factors (primarily nephrotoxins) and the development of AKI in non-critically ill children
- Describe outcomes (including length of stay and mortality) in non-critically ill children with AKI

3.2 Methodology

Our original study protocol can be seen in Appendix 8, and the intention was to obtain long term follow-up data on patients through the Electronic Medical Record (EMR). However, due to Corona Virus Disease 19 (COVID-19) related research taking priority, this unfortunately could not be obtained within the timeframe required for the submission of this thesis and therefore data from a one-week period was obtained instead. This was initially planned as a protocol piloting exercise for the originally planned study.

The methods used are detailed below.

3.2.1 Design

We conducted a prospective one-week study for inpatients at Alder Hey Children's Hospital from 12/04/21 up to and including 18/04/21. Each day, one reviewer (CH) accessed Meditech remotely, and added any details for any newly admitted inpatients from included wards to a spreadsheet. The following day, data for admissions from the previous date

would be inputted into the spreadsheet to ensure any data recorded up until midnight would be captured, as opposed to recording data for a particular date on the same day.

3.2.2 Eligibility Criteria

Table 3.1: Inclusion and exclusion criteria for patients

PICO	Inclusion Criteria	Exclusion Criteria
Population	Non-critically ill children admitted to and treated as inpatients at AHCH (admitted and discharged on different dates)	Critically ill* Outpatients Over the age of 18 Admitted and discharged on the same date (i.e. had no overnight stay)
Intervention	Children with nephrotoxin exposure compared to children without nephrotoxin exposure	N/A
Comparator	Children with AKI compared to children without AKI	N/A
Outcomes	Diagnosis of AKI	N/A

*Critically ill children were defined as those admitted to PICU. We excluded this cohort due to paper prescribing in PICU which meant the data could not be extracted from Meditech remotely. Furthermore, less visitors to PICU were advised at the time of the audit due to the trust taking on additional adult patients to support the Liverpool region.

3.2.3 Data Extraction

We collected and input into a spreadsheet the following data from patients meeting the eligibility criteria:

1. Patient identifiers: Alder Hey number; Name, Date of Birth (DOB) (prior to data removal from the Alder Hey servers for analysis, all data was anonymised and dates of birth removed)
2. Admission details: Date of admission; Date of discharge; Speciality; Admitting consultant; Location (ward)

3. Patient demographics: Age at start of audit; Gender; Ethnicity; Most recent weight on the date of admission (or previous weight if no data for date of admission) (kg); Most recent height on the date of admission (or previous weight if no data for date of admission) (cm); Most recent SCr measurement prior to admission (umol/L); Date of last measured SCr
4. Renal variables for each day: Maximum AKI Stage (0-3); Maximum SCr (umol/L); Number of nephrotoxins exposed to; Which nephrotoxins
5. Secondary patient outcomes: Length of stay; Mortality

After data was collected, we used Microsoft Excel formulas to calculate age on the first day of the audit.

3.2.3.1 Further explanations

3.2.3.1.1 Nephrotoxins

Nephrotoxin exposure was defined as documentation of exposure to any medication from a predefined list of nephrotoxins. This list of nephrotoxins consists of 39 medications, modelled from the Cincinnati group's list[28], which was adapted in February 2020 for use at AHCH to include medications used at the hospital. The list of nephrotoxins can be seen in Appendix 9. However, for a child to meet the criteria to be included in the 'nephrotoxin-exposed' group, they must have been exposed to at least 3 of the nephrotoxins from the list on at least one day of the admission.

3.2.3.1.2 AKI definition

We defined AKI and baseline SCr using the AKI alert system and EMR already in place at AHCH (which can be seen in Appendix 10). The AKI alert system is currently in place for children ≥6 months of age.

AKI is defined using the serum creatinine KDIGO criteria (without the urine output criteria):

- Stage 1 AKI: SCr 1.5-1.9 times baseline OR ≥0.3mg/dl (≥26.5μmol/l) increase
- Stage 2 AKI: SCr 2.0-2.9 times baseline
- Stage 3 AKI: SCr 3.0 times baseline

Baseline serum creatinine from the EMR is defined as:

- The lowest value in the last 7 days
- If no SCr measurement in the previous 7 days, the median is obtained from the previous year
- If no SCr measurement in the previous year, AKI alerts are not flagged

3.2.3.1.3 Admission date, discharge date and mortality

Patient's data was entered from the date of admission, regardless of the time admitted. For example, a patient admitted at 11pm on 12/04/21 would more than likely show "N" (meaning no data recorded for that particular date) for maximum AKI stage or maximum SCr, unless this was done before midnight.

Discharge date was recorded up until and including 18/04/21, however discharge date was recorded as "N" for patients discharged after this date, allowing us to focus analysis on the one week of data captured. Mortality was also recorded in the same way. The reasoning for this is to allow us to focus on outcomes seen within this week. We did not include outcomes including discharge date (and therefore length of stay) and mortality after the audit finished (i.e. there was no follow-up after 18/04/21), as we would not have had recordings for any other events related to AKI warnings or SCr after 18/04/21 either.

3.2.3.1.4 Location

Throughout the week, a separate sheet was created for each location (ward) included in the audit. The following wards were included in the audit, with the main specialities seen on each ward listed in **table 3.2**.

Table 3.2: Table of the specialities seen on each ward included in the audit

Ward	Main specialities admitted to ward
4A	Orthopaedics; Neurosurgery; Spinal surgery; Cranial surgery
3A	Paediatric surgery; Ear, Nose & Throat surgery; Oral Surgery; Gynaecology; Urology
4B	Neurology; Long Term Ventilation; Respiratory
3B	Oncology; Haematology
4C	General Paediatrics; Diabetes
3C	Nephrology; Gastroenterology; Endocrine
1C	Cardiology; Paediatric surgery; Neonatal; Cardiac surgery; Anaesthetics
1B	High Dependency Unit (HDU) (covering all specialities)

If a patient was moved from one inpatient ward included in the audit, to another inpatient ward included in the audit during the week, data was recorded for the first location up until the date they were transferred to another location. For example, a patient moving from the HDU to 1C on 15/04/21 (regardless of time) would have data inputted for 15/04/21 under HDU.

If a patient was moved from an inpatient ward not included in the audit, to an inpatient ward included in the audit during the week, admission date was recorded as their initial admission to the hospital. Data was recorded in the final location on the date of transfer, allowing us to capture more data. For example, a patient moving from PICU to HDU on 15/04/21 (regardless of time) would have data inputted for 15/04/21 under HDU. However, no data would be recorded for 12/04/21-14/04/21 due to medications given in PICU not being available to view on Meditech.

3.2.3.1.5 Baseline measurements (weight, height and SCr)

Most recent height and weight before or on admission (to an included ward) were recorded, or if the patient was already admitted at the start of the audit then their most recent recorded measurements were used (i.e. from before or on the date of admission). Height and weight measurements were not updated if patients had further recordings during their stay.

For patients admitted during the audit, previous SCr was recorded as the most recent SCr before admission (not on the date of admission – i.e. the most recent measurement prior to 12/04/21). Therefore, if the first SCr was measured on the date of admission during the audit, it was recorded under the relevant date instead and no previous SCr would be recorded. For patients already admitted at the start of the audit, their most recent SCr up to (and not including) 12/04/21 was recorded as previous SCr. Measurements for SCr were recorded under each relevant date if recorded during the audit.

3.2.3.1.6 Combining sheets to create an overall dataset

After all data from 12/04/21-18/04/21 was recorded in separate sheets, all sheets were combined to create an overall dataset. Here, each patient was allocated to one row on the spreadsheet. Therefore, if a patient had details recorded across two sheets due to being in two included locations during the audit, these would be combined onto one single row.

If a patient stayed in multiple inpatient locations during their stay, the initial admitting consultant and location were recorded for the patient. For example, a patient admitted to HDU under Consultant X at the start of the audit, moving to 1C midway through the audit under Consultant Y, would have their data for their stay on the overall dataset recorded for location as HDU, and admitting consultant as Consultant X.

If a patient had two separate admissions during the week of the audit, they were combined on one row for the patient for the overall dataset. For example, a patient admitted to 3A from 14/04/21-15/04/21 under Consultant X, then readmitted to 4A from 17/04/21-

18/04/21 under Consultant Y, would have their data recorded for admission date as 14/04/21, discharge date as 18/04/21, location as 3A, and admitting consultant as Consultant X.

For patients who moved from one inpatient ward included in the audit, to another inpatient ward included in the audit during the week, on the summary sheet of combined data, their height, weight, and SCr were not updated and remained as the original recorded measurements from prior to (height, weight, SCr) or on the date of admission (height, weight).

For patients who moved from an inpatient ward not included in the audit (e.g., PICU), to an inpatient ward included in the audit during the week, on the summary sheet of combined data, their height, weight, and SCr were updated and recorded as the most recent measurements prior to (height, weight, SCr) or on admission (height, weight) to the ward included in the audit, not to the previous location.

3.2.3.2 Limitations of data extraction

There were some inconsistencies observed in the documentation of medication administration, for example some ambiguous documentation such as whether the medication had been given by another user, or in another location such as in theatre. This may have meant our data extraction may have missed genuine exposures.

Patients from Ward 3B (predominantly an oncology and haematology ward) were included in this audit. When viewing medications for patients undergoing chemotherapy, many of the drugs were listed as “chemotherapy medication (cytotoxic)” but without the name of the drug prescribed. This is standard practice at Alder Hey, with chemotherapy agents being prescribed using the Chemocare System – which was inaccessible to CH who extracted the data. For this reason, we did not include any medications recorded in this format as a nephrotoxin exposure, due to not knowing if they were nephrotoxins. This may have resulted in an underrepresentation of nephrotoxic medication exposure on ward 3B in particular.

3.2.4 Data Synthesis

From the overall dataset of eligible patients for the week, the pivot table function in Microsoft Excel in combination with the use of International Business Machines Statistical Package for the Social Sciences (IBM SPSS)[60] were used to obtain summary data as described below.

For the analysis of data, we aimed to be able to compare our data as directly as possible to the data from the Cincinnati group's papers[27-29], so for this reason our outcomes are guided by their criteria. These measures are described in **table 3.3**.

Table 3.3: Outcome measures adapted from and as seen in Goldstein 2020[29]

Outcome measure	Numerator	Denominator
AKI prevalence rate (per 1000 patient-days)	Number of patients with high nephrotoxic medication exposure who developed AKI in the calendar week of study	The total number of non-critically ill patient hospital days standardised per 1000 patient-days in the calendar week of study
High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	Number of new patients with high nephrotoxic medication exposure in the calendar week of study	The total number of non-critically ill patient hospital days standardized per 1000 patient-days in the calendar week of study
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	Number of patients with high nephrotoxic medication exposure who developed AKI in the calendar week of study	Number of new patients with high nephrotoxic medication exposure in the calendar week of study
AKI intensity rate (per 100 exposed patient-days)	Number of days nephrotoxin exposed patients have AKI	The total number of exposed patient-days standardized per 100 exposed days

Data synthesis included:

1. An overall summary of data extracted from all eligible participants displayed in a table to include:
    a. Patient demographics: Median age on first day of audit; Number of males and females in the cohort; Median height and weight at admission; Number of patients in each ethnic group; Number of patients admitted under each speciality
    b. Inpatient details: Maximum nephrotoxin exposure during audit per patient; Number of patients with AKI during audit; Maximum AKI stage during audit per patient (AKI episodes); Number of AKI alerts during audit and of what stage (AKI alerts)
2. Outcome measures (see **table 3.3**) guided by the Cincinnati group's studies, displayed in a table to include:
    a. AKI prevalence rate (per 1000 patient-days)
    b. High nephrotoxic medication exposure rate (per 1000 patient-days)
    c. Rate of patients with high nephrotoxic medication exposure who develop AKI (%)
    d. AKI intensity rate (per 100 exposed patient-days)
3. A summary of data from each day of the audit, displayed in a table to include:
    a. Inpatient details: Number of AKI alerts per day and of what stage; Number of patients exposed to nephrotoxins (0-5) per day
4. A summary of data extracted from eligible participants for children with and without AKI separately, displayed in a table to include:
    a. Patient demographics: Median age on first day of audit; Number of males and females in the cohort; Median height and weight at admission; Number of patients in each ethnic group; Number of patients admitted under each speciality
    b. Inpatient details: Maximum nephrotoxin exposure during audit per patient
5. A summary of data extracted from eligible participants, for nephrotoxin-exposed and non-exposed separately, displayed in a table to include:

a. Patient demographics: Median age at on first day of audit; Number of males and females in the cohort; Median height and weight at admission; Number of patients in each ethnic group; Number of patients admitted under each speciality
b. Inpatient details: Number of patients with AKI during audit; Maximum AKI stage during audit per patient (AKI episodes)

Through these summaries, we were able to conduct a quantitative analysis of the primary outcomes to include:

- The overall prevalence of AKI in non-critically ill children at AHCH
- The overall prevalence of NTMx-AKI in non-critically ill children at AHCH
- Risk factors for development of AKI (primarily nephrotoxins) in non-critically ill children

3.2.4.1 Statistical analysis

Firstly, the overall dataset was edited to include demographics and outcomes we wished to report, and to exclude any patient identifiers. The dataset then consisted of the following columns:

a. Date of birth
b. Date of admission and First day of audit (12/4/21), to calculate Age on the first day of the audit
c. Date of discharge
d. Speciality (of admitting consultant)
e. Gender
f. Ethnicity
g. Most recent weight
h. Most recent height
i. Maximum AKI stage during admission
j. Maximum number of nephrotoxins exposed to in any one day during admission

As above, we added a column in the spreadsheet to calculate age on the first day of the audit. We had 5 patients who this formula did not give a valid result for, due to them being born the day of, or after the audit began – resulting in some values of 0.000, and some negative values. For this reason, we set each of these patient's age to 0.003 years (1 day old).

3.2.4.1.1 SPSS methods

Data was read into SPSS. Any cell containing "N" for max AKI stage (indicating there was no SCr measurement done to give an AKI stage) was set as missing data, as we cannot assume these patients had no AKI. This meant that in the AKI vs no AKI comparison, the cohort included 176 patients instead of the eligible 314 patients included. 314 patients were still included for the nephrotoxin-exposed vs non-exposed comparison.

Firstly, overall data including the total number of patients with an AKI during their stay, and the maximum AKI stage during admission was calculated.

Next, continuous and categorical variables were compared between the two groups for each comparison: AKI vs no AKI (n=176), and nephrotoxin-exposed vs non-exposed (n=314). Variables in both comparisons included:

- Median age at beginning of audit
- Gender
- Median weight
- Median height
- Ethnicity
- Speciality (of admitting consultant)

Additionally, the following variable was compared in the AKI vs no AKI group:

- Maximum number of nephrotoxic medications in one day during admission

The following variables were compared in the nephrotoxin-exposed vs non-exposed group:

- AKI or no AKI

- Number of AKI episodes (by stage)

We defined AKI as stage 1, 2 or 3 AKI, and no AKI as stage 0. We defined 'nephrotoxin exposed' as per a simplified version of the Cincinnati group's approach of 3 or more nephrotoxins in one day.

Although patients were reported as being from 14 different ethnic groups, some groups included only a very small number of patients– making the analysis difficult. We therefore reclassified the 14 groups into 3 groups (Not stated, White British, not White British).

3.2.4.1.2 SPSS tests performed

We used simple hypothesis testing to compare variables between groups. For continuous variables (age at start of audit, weight at or prior to admission, height at or prior to admission), a Mann-Whitney U test was performed. This was chosen over the Student's T test as none of the continuous variables analysed were normally distributed across the cohort. The median and interquartile range was reported for each variable for the two groups separately.

For categorical variables (gender, ethnicity, speciality, maximum AKI stage during admission, maximum number of nephrotoxins in any one day during admission), a chi-squared test was performed. For variables with no expected cell count <5, the Pearson Chi-Square test was used. For any variables with 1 or more expected cell count <5, the Fisher's Exact Test was used.

Any P value less than 0.05 was assumed statistically significant and the null hypothesis (that for the variable in question there is no difference between groups) was rejected.

3.3 Results

The data audit identified 314 inpatients admitted to AHCH throughout a week in April 2021, which accounted for 1127 inpatient hospital days. 4 patients were excluded for age greater than 18 years, therefore results are presented for the remaining 314.

3.3.1 Baseline demographics

Baseline demographics for the eligible cohort of non-critically ill children included in our audit can be seen in **table 3.4**. Continuous variables are presented as median (IQR). All variables are for the total cohort (n=314) unless otherwise stated due to missing data.

The median age of patients included in our audit was 4.05 years (IQR 10.9). 54.1% of the cohort were male (n=170), and 45.9% were female (n=144). The median weight and height on admission (or most recent measurement prior to admission if no data recorded on admission) were 16.8kg (IQR 33.95) and 101cm (IQR 77) respectively. Of the entire cohort (n=314), 71.3% of patients were White British, 9.87% were of another Ethnic group, and 18.8% had their ethnicity recorded as 'not stated'. 41.7% of the patients were admitted under surgical specialities, 39.5% under medical specialities, 11.5% under cardiology, and 7.23% under either haematology or oncology.

Table 3.4: Baseline demographics for entire cohort

Variable	All eligible patients (n=314)
Age at beginning of audit (median, IQR)*	4.05 (10.9)
Gender (n, %)	
Male	170 (54.1)
Female	144 (45.9)
Average weight (kg) (median, IQR)† (n=312)	16.8 (34.0)
Average height (cm) (median, IQR)† (n=170)	101 (77.0)
Ethnicity (n, %)	
White British	224 (71.3)
Any Other Ethnic Group	31 (9.87)
Not stated	59 (18.8)
Speciality (n, %)	
Surgical	131 (41.7)
Medical	124 (39.5)
Cardiology	36 (11.5)
Haematology & Oncology	23 (7.32)
Maximum number of nephrotoxic medications in one day during admission (n, %)	
0	154 (49.0)
1	108 (34.4)
2	35 (11.2)
3	13 (4.14)
4	3 (0.96)
5	1 (0.32)
Patients with SCr measurement during stay (n, %)	176 (56.1)
AKI	12 (3.82)
No AKI	164 (52.2)
Not measured	138 (44.0)
AKI episodes (n, %‡)	
Stage 0	164 (93.1)
Stage 1	8 (4.55)
Stage 2	3 (1.70)
Stage 3	1 (0.57)
Missing (N)	138
AKI alerts (n, %‡)	25
Stage 0	395 (94.1)
Stage 1	20 (4.76)
Stage 2	3 (0.71)
Stage 3	2 (0.48)
Missing (N) or QNS§	707

*Age at beginning of audit, unless born during audit then age was inputted as 0.003 (one day old)

†Average weight and height on admission or most recent measurement if not recorded on admission

‡Percentage calculated following exclusion of missing data.

§*QNS*: Quantity Not Sufficient for analysis

3.3.1.1 Ethnicity

Due to the large number of groups with a small number of patients listed for Ethnicity, the decision was made to group together certain Ethnic groups as 'Any other Ethnic Group' to facilitate analysis. Of the entire cohort (n=314), the Ethnic breakdown was as seen in **table 3.5**.

Table 3.5: Ethnic group breakdown

Ethnicity	Number of patients (n=314) (n, %)
Any other Asian background	2 (0.64)
Any other Black background	4 (1.27)
Any other Ethnic group	11 (3.50)
Any other Mixed background	4 (1.27)
Any other White background	1 (0.32)
Bangladeshi	1 (0.32)
Black Caribbean	1 (0.32)
Indian	1 (0.32)
Pakistani	2 (0.64)
White and Asian	1 (0.32)
White and Black African	1 (0.32)
White and Black Caribbean	2 (0.64)
White British	224 (71.3)
Not Stated	59 (18.7)

3.3.1.2 Speciality

Children were admitted under a large range of specialities, so similarly to Ethnicity, the decision was made to group similar specialities together. Of the entire cohort (n=314), the breakdown was as seen in **table 3.6**.

Table 3.6: Speciality group breakdown

Speciality	Number of patients (n=314) (n, %)
Anaesthetics	3 (0.96)
Cardiology	36 (11.5)
Cranial surgery	4 (1.27)
Cardiac surgery	1 (0.32)
Diabetes	1 (0.32)
Endocrine	1 (0.32)
Ear, Nose & Throat	8 (2.55)
Gastroenterology	9 (2.87)
Gynaecology	1 (0.32)
Haematology	8 (2.55)
Long term ventilation	9 (2.87)
Neonatal	6 (1.91)
Nephrology	7 (2.23)
Neurology	7 (2.23)
Neurosurgery	23 (7.32)
Oncology	15 (4.78)
Orthopaedics	33 (10.5)
Oral surgery	3 (0.96)
General paediatrics	86 (27.4)
Paediatric surgery	44 (14.0)
Respiratory	4 (1.27)
Spinal surgery	2 (0.64)
Urology	3 (0.96)

3.3.2 Nephrotoxin exposures

As seen in **table 3.4**, 49.0% (154 of 314) patients were not exposed to nephrotoxins during their stay. Therefore 51.0% of patients were exposed to at least one nephrotoxin during their admission. 34.4% (n=108) of patients were exposed to a maximum of one nephrotoxin, 11.2% (n=35) to two, 4.14% (n=13) to three, 0.96% (n=3) to four, and 0.32% (n=1) to a maximum of five nephrotoxins during the admission.

3.3.3 AKI alerts

56.1% (n=176) of patients had a SCr measurement during their stay, and therefore an AKI recording. Of the 12 patients experiencing AKI, 66.7% (n=8) had a Stage 1 AKI, 25.0% (n=3) had a Stage 2 AKI, and 8.33% (n=1) had a Stage 3 AKI. There was a total of 25 AKI alerts during the audit. These can be broken down into 80.0% (n=20) Stage 1 alerts, 12.0% (n=3) Stage 2 alerts, and 8.00% (n=2) Stage 3 alerts as seen in **table 3.4**.

3.3.4 AKI prevalence

During the 7 days, 12 of the non-critically ill patients (n=314) experienced an AKI episode. Of nephrotoxin exposed patients (n=17) (defined as exposure to $\geq$3 nephrotoxins in any one day), 4 experienced an AKI episode. The prevalence of AKI in non-critically ill children (entire cohort) was therefore 3.82%, and the prevalence in nephrotoxin-exposed non-critically ill children was 23.5%.

3.3.5 Secondary outcome measures

Due to the short-term nature of the audit, we felt we would not have sufficient data to analyse length of stay and mortality. These outcomes would have been difficult to interpret due to the nature of the project meaning we had one week's worth of manually-extracted data to interpret, rather than the larger dataset we originally hoped we could extract. No mortality was reported during the dates included in the audit.

3.3.6 Cincinnati group guided measures

We calculated outcomes as guided the Cincinnati group's outcome measures, for which the calculations can be seen in **table 3.7**.

- The AKI prevalence rate was 3.55 per 1000 patient-days.
- The high nephrotoxic medication exposure prevalence rate was 15.08 per 1000 patient-days.
- The rate of patients with high nephrotoxic medication exposure who develop AKI was 23.5%.
- The AKI intensity rate was 34.2 per 100 patient-days.

Table 3.7: Outcome measures adapted from and as seen in Goldstein 2020[29]

Outcome measure	Numerator (n)	Denominator (n)	Result
AKI prevalence rate (per 1000 patient-days)	4	1127	3.55
High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	17	1127	15.08
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	4	17	23.5
AKI intensity rate (per 100 exposed patient-days)	12	35	34.2

3.3.7 Summary of each day

The number of nephrotoxin exposures and AKI alerts throughout the week were similar with no real differences between weekdays and the weekend. This can be seen in **table 3.8 and figure 3.3**.

Table 3.8: Summary of each day during the audit

Outcome measure	Monday (n=148)	Tuesday (n=165)	Wednesday (n=174)	Thursday (n=166)	Friday (n=160)	Saturday (n=152)	Sunday (n=162)
AKI alerts per day							
0	63	64	52	62	51	52	51
1	5	3	2	2	3	2	3
2	0	1	0	0	0	1	1
3	0	0	0	0	1	1	0
Missing (N) or QNS*	80	97	120	102	105	96	107
Total AKI alerts per day	5	4	2	2	4	4	4
Nephrotoxin exposures per day†							
0	82	92	92	91	97	91	101
1	44	53	61	53	42	40	38
2	17	15	14	18	15	18	18
3	4	3	3	2	5	3	5
4	0	2	4	2	1	0	0
5	1	0	0	0	0	0	0

**QNS*: Quantity Not Sufficient for analysis

†Exposure here is defined as any single nephrotoxin from the pre-defined list, as opposed to ≥3 nephrotoxins.

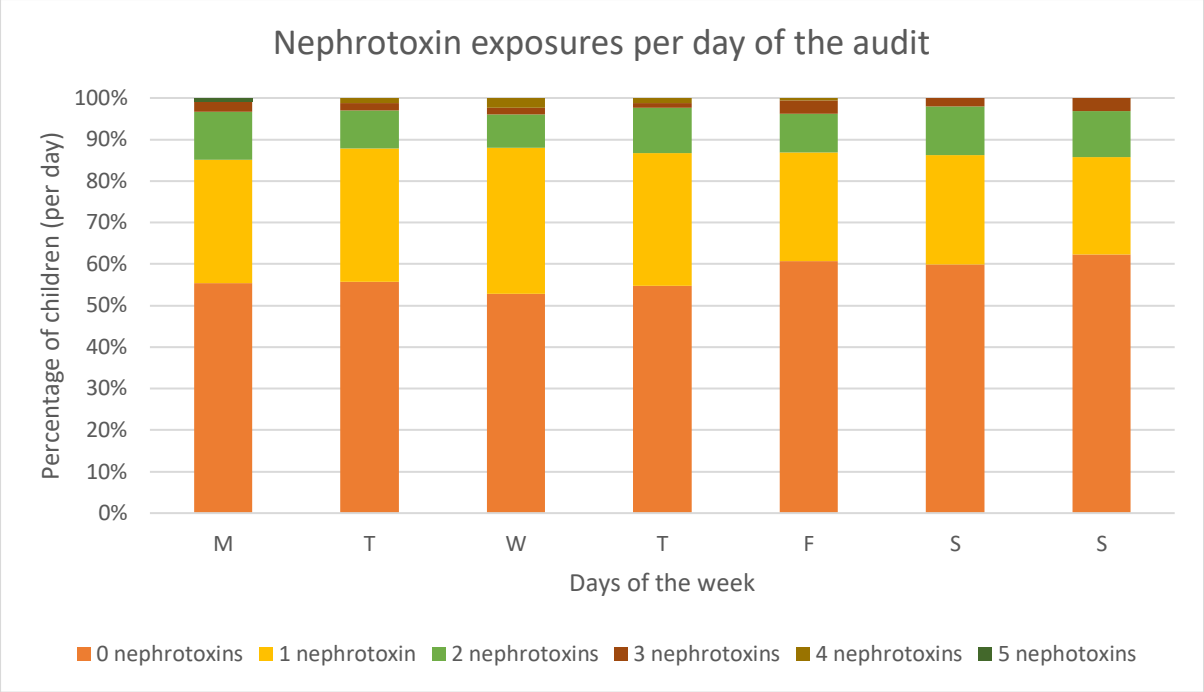


Figure 3.1: Nephrotoxin exposures during the audit

3.3.8 AKI vs no AKI

We made comparisons between patients with AKI (n=12) and patients without AKI (n=164). 138 patients had to be excluded from this comparison due to missing SCr measurements and therefore missing AKI alerts. All variables are for the total cohort (n=176) unless otherwise stated due to missing data.

There were no significant differences in age (p=0.814), gender (p=0.605), weight (p=0.688), height (p=0.206) or ethnicity (p=0.622) between children with or without AKI.

There were significant differences between the AKI and no AKI group in speciality and maximum number of nephrotoxins per day. Children admitted under cardiology or haematology and oncology were more likely to develop AKI than those admitted under surgical or medical specialities (p=0.029). Children with AKI were exposed to a higher number of nephrotoxins in a day during their admission than those who did not have AKI (p=0.027).

Of the 12 patients with AKI, 10 had a height measurement recorded. Of these, eight were recorded within two months prior to admission. The other two patients with height measurements recorded were within 4 and 40 months of admission. The impact of this is considered in the discussion section of this chapter.

Table 3.9: Comparison of children with AKI to without AKI

Variable	AKI (any stage) (n=12)	No AKI (n=164)	P value
Age at beginning of audit (median, IQR)*	4.42 (6.13)	3.00 (12.1)	0.814‡
Gender (n, %)			0.605§
Male	5 (41.7%)	81 (49.4%)	
Female	7 (58.3%)	83 (50.6%)	
Average weight (kg) (median, IQR)† (n=174)	14.9 (20.2)	14.0 (41.3)	0.688‡
Average height (cm) (median, IQR)† (n=97)	78.0 (62.0)	106 (88.0)	0.206‡
Ethnicity (n, %)			0.622¶
White British	10 (83.3%)	118 (72.0%)	
Any Other Ethnic Group	1 (8.33%)	16 (9.76%)	
Not Stated	1 (8.33%)	30 (18.3%)	
Speciality (n, %)			0.029¶
Surgical	2 (16.7%)	57 (34.8%)	
Medical	3 (25.0%)	72 (43.9%)	
Cardiology	4 (33.3%)	24 (14.6%)	
Haematology & Oncology	3 (25.0%)	11 (6.71%)	
Maximum number of nephrotoxic medications in one day during admission (n, %)			0.027¶
0	3 (25.0%)	71 (43.3%)	
1	4 (33.3%)	55 (33.5%)	
2	1 (8.33%)	26 (15.9%)	
3	3 (25.0%)	10 (6.10%)	
4	0 (0.00%)	2 (1.22%)	
5	1 (8.33%)	0 (0.00%)	

*Age at beginning of audit, unless born during audit then age was inputted as 0.003 (one day old)

†Average weight and height on admission or most recent measurement if not recorded on admission

‡Mann-Whitney U test

§Pearson Chi-Square test

¶Fisher's Exact test

3.3.9 Nephrotoxin exposed vs non-exposed

We made comparisons between patients exposed to nephrotoxins (defined as exposure to ≥3 nephrotoxins from our predefined list in any one day of the admission) (n=17) and patients not exposed to nephrotoxins (defined as exposure to <3 nephrotoxins in any one day of the admission) (n=297). All variables are for the total cohort (n=314) unless otherwise stated due to missing data.

There were no significant differences in age (p=0.511), weight (p=0.595), height (p=0.117) or ethnicity (p=0.441) between nephrotoxin exposed children or non-exposed children.

There were significant differences between the exposed and non-exposed group in gender, speciality, and the development of AKI. Of the nephrotoxin exposed patients, 70.6% (n=17) were female and 29.4% (n=5) male, meaning females were more likely to be exposed to nephrotoxins than males (p=0.035). Children exposed to nephrotoxins were more likely to have been admitted under cardiology or haematology and oncology, than those not exposed to nephrotoxins (p<0.001). Importantly, the nephrotoxin exposed patients were more likely to develop an AKI during their admission than their non-exposed counterparts (p=0.015). Of the nephrotoxin exposed patients with SCr measurements during their stay (n=16), 25.0% (n=4) developed an AKI, in comparison to 5.00% (n=8) of the patients not exposed with an SCr measurement (n=160).

Table 3.10: Comparison of children exposed to nephrotoxins to not exposed to nephrotoxins

Variable	Nephrotoxin exposed (n=17)	Not highly exposed (n=297)	P value
Age at beginning of audit (median, IQR)*	1.05 (10.0)	4.13 (11.0)	0.511‡
Gender (n, %)			0.035§
Male	5 (29.4)	165 (55.6)	
Female	12 (70.6)	132 (44.4)	
Average weight (kg) (median, IQR)† (n=312)	9.30 (42.4)	16.85 (33.4)	0.595‡
Average height (cm) (median, IQR)† (n=170)	72.5 (99.0)	105 (76.0)	0.117‡
Ethnicity (n, %)			0.441¶
White British	10 (58.8)	214 (72.0)	
Any Other Ethnic Group	2 (11.8)	29 (9.76)	
Not Stated	5 (29.4)	54 (18.2)	
Speciality (n, %)			<0.001¶
Surgical	6 (35.3)	125 (42.2)	
Medical	1 (5.88)	123 (41.4)	
Cardiology	6 (35.3)	30 (10.1)	
Haematology & Oncology	4 (23.5)	19 (6.40)	
Patients with SCr measurement during stay (n, %)	16 (94.1)	160 (53.9)	0.015¶
AKI	4 (23.5)	8 (2.69)	
No AKI	12 (70.6)	152 (51.2)	
Not measured	1 (5.88)	137 (46.1)	
AKI episodes (n, %)			0.012¶
Stage 0	12 (70.6)	152 (51.2)	
Stage 1	2 (11.8)	6 (2.02)	
Stage 2	2 (11.8)	1 (0.34)	
Stage 3	0 (0.00)	1 (0.34)	
Missing (N)	1 (5.88)	137 (46.1)	

*Age at beginning of audit, unless born during audit then age was inputted as 0.003 (one day old)

†Average weight and height on admission or most recent measurement if not recorded on admission

‡Mann-Whitney U test

§Pearson Chi-Square test

¶Fisher's Exact test

3.4 Discussion

Importantly, our data showed that more than half of non-critically ill inpatients at Alder Hey were exposed to at least one nephrotoxin during their admission. Our findings showed significant differences in variables including admitting speciality and exposure to nephrotoxins between the AKI and non-AKI group, and gender, admitting speciality, and the development of AKI in the nephrotoxin exposed and unexposed group.

Children with AKI were more likely to have been admitted under cardiology or haematology, and oncology than medical or surgical specialities. Children with AKI were also exposed to a higher maximum number of nephrotoxins during a day of their admission than children without AKI.

Significant differences between the nephrotoxin-exposed (≥3 nephrotoxins in a day) and non-exposed group included gender, speciality, and the development of AKI. Exposed patients were more likely to be female than male and more likely to have been admitted under cardiology or haematology and oncology than medical or surgical specialities. Notably, nephrotoxin exposed patients were significantly more likely to develop an AKI during their admission than non-exposed patients.

No significant differences were seen between groups in relation to height or weight. Notably, the AKI cohort had a higher median age (4.42 years) than the group without AKI (3.00 years), but a smaller median height than the group without AKI (78.0cm vs 106cm respectively). On further analysis of the data, of the 174 patients included in the AKI vs no AKI comparison, 97 had data recorded for height. 10 of the 12 children with AKI had a height measured (eight within two months of admission, the others within four and 40 months). The child with a height measured 40 months ago was 3 years and 9 months of age at admission. This meant that their most recent height measurement was from when they were 6 months old. Due to only a small number (n=12) of cases, this one result could have

impacted on our results and caused the median height in the AKI cohort to be much lower than expected.

3.4.1 Comparison to other studies

Our single centre single week audit has provided us with sufficient data to begin to analyse and compare to other studies such as those by the Cincinnati group. By using their studies to guide our own reporting, we have been able to directly compare outcome measures to those seen in their studies. This is displayed in **tables 3.11** and **3.12**, with data from the Cincinnati group's 2013[27], 2016[28], and 2020[29] papers compared to our own study.

Table 3.11: Comparison of outcome measures from Cincinnati group studies to our AHCH data

	Goldstein 2013[27]		Goldstein 2016[28]		Goldstein 2020[29]		AHCH audit
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	N/A
AKI prevalence rate (per 1000 patient-days)	2.6	1.9	2.96	1.06	1.7	1.3	3.55
High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	7.6	11.6	11.63	7.24	7.0	6.9	15.08
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	25.5	25.5	23.3	15.4	23.6	15	23.5
AKI intensity rate (per 100 exposed patient-days)	33.6	11.6	27.7	19.1	11.2	11.2	34.2

Table 3.12: Comparison of study design of Cincinnati group studies and our AHCH data

	Goldstein 2013[27]	Goldstein 2016[28]	Goldstein 2020[29]	AHCH audit
Setting	Single quaternary paediatric hospital	Single quaternary paediatric hospital	9 centre collaborative	Single specialist paediatric hospital
AKI definition	pRIFLE, without UO criteria	KDIGO, without UO criteria	KDIGO, without UO criteria	KDIGO, without UO criteria
Intervention	• HER screening for nephrotoxin exposure* and decision to support process. • Recommended daily SCr monitoring in exposed patients. • Substitution of a non-nephrotoxic or less nephrotoxic medication and/or pharmacokinetic drug concentration monitoring if appropriate. • NB screening was done in 2 phases – initially manually (4 months), followed by automated (final 8 months).	• HER screening for nephrotoxin exposure† and decision to support process. • Recommended daily SCr monitoring in exposed patients. • Substitution of a non-nephrotoxic or less nephrotoxic medication and/or pharmacokinetic drug concentration monitoring if appropriate.	• HER screening for nephrotoxin exposure‡ and decision to support process. • Recommended daily SCr monitoring in exposed patients - for the duration of, and two days after, exposure ending. • Substitution of a non-nephrotoxic or less nephrotoxic medication.	• None. • Patients manually screened for exposure§.
Exclusion criteria	ICU, CKD, kidney transplant, UTI	ICU, CKD, kidney transplant, UTI	ICU and UTI	ICU

*Exposure is defined as exposure to ≥3 nephrotoxins or an IV aminoglycoside (AG) for ≥3 days. Considered exposed for 48hrs after stopping IV AG or reducing to <3 nephrotoxins

†Exposure is defined as exposure to ≥3 nephrotoxins or an IV AG. Exposure started to be counted on the third day of AG. Considered exposed for 48hrs after stopping IV AG or reducing to <3 nephrotoxins

‡Exposure is defined as exposure to ≥3 nephrotoxins on the same calendar day or an IV aminoglycoside (AG) on ≥3 consecutive days. Considered exposed for 2 days after exposure ended.

§Exposure is defined as exposure to ≥3 nephrotoxins in one day from our predefined list

3.4.1.1 AKI prevalence rate

In the Cincinnati group's initial 2013 paper[27], the pRIFLE criteria was used to define AKI, compared to the KDIGO criteria used in the more recent 2016[28] and 2020[29] papers. As recognised in Chapter 2, use of the pRIFLE criteria can potentially overestimate the incidence of AKI by having a higher sensitivity than the KDIGO criteria. The AKI prevalence rate in the 2013 paper (2.6 per 1000 patient-days) was the highest seen in their three papers (compared to 2.96[28] and 1.7[29] per 1000 patient-days), however the rate seen at AHCH was the highest, at 3.55 per 1000 patient days. Our study was a snapshot of one week at AHCH, and although we hope this gives a good overview of the rates seen here, we cannot confirm whether this is representative of a typical week. Furthermore, our study could have potentially included more patients at risk of exposure to nephrotoxins, by not excluding those with UTIs as the Cincinnati studies did. Although numbers in our study are small, this may contribute to the higher AKI prevalence rate. In all three of the interventional studies, AKI prevalence rates decreased following implementation of the intervention (as described in **table 3.12**). For this reason, we hope to be able to implement similar interventions at AHCH to have the same positive outcome.

3.4.1.2 High nephrotoxic medication exposure rate

High rates of nephrotoxin exposure were seen in patients at AHCH in our study, with data analysis concluding the high nephrotoxic medication exposure prevalence rate was 15.08 per 1000 patient days. In comparison to each of the Cincinnati studies pre-intervention rates, our exposure rate was higher. Although the cohort of our study was smaller, we can begin to suggest possible reasons for this. Firstly, we included all admissions with an overnight stay, excluding patients admitted to PICU. Two Cincinnati papers[27, 28] excluded PICU patients, but also those with CKD, kidney transplants, and urinary tract infections (UTIs), and the most recent[29] does not state that those with CKD or kidney transplants are excluded, therefore just excluding those in PICU or UTIs. By including these patients, we may have included patients more likely to be exposed to nephrotoxins, such as those prescribed nephrotoxic medications to treat active UTIs. Secondly, the three studies we have compared to are US studies (due to lack of homogenous UK data with comparable outcome measures reported), where prescribing practices and guidelines may differ to UK practice. In Goldstein et al's 2013 paper[27], the authors state the reason for the high

exposure rate seen in their study was related to the population spectrum admitted to the hospital during the study as well as these services routinely using nephrotoxins. Although rates in our study were higher still, this same reason could contribute to an explanation for the high exposure rates seen in our study.

Goldstein et al's 2016 paper[28] successfully demonstrates a decrease in high nephrotoxic medication exposure prevalence rate following the interventions (a reduction from 11.63 to 7.24 per 1000 patient-days). In the 2013 paper[27], the rate actually increased post-intervention (7.6 to 11.6 per 1000 patient-days), however this coincided with the replacement of manual chart data extraction with HER detection reports – emphasising the value of these electronic trigger systems. These findings suggest that with the implementation of a trigger system, high exposures can be avoided and therefore NTMx-AKI can potentially be prevented.

3.4.1.3 Rate of patients with high nephrotoxin exposure who develop AKI

The rate of children with nephrotoxin exposure who developed AKI in our study (23.5%) was comparable in our study to the rates seen before any intervention in the other three studies (25.5%[27], 23.3%[28] and 23.6%[29]). Due to our limited dataset, our study did not have large numbers of exposed patients go on to develop AKI (n=4), or patients considered exposed (n=17). Nevertheless, the data shows similar findings to those seen in the larger[27, 28], and multicentre[29] studies. Interestingly, one of the exposed patients in our study did not have any renal function tests (SCr measurement) during their stay, and hence we would not know whether they developed an AKI or not. This patient was exposed to 4 nephrotoxins including piperacillin/tazobactam, teicoplanin, vancomycin and trimethoprim. The high rates of NTMX-AKI seen in our study and the studies discussed in this chapter emphasise the importance of monitoring these patient's exposure to nephrotoxins, and considering where substitutions for less nephrotoxic agents could be made.

3.4.1.4 AKI intensity rate

Our AKI intensity rate (34.2 per 100 exposed patient-days) was relatively high compared to the rate seen in the other studies before interventions were implemented. The Cincinnati group's papers had rates of 33.6[27], 27.7[28] and 11.2[29] per 100 exposed patient-days. Further

analysis of AHCH data is required to determine whether this rate is representative of rates at the hospital, or whether this is higher than a typical week. We can speculate that a contributing factor to this high rate could be the high numerator for this calculation – made up of a relatively small cohort (n=4) accounting for a high number of AKI days (n=12). These four patients experienced 3, 3, 1 and 5 AKI days. Our denominator may be proportionally lower and therefore make our rate higher due to the limitations in identifying nephrotoxins such as chemotherapy agents, as discussed in the methods section of this chapter.

After interventions (described in **table 3.12**) were implemented in the 2013[27] and 2016[28] studies, AKI intensity rates reduced considerably. Whether the AKI intensity rate at our trust is an overestimation or not, the finding is still important and should highlight the potentially high rate in comparison to other centres. These two findings in combination demonstrate the potential benefit and improvement in patient outcomes that could be seen if similar interventions were applied to our centre.

The authors note that whilst exposure rates did not decrease (7.0 to 6.9 per 1000 patient-days), the rates of AKI in exposed patients did decrease. They suggest an earlier reduction in nephrotoxin exposure or alternate medication combinations as a result of the intervention may have contributed to this, by decreasing the denominator for this outcome measure. Furthermore, the nature of a multicentre collaborative and the implementation of the interventions in different centres may make interpreting outcome measures more difficult. However, AKI intensity rates in the previous two studies[27, 28] did decrease, emphasising the importance of further research into nephrotoxic burden and outcomes for patients.

3.4.2 Interventions and further work

The long-term aim, which is currently in discussion, is to incorporate an alert system into the existing AKI dashboard, to flag patients who would benefit from a medication review or more frequent monitoring – ultimately reducing AKI rates and thus improving patient's outcomes. Analysis of this week of data has provided insight into the importance of this, highlighting that ultimately nephrotoxin-exposed patients are more likely to develop an AKI. It would be valuable to collect similar data week-by-week, and compare this data over time to provide a larger-scale study.

Further prospective studies would provide useful insight into longer-term outcomes in this cohort, including length of stay, mortality, and progression to CKD, as well as the effect of interventions implemented.

3.5 Limitations

Our study was a single centre study with a small population, therefore limiting our data analysis. The data was manually extracted for one week, meaning human error could have been apparent. Furthermore, our results cannot be applied across the entire paediatric population such as those critically ill, leaving scope for further valuable research. The Cincinnati group have begun this research, by implanting the NINJA initiative in a critically ill neonatal population. It would be advantageous for us to conduct a similar audit to the one we have conducted, applying the criteria to the critically ill population at AHCH – allowing us to compare the rates in this vulnerable population.

Importantly, not all children included in the audit had SCr measured during their admission, meaning that our AKI prevalence rate is a minimum and could in theory be higher than our findings show.

The extraction of the data for height and weight produced non-significant results. As noted in the discussion, just over half of the cohort had a height recorded. Furthermore, using the most recent height and weight without a limit on how recent the measurements needed to have been could have influenced the results. Improving the recording of height and weight measurements on admission of patients would provide more accurate data, allowing more representative comparisons to be made.

As detailed in **section 3.2.3.1.2**, the AKI alert system used at Alder Hey is currently in place for children $\geq$6 months of age. Our audit included 68 children under the age of 6 months, which the EMR system would not have picked up AKI episodes in – potentially contributing to implying a lower AKI prevalence rate. In future research, it could be beneficial to consider other methods to analyse data in children <6 months old.

Lastly, our audit is a snapshot of one particular week of data at the trust. We cannot confirm whether patients admitted during the time our audit was conducted (April 2021) were representative of a typical week. The study was conducted during the COVID-19 pandemic, where differences in the reasons patients were admitted to the trust could have been possible. Conducting a similar study in the near future could provide insight into whether this is the case.

We believe these limitations do not negate the importance of this project and the findings it has produced, and hope the results can be used to guide the implementation of similar interventions in our trust successfully.

3.6 Conclusion

The findings from our study highlight the high nephrotoxin exposure rate at AHCH, which resulted in a comparable rate of NTMx-AKI to similar studies. When compared to other studies in similar populations, our AKI prevalence rate and AKI intensity rate were higher. These other studies demonstrate improvements in outcome measures after implementing increased surveillance for both high nephrotoxic medication exposure and renal function tests, followed by earlier intervention involving reducing nephrotoxic burden. These figures indicate that AKI episodes can potentially be avoided, and that NTMx-AKI is a preventable cause of AKI among non-critically ill hospitalised children.

Chapter 4 Discussion and main findings

4.1 Summary of findings

The results seen in both Chapter 2 and Chapter 3 demonstrate the burden of NTMX-AKI in the paediatric population. We have been able to observe similarities and differences seen in different populations, including non-critically ill children, critically ill children, children with pre-existing renal pathology and more.

The systematic review in Chapter 2 helped identify key themes including potential risk factors for AKI (including but not limited to age, weight and nephrotoxin exposure) and associated outcomes such as length of hospital stay, treatment modality and mortality. As discussed in Chapter 2, some of these findings were significant in various populations when considered in individual papers, but pooled data in the meta-analysis did not consistently produce significant results.

For example, in both non-critically ill and critically ill children, children with AKI were younger than those without. However, after pooling data (in separate meta-analysis for each population), the associations were not significant. As expected, children with nephrotic syndrome with AKI were older than those without – suggesting that exposure to nephrotoxins over a longer disease course leaves older children at a higher risk of AKI than younger children.

Nephrotoxin exposure was considered in all studies included in chapter 2 (part of our inclusion criteria), and often reported as a well-recognised risk factor for AKI development. In non-critically ill children included in our systematic review, all included papers considered nephrotoxin exposure as a risk factor for AKI, however meta-analysis was not possible due to limited data and insufficient homogeneity. The correlation between nephrotoxin exposure and AKI was poorly reported in critically ill children, however toxic nephropathy was documented as a cause for AKI in both included studies. In critically ill neonates (who may already be more vulnerable due to less mature renal development), implementing similar interventions to those seen in previous studies (Cincinnati group's 2013[27], 2016[28], and 2020[29] papers) resulted in reduction of AKI prevalence rates, high nephrotoxic

medication exposure rates, AKI rates in exposed patients, and also AKI intensity rate[52]. These results suggest that reducing nephrotoxin exposure and increasing surveillance of renal function in critically ill neonates is associated with preventing AKI episodes.

Length of hospital stay was not significantly associated with AKI in either non-critically ill children or children with nephrotic syndrome following meta-analysis. However, when considered in individual papers the findings were significant in both populations. In critically ill children, AKI (and more severe AKI) was significantly associated with increased length of stay in both PICU and during the total admission.

Although data was insufficient for meta-analysis, in individual studies of both non-critically ill and critically ill children, AKI was significantly associated with mortality and also more likely to occur in those with severe AKI. The same was seen in children with nephrotic syndrome, however pooled data did not produce reach statistical significance when meta-analysis was performed. In all populations considered, increased risk of mortality is an important finding that should be used to convey the importance of earlier AKI detection, prevention and treatment.

The systematic review also allowed us to identify populations potentially at higher risk of AKI, for example critically ill neonates and those with nephrotic syndrome, as discussed above. One of the papers included in our systematic review studied AKI in patients undergoing congenital heart surgery. Although after adjusting for cofounders the association with nephrotoxins and AKI in this cohort was not statistically significant, the study demonstrates that nephrotoxins are commonly prescribed, and the rate of AKI is high in this vulnerable population.

Observing the lack of available data helped to guide our audit and data analysis in Chapter 3, which demonstrated nephrotoxin exposure was a significant risk factor for the development of AKI in noncritically ill children at AHCH. After studying various populations in the systematic review, we included admitting speciality as part of our data extraction in Chapter 3. From this, we were able to demonstrate which populations were at significantly higher risk of AKI than those admitted under other specialities at AHCH. A large proportion of our

exposed cohort were admitted under cardiology (6 of the 17 children), and of our 12 AKI cases, 4 were cardiology patients. 2 of these 4 children with AKI were exposed to ≥3 nephrotoxins on at least one day of their admission.

Our results from Chapter 3 have allowed us to begin to understand the impact of AKI and nephrotoxic AKI in non-critically ill children at AHCH. Our AKI prevalence rate, high nephrotoxic medication exposure rate, and AKI intensity rate were all higher than rates seen in the Cincinnati group's three studies[27-29]. Although our dataset was limited by a smaller sample size, comparing these outcome measures has highlighted the potentially high rates and burden of nephrotoxin exposure and AKI at AHCH. Despite a higher proportion of children at Alder Hey being exposed to nephrotoxins, the rate of patients with high nephrotoxic medication exposure who developed AKI was similar to the rates seen before interventions were implemented in the Cincinnati studies. These results suggest that although more children were exposed at Alder Hey, a similar proportion of nephrotoxin-exposed children (within the calendar week studied) go on to develop an NTMx-AKI as that seen in the other centres. The AKI intensity rate in our study was higher than seen in the Cincinnati studies. The numerator for this calculation involves the number of days that nephrotoxin exposed children experience AKI for. These results imply that children at Alder Hey had longer episodes of AKI than children at other centres. This could be further explored at out trust by analysing a similar dataset over a longer period, to observe whether more nephrotoxin exposed children did go on to develop AKI.

4.2 Context

The literature we have described in this thesis, and the results from our audit contribute to existing evidence from paediatric and adult literature. By conducting the audit for one week at Alder Hey, we hope to have provided insight into the AKI and nephrotoxin exposure rates seen at a specialist children's hospital in the UK, and the relationship between nephrotoxins and AKI at our trust. We hope that these findings can provide similar trusts with a way to consider AKI and NTMx-AKI rates in their centres, and consider similar interventions to those described and in Chapter 2 and 3.

We can learn from existing adult evidence and research recommendations to continue to build on paediatric research and guidance. Although research in the adult population to date is more comprehensive, further research to better understand risk factors for NTMx-AKI, outcomes, and mechanisms would be valuable.

Research in the adult population has described nephrotoxins and their mechanisms of injury (as seen in **table 1.5**), as well as identified interventions for prevention of NTMx-AKI. For example, risk scores and evaluation of preventative treatments in adult patients have been developed[61, 62] following identification of contrast as a risk factor for AKI, causing contrast-induced nephropathy. Fu et al[61] categorised patients into four groups based on their risk score, scoring between 2 and 4 points for each of nine recognised risk factors: contrast medium dose, eGFR level, emergency Percutaneous Coronary Intervention (PCI), age, hypotension, Myocardial Infarction (MI) history, left ventricular ejection fraction, anaemia and a history of diabetes. Tziakas et al[62] developed a simpler risk score in comparison, scoring between 1 and 2 points for five risk factors including pre-existing renal disease, metformin use, previous PCI, peripheral arterial disease, and injected volume of contrast medium. These risk scores would be relatively simple to implement in a clinical setting – the EMR could calculate these risk scores, so physicians can make decisions guided by these scores and consider preventative treatments in high-risk (high scoring) patients. Contrast was recognised as a nephrotoxic medication in several of the papers included in chapter 2, however considering interventions such as discussed here could prove useful in the paediatric population. National Institute for Health and Care Excellence (NICE) guidelines[32] provide recommendations for monitoring and preventing deterioration in adults and children with or at high risk of AKI, as well as prevention of AKI in adults needing iodine-based contrast media. These guidelines advise encouraging oral hydration before and after procedures in adults at increased risk of contrast-induced AKI. Examples of high-risk adults include similar risk factors described above, including[32]:

- An eGFR <30ml/min/1.73m^2
- Have had a renal transplant
- Require a large volume of contrast medium

- Intra-arterial administration of contrast medium with first-pass renal exposure being used

Recommendations are also made surrounding temporarily stopping the use of ACEI and ARBs, and discussion with nephrologists.

Research in the adult population has well described increased costs in caring for adults with AKI than those without[16], with KDIGO Clinical Practice Guideline for AKI[1] also recognising that the cost per person of managing AKI is high. Hospital costs in association to AKI have begun to be described in paediatric studies[21, 63], however further studies are needed to confirm this association. Paediatric literature so far has shown longer lengths of hospital stay in children with AKI, and therefore we can expect costs of their care to be increased alongside this. Future research in adult and paediatric populations to analyse the benefits of increased surveillance (including renal function monitoring) in terms of both AKI rates and hospital costs would provide useful insight into the most efficient treatment approaches.

There is recent, interesting research being published describing associations with AKI and COVID-19, and outcomes in both adults and paediatric populations. Although currently limited, available research suggests AKI in COVID-19 patients is multifactorial[64]. A retrospective cohort study concluded that one-fifth of hospitalised children with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection had an AKI, which was associated with increased morbidity and mortality[65]. These existing findings emphasise the importance of early recognition and treatment of AKI including in patients with COVID-19. With COVID-19 being a disease we are continually learning about, anything to potentially improve outcomes should be considered. As discussed throughout this thesis, NTMx-AKI is a potentially avoidable cause of AKI and to lessen the chance of this contributing to AKI in this population, would hopefully contribute to improving patient's outcomes.

4.3 Limitations

Chapter 2 provided a comprehensive overview of current literature surrounding NTMx-AKI in different populations of children. Our meta-analysis was limited by the small number of papers in each population and differences in the reporting of outcome measures. For this

reason, we could not perform meta-analysis for the same outcomes in each group of patients described and instead gave a descriptive narrative of findings from eligible studies. As available research continues to develop, similar meta-analysis could be repeated and provide a quantitative analysis of outcomes in further populations. The development of a core outcome set may also be valuable, for studies to report comparable outcomes to allow further analysis of data.

The generalisability of our results in chapter 3 was limited by the small sample size and limited to non-critically ill children. Another limitation was that not all children included had renal function tests and therefore a SCr measurement during their admission. Finally, the AKI alert system in place at AHCH does not flag alerts for children less than 6 months of age. For these reasons, our AKI rates are a minimum of the true rates at the trust. However, by using the outcome measures defined by the Cincinnati group, our results were still able to be compared to other similar, larger-scale studies – allowing us to begin to understand the impact of AKI and in particular NTMX-AKI in non-critically ill children at AHCH. Future studies considering a longer duration and another method of including those less than 6 months old would be beneficial.

4.4 Implications for clinical practice

Implementing changes such as increased surveillance could benefit patients in terms of improved outcomes, and also benefit trusts in terms of reduced hospital costs. Increased surveillance could include EMR screening for patients exposed to $\geq$3 nephrotoxins, followed by regular renal function monitoring in at-risk patients (due to nephrotoxin exposure or other recognised risk factors). We hope that the findings from our review along with our findings from our audit at Alder Hey can provide clinicians both at AHCH and wider trusts with information and reason to be aware of nephrotoxin exposure in children. Raising awareness of the positive impacts that reducing exposure rates can have could improve patient outcomes both in our trust and beyond.

4.4.1 Common nephrotoxins

The most recent paper from the Cincinnati group (Goldstein et al 2021[30]) contains a list of medications they consider and class as nephrotoxins, which has been used in and adapted from their previous studies in 2011[21], 2013[27], 2016[28] and 2020[29]. The original list of nephrotoxins first used in earlier papers has since been adapted with the addition of several nephrotoxins (including iodinated contrast agents and other medications such as aspirin and naproxen), resulting in the most recent list as seen in **table 4.1**.

Table 4.1: List of nephrotoxins, adapted from the Cincinnati group[21, 27-30]

Aciclovir	Gadopentetate	Methotrexate
Ambisome	dimeglumine*	Mitomycin
Amikacin	Gadoextate disodium*	Nafcillin
Amphotericin B*	Ganciclovir	Naproxen
Aspirin**	Gentamicin	Pamidronate disodium
Captopril	Ibuprofen	Pentamidine
Carboplatin	Ifosfamide	Piperacillin/tazobactam
Cefotaxime	Indomethacin	Piperacillin
Ceftazidime	Iodixanol*	Sirolimus
Cefuroxime	Iohexol*	Sulfasalazine
Celecoxib	Iopamidol*	Tacrolimus
Cidofovir*	Iopromide*	Tenofovir
Cisplatin	Ioversol*	Ticarcillin/clavulanic acid
Colistemethate	Ioxaglate meglumine and	Tobramycin
Cyclosporin	ioxaglate sodium*	Topiramate
Dapsone	Ioxilan*	Valacyclovir
Diatrizoate meglumine	Ketorolac	Valganciclovir
Diatrizoate sodium	Lisnopril	Valsartan
Enalapril	Lithium	Vancomycin
Enalaprilat	Losartan	Zoledronic acid
Foscarnet	Mesalamine	Zonisamide

*Medications counted for 7 days after administration toward exposure due to their long half-life. All other listed medications count for 48 additional hours after exposure

It is worth noting that furosemide is not included in any of the above lists of nephrotoxic medications monitored in the above studies. The authors state in the earliest paper[21] to document the list of nephrotoxins, that furosemide was not included due to its common use as a treatment for AKI – meaning that quantifying the contribution of furosemide to the course of AKI would be challenging. The list of included nephrotoxins used for our audit in Chapter 3 is adapted from this list, to include nephrotoxins in use at AHCH. We did include furosemide as a nephrotoxin in our audit, due to frequent use and previous association with AKI at AHCH.

4.5 Implications for clinical research

The information obtained from the systematic review and meta-analysis in Chapter 2 has allowed us to combine available research and build on this knowledge with our audit in Chapter 3. However, there is scope for further research to contribute to our understanding of NTMx-AKI in children – including risk factors and short- and long-term outcomes.

The KDIGO guidelines[1] make several research recommendations, including research surrounding nephrotoxic medications, and also the need for research with follow up beyond hospital stay, to better understand the clinical consequences of AKI in patients with and without underlying CKD. It is important that research into these areas is continued, in order to begin to bridge these notable knowledge gaps and ultimately improve patient care, through better understanding and management of NTMx-AKI.

Multiple study designs could prove useful. Retrospective studies to analyse AKI rates and nephrotoxin exposures at various hospitals and in the wider paediatric population would allow us to compare rates seen at AHCH to other centres. This would also provide more insight into the epidemiology of NTMx-AKI in children. Further research to identify risk factors for AKI development would provide scope to educate clinicians to consideration of these factors when prescribing nephrotoxins, and identify patients at increased risk of AKI at an earlier stage.

Similar to our audit conducted in Chapter 3, a prospective study performed over a longer period of time, including younger children, and including critically ill children, with analysis in real-time would provide beneficial information on AKI rates and nephrotoxin exposure rates at a specialist children's centre. This would allow confirmation of the audit results and could hopefully be extrapolated to other UK centres. Follow up at a later date in future studies would provide useful insight into patient outcomes including length of hospital stay and disease duration, as well as rates of children going on to develop long-term complications such as CKD or death.

Lastly, it would be important to implement interventions (such as screening for exposed patients to identify those at higher risk of AKI, regular SCr monitoring, and encouraging substitution for less nephrotoxic agents where possible or deprescribing if suitable) as described in papers included in the systematic review and compared to in our audit. Alongside implementing a change, it is important to monitor the impact of these interventions (calculation of AKI rates pre- and post-intervention) upon prevalence of AKI and NTMx-AKI, as well as patient outcomes.

A core outcome set could prove beneficial in ensuring future studies follow a consistent method of both defining AKI and reporting outcomes. This would allow for comparison and further data analysis. An example of a potential core outcome set developed with guidance from papers (Cincinnati group papers[27-29, 41, 52, 58]) included in this thesis can be seen in **table 4.2**.

Table 4.2: Potential core outcome set

Outcome measure	Numerator	Denominator
Primary Outcomes		
SCr compliance (%)	Number of SCr values obtained	Number of SCr values that should be obtained per NINJA protocol (daily SCr in high nephrotoxin exposed patients)
AKI prevalence rate (%)	Number of patients with AKI in the calendar week of study	The total number of patients in the calendar week of study
AKI prevalence rate (per 1000 patient-days)	Number of patients with high nephrotoxic medication exposure who developed AKI in the calendar week of study	The total number of patient hospital days standardised per 1000 patient-days in the calendar week of study
High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	Number of new patients with high nephrotoxic medication exposure in the calendar week of study	The total number of patient hospital days standardized per 1000 patient-days in the calendar week of study
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	Number of patients who develop AKI	Number of new patients with high nephrotoxic medication exposure in the calendar week of study
AKI intensity rate (per 100 exposed patient-days)	Number of days nephrotoxin exposed patients have AKI	The total number of exposed patient-days standardized per 100 exposed days
Secondary Outcomes		
Mortality rate (%)	Number of patients who died within 28 days of an AKI episode	Number of patients who developed AKI
Progression to CKD rate (%)	Number of patients who developed CKD* at follow-up appointments	Number of patients who developed AKI
Length of hospital stay (days)†	Number of days between date of admission and date of discharge	

*CKD defined as has been seen in previous studies (persistent deterioration in renal function for more than 3 months)[56]

†Not calculated as a rate and therefore no numerator or denominator

4.6 Conclusion

This thesis provides an overview of the epidemiology of NTMx-AKI in children, firstly in a systematic review and meta-analysis (Chapter 2) of the current literature, and then in an audit of nephrotoxin exposure and AKI at AHCH (Chapter 3).

The meta-analysis allowed us to combine available data and compare outcomes. The risk and rate of AKI is high, and higher in particular cohorts of patients, and those exposed to nephrotoxins. Importantly, our review has conveyed that NTMx-AKI is a potentially avoidable cause of AKI, with interventional studies demonstrating that episodes of AKI can be prevented without compromising other areas of patients' treatment. The conclusions drawn from this systematic review will contribute to the current literature, and helped to inform the audit completed in Chapter 3.

The data analysis of inpatients during one week at AHCH in Chapter 3 contributed to improving current understanding of the AKI and nephrotoxin exposure rates in our trust. Our findings highlighted the higher rate of nephrotoxin exposure seen at Alder Hey, and similar rate of NTMx-AKI, compared to other studies. AKI prevalence rate and AKI intensity rate were higher at our trust than seen in other studies. These findings emphasise the importance of considering interventions to reduce nephrotoxin exposure and AKI rates, and will help to guide future research and recommendations in both our trust and other centres.

This work has important implications for clinical practice and future research. On the basis of this work, increased surveillance of nephrotoxin-exposed patients, should be introduced to clinical practice. Medication reviews and daily monitoring of renal function can lead to improved patient outcomes and reduced hospital costs. A core outcome set has been proposed for use in future research to ensure clinical relevance and comparability between studies. Importantly these can be applied to interventional prospective studies with longer-term follow-up to assess the effect of these changes. This will contribute to improving understanding of the clinical consequences of AKI in various populations, and ultimately improvements in patient care through better understanding and management of NTMx-AKI.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter. Suppl. 2012;2:1-138.
2. National Kidney Foundation. Acute Kidney Injury (AKI) [updated 10th March 2020Accessed 30th July 2020]. Available from: https://www.kidney.org/atoz/content/AcuteKidneyInjury.
3. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.
4. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028-35.
5. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
6. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Medicine. 2009;35(10):1692-702.
7. Huber W, Schneider J, Lahmer T, Küchle C, Jungwirth B, Schmid RM, et al. Validation of RIFLE, AKIN, and a modified AKIN definition ("backward classification") of acute kidney injury in a general ICU: Analysis of a 1-year period. Medicine. 2018;97(38).
8. National Kidney Foundation. MDRD Study Equation [Accessed 15th May 2021]. Available from: https://www.kidney.org/content/mdrd-study-equation.
9. National Kidney Foundation. Cockcroft-Gault Formula [Accessed 15th May 2021]. Available from: https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc.
10. National Kidney Foundation. Creatinine-Based "Bedside Schwartz" Equation (2009) [Accessed 15th May 2021]. Available from: https://www.kidney.org/content/creatinine-based-%E2%80%9Cbedside-schwartz%E2%80%9D-equation-2009.
11. Death NCEiPOa. Acute Kidney Injury: Adding Insult to Injury. 2009.
12. Wang HE, Muntner P, Chertow GM, Warnock DG. Acute Kidney Injury and Mortality in Hospitalized Patients. American Journal of Nephrology. 2012;35(4):349-55.
13. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442-8.
14. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in Hospitalized Children: Epidemiology and Clinical Associations in a National Cohort. 2013(10):1661.
15. Abitbol CL, Bauer CR, Montané B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. Pediatric nephrology (Berlin, Germany). 2003;18(9):887-93.
16. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365-70.

17. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute Kidney Injury Associated with High Nephrotoxic Medication Exposure Leads to Chronic Kidney Disease after 6 Months. The Journal of Pediatrics. 2014;165(3):522-7.e2.
18. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. 2017. p. 11-20.
19. Madsen NL, Goldstein SL, Frøslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. 2017.
20. Uber AM, Sutherland SM. Nephrotoxins and nephrotoxic acute kidney injury. Pediatric Nephrology: Journal of the International Pediatric Nephrology Association. 2019:1.
21. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clinical journal of the American Society of Nephrology : CJASN. 2011;6(4):856-63.
22. Hanna MH, Askenazi DJ, Selewski DT. Drug-induced acute kidney injury in neonates. Curr Opin Pediatr. 2016;28(2):180-7.
23. Ehrmann S, Helms J, Joret A, Martin-Lefevre L, Quenot J-P, Herbrecht J-E, et al. Nephrotoxic drug burden among 1001 critically ill patients: impact on acute kidney injury. Ann Intensive Care. 2019;9(1):106.
24. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. Am J Kidney Dis. 2005;45(1):96-101.
25. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter. Suppl. 2013;3:1-150.
26. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerda J, et al. Phenotype standardization for drug-induced kidney disease. Kidney international. 2015;88(2):226-34.
27. Goldstein SL, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, et al. Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury. Pediatrics. 2013;132(3):e756-e67.
28. Goldstein SL, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney International. 2016;90(1):212-21.
29. Goldstein SL, Dahale D, Kirkendall ES, Mottes T, Kaplan H, Muething S, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. Kidney International. 2020;97(3):580-8.
30. Goldstein SL, Krallman KA, Schmerge A, Dill L, Gerhardt B, Chodaparavu P, et al. Urinary neutrophil gelatinase-associated lipocalin rules out nephrotoxic acute kidney injury in children. Pediatric Nephrology. 2021.
31. Delanaye P, Mariat C, Cavalier E, Maillard N, Krzesinski JM, White CA. Trimethoprim, Creatinine and Creatinine-Based Equations. Nephron Clinical Practice. 2011;119(3):c187-c94.
32. National Institute for Health and Care Excellence. Acute kidney injury: prevention, detection and management. NG148. 2019 [Accessed 11th September 2020]. Available from: https://www.nice.org.uk/guidance/ng148.
33. Think Kidneys, BAPN. Guidance for clinicians managing children at risk of, or with, acute kidney injury. 2019.

34. Greenberg JH, Parikh CR. Biomarkers for Diagnosis and Prognosis of AKI in Children: One Size Does Not Fit All. Clin J Am Soc Nephrol. 2017;12(9):1551-7.
35. National Institute for Health and Care Excellence. Healthcare Databases Advances Search (HDAS) [Accessed 6th November 2020]. Available from: https://hdas.nice.org.uk/.
36. Cochrane Database of Systematic Reviews [Accessed 18 March 2021]. Available from: https://www.cochranelibrary.com/.
37. Joanna Brigg's Institute. Critical Appraisal Tools: Checklist for Case Control Studies 2020 [updated 2020, Accessed 6th November 2020]. Available from: https://jbi.global/critical-appraisal-tools.
38. Joanna Brigg's Institute. Critical Appraisal Tools: Checklist for Cohort Studies 2020 [updated 2020, Accessed 6th November 2020]. Available from: https://jbi.global/critical-appraisal-tools.
39. Review Manager (RevMan) [Computer program]. Version 5.3 ed. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
40. Higgins JPT, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.
41. Benoit SW, Goldstein SL, Dahale DS, Haslam DB, Nelson A, Truono K, et al. Reduction in Nephrotoxic Antimicrobial Exposure Decreases Associated Acute Kidney Injury in Pediatric Hematopoietic Stem Cell Transplant Patients. Biol Blood Marrow Transplant. 2019;25(8):1654-8.
42. Kim MY, Cho MH, Kim JH, Ahn YH, Choi HJ, Ha IS, et al. Acute kidney injury in childhood-onset nephrotic syndrome: Incidence and risk factors in hospitalized patients. Kidney Res Clin Pract. 2018;37(4):347-55.
43. Kirkley MJ, Boohaker L, Griffin R, Soranno DE, Gien J, Askenazi D, et al. Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database. Pediatr Nephrol. 2019;34(1):169-76.
44. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, et al. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. American Journal of Kidney Diseases. 2016;67(3):384-90.
45. Prasad BS, Kumar M, Dabas A, Mishra K. Profile of Acute Kidney Injury in Hospitalized Children with Idiopathic Nephrotic Syndrome. Indian pediatrics. 2019;56(2):119-22.
46. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL, Seamon M, et al. AKI in Children Hospitalized with Nephrotic Syndrome. Clinical Journal of the American Society of Nephrology. 2015;10(12):2110-8.
47. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. The Journal of Maternal-Fetal & Neonatal Medicine. 2014;27(14):1485-90.
48. Safder OY, Alhasan KA, Shalaby MA, Khathlan N, Al Rezgan SA, Albanna AS, et al. Short-term outcome associated with disease severity and electrolyte abnormalities among critically ill children with acute kidney injury. BMC Nephrol. 2019;20(1):89.
49. Schaffzin JK, Dodd CN, Nguyen H, Schondelmeyer A, Campanella S, Goldstein SL. Administrative Data Misclassifies and Fails to Identify Nephrotoxin-Associated Acute Kidney Injury in Hospitalized Children. Hospital Pediatrics. 2014;4(3):159-66.

50. Shalaby M, Khathlan N, Safder O, Fadel F, Farag YM, Singh AK, et al. Outcome of acute kidney injury in pediatric patients admitted to the intensive care unit. Clin Nephrol. 2014;82(6):379-86.
51. Sharma M, Mahanta A, Barman AK, Mahanta PJ. Acute kidney injury in children with nephrotic syndrome: a single-center study. Clinical Kidney Journal. 2018;11(5):655-8.
52. Stoops C, Stone S, Evans E, Dill L, Henderson T, Griffin R, et al. Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in the Neonatal Intensive Care Unit. The Journal of Pediatrics. 2019;215:223-8.e6.
53. Tresa V, Yaseen A, Lanewala AA, Hashmi S, Khatri S, Ali I, et al. Etiology, clinical profile and short-term outcome of acute kidney injury in children at a tertiary care pediatric nephrology center in Pakistan. Ren Fail. 2017;39(1):26-31.
54. Uber AM, Montez-Rath ME, Kwiatkowski DM, Krawczeski CD, Sutherland SM. Nephrotoxin exposure and acute kidney injury in critically ill children undergoing congenital cardiac surgery. Pediatric nephrology (Berlin, Germany). 2018;33(11):2193-9.
55. Xiong M, Wang L, Su L, Luo W, Li Y, Li L, et al. Acute kidney injury among hospitalized children with cancer. Pediatric Nephrology. 2021;36(1):171-9.
56. Yang EM, Yoo KH, Ahn YH, Kim SH, Lee JW, Chung WY, et al. Lower albumin level and longer disease duration are risk factors of acute kidney injury in hospitalized children with nephrotic syndrome. Pediatric Nephrology. 2020.
57. Yaseen A, Tresa V, Lanewala AA, Hashmi S, Ali I, Khatri S, et al. Acute kidney injury in idiopathic nephrotic syndrome of childhood is a major risk factor for the development of chronic kidney disease. Ren Fail. 2017;39(1):323-7.
58. Young J, Dahale D, Demmel K, O'Brien M, Geller J, Courter J, et al. Reducing acute kidney injury in pediatric oncology patients: An improvement project targeting nephrotoxic medications. Pediatr Blood Cancer. 2020;67(8):e28396.
59. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med. 2010;36(10):1657-65.
60. IBM SPSS Statistics for Mac [Computer program]. Version 27 (IBM Corp., Armonk, N.Y., USA) ed.
61. Fu N, Li X, Yang S, Chen Y, Li Q, Jin D, et al. Risk score for the prediction of contrast-induced nephropathy in elderly patients undergoing percutaneous coronary intervention. Angiology. 2013;64(3):188-94.
62. Tziakas D, Chalikias G, Stakos D, Altun A, Sivri N, Yetkin E, et al. Validation of a new risk score to predict contrast-induced nephropathy after percutaneous coronary intervention. Am J Cardiol. 2014;113(9):1487-93.
63. Zappitelli M, Moffett BS, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study. Nephrology Dialysis Transplantation. 2010;26(1):144-50.
64. Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nature Reviews Nephrology. 2020;16(12):747-64.
65. Kari JA, Shalaby MA, Albanna AS, Alahmadi TS, Alherbish A, Alhasan KA. Acute kidney injury in children with COVID-19: a retrospective study. BMC Nephrol. 2021;22(1):202.

Appendix

Appendix 1 – PROSPERO registration of systematic review protocol

Can also be accessed via:

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020215439

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

What is the epidemiology of drug-induced acute kidney injury in children?

Charlotte Hankinson, Louise Oni, Stephen McWilliam, Andrea Jorgensen

Citation

Charlotte Hankinson, Louise Oni, Stephen McWilliam, Andrea Jorgensen. What is the epidemiology of drug-induced acute kidney injury in children?. PROSPERO 2020 CRD42020215439 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020215439

Review question

What is the Epidemiology of drug-induced Acute Kidney Injury in Children?

Searches

MEDLINE, EMBASE and CINAHL will be searched from January 2000 to the date when the actual search is performed, for English language texts. The Cochrane Library will also be searched.

Types of study to be included

Studies reported in full text format and published in English will be included.

Narrative reviews will not be included.

Condition or domain being studied

Drug-induced acute kidney injury.

Participants/population

Inclusion Criteria: children admitted to hospital and documentation of in-hospital nephrotoxin exposure; diagnosis of AKI

Exclusion Criteria: non-human; outpatients; over the age of 18; no exposure to any nephrotoxins documented; consideration only of a specific nephrotoxin or nephrotoxin combination.

Intervention(s), exposure(s)

The intervention of interest is the use of nephrotoxins and the subsequent development of AKI.

Comparator(s)/control

There will be no comparator

Main outcome(s)

The main outcome of the review will be to describe the epidemiology of drug-induced acute kidney injury in children.

The incidence of AKI will be studied by looking at the number of AKI diagnoses (as is part of our inclusion criteria) in included papers, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria, AKI Network (AKIN) criteria, or Paediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria.

* Measures of effect

We will report:

1. The overall incidence of AKI

2. The incidence of AKI in children exposed to nephrotoxic medications

3. The relative risk of AKI for children exposed to nephrotoxic medications

As part of the data synthesis, we will include a summary table of data extracted from eligible papers, part of which will include effect estimates (adjusted and raw), and standard errors, if the data displayed in included papers allows. This will be confirmed after the main searches have been conducted and we know what data will be analysed.

Additional outcome(s)

In addition to the primary outcome, we will:

Conduct a quantitative analysis of the primary outcome

Describe outcome measures to report AKI epidemiology in children

Describe identified risk factors for the development of AKI in children

Describe strategies that have demonstrated improvements/have been shown to mitigate AKI

* Measures of effect

Not applicable.

Data extraction (selection and coding)

Databases will be searched by one reviewer (CH) using the search terms defined in the attached protocol. Using the titles and abstracts, a list of articles potentially meeting the eligibility criteria will be produced independently by two reviewers (CH and SM). Any disagreements will firstly be discussed between CH and SM, and failing this will be resolved by a third reviewer (LO). Full text review and quality assessment will be done independently by the same reviewers (CH and SM). Data extraction and critical appraisal of identified studies will be conducted by one reviewer (CH), taking into account the inclusion and exclusion criteria.

The following data will be collected from studies meeting the eligibility criteria: Author, Title, Year, Type of study, Number of patients per study, Patient age, Patient demographics (anything available including BMI, ethnicity, primary renal disease, weight), Treatment modality (RRT), AKI alerts, Peak AKI Stage, Stages of AKI when alert flagged, Exposure to nephrotoxins, Length of hospital stay, Mortality, Reason for admission, Critical care admission

Risk of bias (quality) assessment

To reduce the level of bias in the studies for selected inclusion, a second assessor (SM) will independently screen the search results against the eligibility criteria to obtain the articles for inclusion. Any discrepancies will be resolved by discussion and in liaison with the third reviewer (LO).

To assess the risk of bias and check the quality of studies identified after searching, the checklists developed by the Joanna Briggs Institute will be used, along with personal consideration. This checklist will involve assessing characteristics including but not limited to: recruitment; exposure measures in exposed and unexposed groups; identification of confounding factors; measurement of outcomes; appropriateness of statistical analysis. The findings of the quality assessment will be displayed in a table in the results section of the systematic review.

Quality assessment will be done independently by two reviewers (CH and SM). Any differences in assessment outcome will firstly be discussed between the two reviewers, with any disagreements being resolved by a third reviewer (LO).

Furthermore, when working towards checking the final review, our own systematic review will be quality assessed using the PRISMA 2009 checklist.

Strategy for data synthesis

Study selection, data extraction, and data synthesis will be performed by two authors (CH and SM) and any discrepancies will be resolved by a third reviewer (LO).

Data synthesis will include:

1. A PRISMA flow diagram

2. A summary of data extracted from eligible papers displayed in a table to include:

a. Bibliographic information (Author; Title; Year; Type of study)

b. Study design (Type of study; Number of patients per study; Setting (primary/secondary/tertiary care) although we expect most will be secondary or tertiary))

c. Exposure(s) and outcomes

d. Patient demographics (Age; BMI; Ethnicity; Primary renal disease; Weight)

e. Inpatient details (Treatment modality (RRT); AKI alerts; Peak AKI stage; Stages of AKI when alert flagged; Exposure to nephrotoxins; Length of hospital stay; Mortality; Reason for admission; Critical care admission)

f. Effect estimates (adjusted and raw), and standard errors

3. If papers sufficiently homogenous, we aim to conduct a quantitative analysis of the primary outcome of the epidemiology of drug-induced AKI in children, to include:

a. The overall incidence of drug-induced AKI in children across all included papers

i. With subgroup analysis for different patient populations (eg pre-existing renal disease, cardiac patients, oncology patients, critically and non-critically ill patients)

b. Calculation of summary statistics of drug-induced AKI for each study (eg risk ratios)

4. If the papers are not suitable for quantitative analysis, a narrative analysis will be performed to describe:

a. An estimate of drug-induced AKI incidence for each study

b. Calculation of summary statistics for each study (eg risk ratios)

5. Whether criteria for homogeneity are met or not, we will:

a. Describe outcome measures to report AKI epidemiology in children

b. Describe identified risk factors for the development of AKI in children

c. Describe strategies that have demonstrated improvements/have been shown to mitigate AKI

Analysis of subgroups or subsets

As above, if papers sufficiently homogenous, we aim to conduct a quantitative analysis of the primary outcome of the epidemiology of drug-induced AKI in children. This aims to include subgroup analysis for different patient populations (eg pre-existing renal disease, cardiac patients, oncology patients, critically and non-critically ill patients).

Contact details for further information

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

08 December 2020

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Organisational affiliation of the review
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Review team members and their organisational affiliations
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Type and method of review
Systematic review

Anticipated or actual start date
09 November 2020

Anticipated completion date
01 January 2021

Funding sources/sponsors
None.

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Acute Kidney Injury; Child; Drug-Related Side Effects and Adverse Reactions; Humans

Date of registration in PROSPERO
08 December 2020

Date of first submission
02 November 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

08 December 2020

Appendix 2 – Systematic Review Protocol

Review Protocol: What is the epidemiology of drug-induced Acute Kidney Injury in children?

Team Information

Project Lead	Charlotte Hankinson[1]
Research Team Members	Charlotte Hankinson[1], Dr Louise Oni[1], Andrea Jorgensen[2], Dr Stephen McWilliam[1]
Date	21/10/2020
Institution(s)	1. Department of Women's and Children's Health, University of Liverpool, Institute in the Park, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP, UK 2. Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background

Nephrotoxic medication associated Acute kidney injury (NTMx-AKI) is a common and potentially preventable cause of AKI in children[1, 17, 20, 21], accounting for some part of AKI in 20 -30% of patients[1]. Despite this, comprehensive research around the topic remains limited. Studies to date have conveyed the association of AKI with poor short- and long-term outcomes[14-18], such as residual kidney damage following an acute deterioration in kidney function – highlighting the importance of increasing understanding around the subject area.

Objective

A systematic review was published by Uber and Sutherland in 2019 on Nephrotoxins and Nephrotoxic AKI[20]. This review summarises the epidemiology of drug-induced AKI, mainly focussing on the mechanisms in which different classes of nephrotoxins act. Therefore, we feel that this literature review is justified to provide an up-to-date, comprehensive summary of the current literature surrounding NTMx-AKI, taking into account other published studies since Uber & Sutherlands'. This literature review focus on the paediatric population and will be important to guide future research and interventions to improve the quality of patient's outcomes.

Review Question

Full Review Question: What is the epidemiology of drug-induced Acute Kidney Injury in children?

Primary objective: Describe the epidemiology of drug-induced AKI in children

Secondary objectives: In addition to the primary outcome, we will:

- Conduct a quantitative analysis of the primary outcome
- Describe outcome measures to report AKI epidemiology in children
- Describe identified risk factors for the development of AKI in children
- Describe strategies that have demonstrated improvements/have been shown to mitigate AKI

Population	Children admitted to hospital / children treated as inpatients in hospital
Intervention	Documentation of in-hospital nephrotoxin exposure
Comparator	No comparison will be used
Outcomes	Primary outcome: diagnosis of AKI

Search Strategy

Databases: MEDLINE, EMBASE and CINAHL using NICE Healthcare Databases Advanced Search (HDAS).

Search terms MEDLINE: ((*"ACUTE KIDNEY INJURY"/ OR *"KIDNEY TUBULAR NECROSIS, ACUTE"/ OR (("Acute Kidney Injury" OR "Acute Kidney Failure" OR "Acute Kidney Insufficiency" OR "Acute Renal Failure" OR "Acute Renal Injury" OR "Acute Renal Insufficiency" OR "Kidney Failure, Acute" OR "Kidney Insufficiency, Acute" OR "Renal Failure, Acute" OR "Renal Insufficiency, Acute" OR "Acute Kidney Tubular Necrosis" OR "Lower Nephron Nephrosis") NOT review*).ti) AND (*"ABNORMALITIES, DRUG-INDUCED"/ OR ((Nephro* OR "drug-induced" OR "contrast-induced") NOT review*).ti)) [DT 2000-2020] [Human age groups Infant,newborn OR Infant OR Child,preschool OR Child OR Adolescent] [Languages English]

Search terms EMBASE: (((*"ACUTE KIDNEY FAILURE"/ OR *"ACUTE KIDNEY INJURY"/ OR *"ACUTE KIDNEY INSUFFICIENCY"/ OR *"ACUTE KIDNEY TUBULE NECROSIS"/ OR (("Acute Kidney Injury" OR "Acute Kidney Insufficiency" OR "Acute Renal Failure" OR "Acute Renal Insufficiency" OR "Kidney Acute Failure" OR "Kidney Failure, Acute" OR "Kidney Insufficiency, Acute" OR "Renal Insufficiency, Acute" OR "Acute Kidney Tubule Necrosis" OR "Acute Renal Tubular Failure" OR "Acute Renal Tubular Necrosis" OR "Acute Tubular Necrosis" OR "Kidney Tubule Necrosis, Acute") NOT review*).ti) AND (*"DRUG INDUCED DISEASE"/ OR *"CONTRAST INDUCED NEPHROPATHY"/ OR *TOXICITY/ OR *NEPHROTOXICITY/ OR *"ACUTE TOXICITY"/ OR *"DRUG TOXICITY"/ OR *"ACUTE TUBULAR NECROSIS"/ OR *"DRUG TOXICITY AND INTOXICATION"/ OR (("drug-induced disease" OR "contrast

induced nephro*" OR "contrast induced renal dysfunction" OR "contrast induced renal failure" OR "contrast media induced nephro*" OR "contrast agent induced nephro*" OR "contrast induced acute renal failure" OR "contrast media induced renal failure" OR "contrast medium induced nephro*" OR "contrast medium induced renal failure" OR "contrast nephro*" OR "contrast agent-inducing nephro*" OR "radio-contrast nephro*" OR "radio-contrast-induced nephro*" OR "radiocontrast nephro*" OR "radiocontrast-induced nephro*" OR "RC-induced nephro*" OR nephro* OR "kidney toxicity" OR "nephro toxicity" OR "renal toxicity" OR hypertoxicity OR "subacute toxicity" OR "tissue toxicity" OR "toxic actions" OR "toxic effect" OR toxigenicity OR "acute tubular necrosis" OR pharmacotoxicity OR "toxicity, drug") NOT review*).ti)) AND (*PEDIATRICS/ OR (*ADOLESCENT/ OR *"HOSPITALIZED ADOLESCENT"/ OR *JUVENILE/ OR *"HOSPITALIZED CHILD"/ OR *"HOSPITALIZED INFANT"/ OR *"HOSPITALIZED PATIENT"/ OR *"HOSPITALIZED PATIENTS"/ OR *"HOSPITALIZED TEENAGER"/ OR *INFANT/ OR *BABY/ OR *CHILD/ OR *BOY/ OR *GIRL/ OR *"PRESCHOOL CHILD"/ OR *"SCHOOL CHILD"/ OR *TODDLER/) OR ((paediatric* OR pediatric* OR "paediatric aspect" OR "paediatric care" OR "paediatric practice" OR "paediatric research" OR "paediatric service" OR "pediatric aspect" OR "pediatric care" OR "pediatric practice" OR "pediatric research" OR "pediatric service" OR adolescen* OR teen* OR "hospitalised adolescen*" OR "hospitalized teen*" OR "adolescen*, hospitalized" OR "hospitalised teen*" OR "hospitalised child*" OR "child*, hospitalized" OR "hospitalised infant*" OR infant* OR baby OR babies OR juvenil* OR youth* OR child* OR girl* OR "female child*" OR "female infant*" OR "infant female*" OR boy* OR "infant male*" OR "male child*" OR "male infant*" OR "preschool child*" OR preschool* OR "child*, preschool*" OR "pre-school child*" OR "pre-school going child*" OR pre-school* OR "school child*" OR "child*, school*" OR "school boy*" OR "school girl*" OR "school-going (boy*)" OR "school-going (child*)" OR "school-going (girl*)" OR school* OR "schoolgoing (child*)" OR toddler*) NOT review*).ti)) [DT 2000-2020] [English language]

Search terms CINAHL: (((*"KIDNEY FAILURE, ACUTE"/ OR *"RENAL INSUFFICIENCY"/ OR (("acute kidney injury" OR "kidney failure, acute" OR "renal insufficiency") NOT review*).ti) AND (*NEPHROTOXICITY/ OR *"DRUG TOXICITY"/ OR ((drug-induced OR nephro* OR "drug toxic*") NOT review*).ti)) AND (*PEDIATRICS/ OR (*CHILD/ OR *"CHILD, HOSPITALIZED"/ OR *"CHILD, PRESCHOOL"/ OR *INFANT/ OR *ADOLESCENCE/ OR *"MINORS (LEGAL)"/ OR *"INFANT, DRUG-EXPOSED"/ OR *"INFANT, HOSPITALIZED"/ OR *"INFANT, NEWBORN"/) OR ((pediatric* OR paediatric* OR child* OR "child*, hopsitalized" OR "child*, preschool*" OR infant* OR adolescen* OR minor* OR "minor* (legal)" OR "infant*, drug-exposed" OR "infant*, hospitalized" OR "infant*, newborn") NOT review*).ti)) [DT 2000-2020] [Languages eng]"

Hand searching: none

Experts or stakeholders: none

Reference searches: none

Eligibility Criteria

PICO	Inclusion Criteria	Exclusion Criteria
Population	Children admitted to hospital / children treated as inpatients in hospital	Non-human Outpatients Over the age of 18
Intervention	Documentation of in-hospital nephrotoxin exposure	No exposure to any nephrotoxins documented Consideration only of a specific nephrotoxin or nephrotoxin combination
Comparator	N/A	N/A
Outcomes	Diagnosis of AKI	N/A
Publication type	Reported in full text format Published in English	Narrative reviews

Data Extraction

Databases will be searched by one reviewer (CH) using the search terms defined above. Using the titles and abstracts, a list of articles potentially meeting the eligibility criteria will be produced independently by two reviewers (CH and SM). Any disagreements will firstly be discussed between CH and SM, and failing this will be resolved by a third reviewer (LO). Full text review and quality assessment will be done independently by the same reviewers (CH and SM). Data extraction and critical appraisal of identified studies will be conducted by one reviewer (CH), taking into account the inclusion and exclusion criteria.

The following data will be collected from studies meeting the eligibility criteria: Author, Title, Year, Type of study, Number of patients per study, Patient age, Patient demographics (anything available including BMI, ethnicity, primary renal disease, weight), Treatment modality (RRT), AKI alerts, Peak AKI Stage, Stages of AKI when alert flagged, Exposure to nephrotoxins, Length of hospital stay, Mortality, Reason for admission, Critical care admission

Study Quality Assessment

To assess the risk of bias and check the quality of the studies identified after searching, the Joanna Briggs Institute (JBI) appraisal checklists will be used.

Data Synthesis

The aim is to quantify results as much as possible, such as non-critically ill patients compared to critically ill patients, but this systematic review aims to provide a comprehensive summary and descriptive narrative of the current literature.

Project Timetable

	Sept	Oct	Nov	Dec	Jan
Preparation					
Literature searches					
Pilot test eligibility criteria					
Title/Abstract + Full Text Selection					
Pilot risk of bias assessments					
Conduct quality assessments					
Pilot test data collection					
Data extraction and analysis/synthesis					
Write up and editing					

Research Team Member Roles

Task	Description	Team Member Responsible
Literature search	Search EMBASE and PubMed with the search terms outlined above.	CH
Title/Abstract Selection	Identify a list of potential articles that meet the eligibility criteria, using the titles and abstracts. A 3rd reviewer (LO) will resolve any disagreements.	CH, SM, LO
Full text review (and quality assessment)	Identify studies that meet the eligibility criteria and are of high enough quality following the use of the JBI checklists.	CH and SM
Data extraction and analysis/synthesis	Extract and record relevant information form the articles.	CH
Write up and editing	Publish the systematic review in a peer reviewed journal.	CH, SM, LO

Appendix 3 – Search strategy used for systematic review of the epidemiology drug-induced AKI in children

After scoping searches, three bibliographic databases (EMBASE, MEDLINE and CINAHL) using NICE Healthcare Databases Advanced Search (HDAS) were searched for literature from January 2000 until November 2020. Table 1 details the search syntax used for each database. Reference lists of included systematic reviews were not examined for additional relevant literature as the database searches were comprehensive.

Table 1: Search Syntax

Database	Syntax Criteria
EMBASE	(((*"ACUTE KIDNEY FAILURE"/ OR *"ACUTE KIDNEY INJURY"/ OR *"ACUTE KIDNEY INSUFFICIENCY"/ OR *"ACUTE KIDNEY TUBULE NECROSIS"/ OR (("Acute Kidney Injury" OR "Acute Kidney Insufficiency" OR "Acute Renal Failure" OR "Acute Renal Insufficiency" OR "Kidney Acute Failure" OR "Kidney Failure, Acute" OR "Kidney Insufficiency, Acute" OR "Renal Insufficiency, Acute" OR "Acute Kidney Tubule Necrosis" OR "Acute Renal Tubular Failure" OR "Acute Renal Tubular Necrosis" OR "Acute Tubular Necrosis" OR "Kidney Tubule Necrosis, Acute") NOT review*).ti) AND (*"DRUG INDUCED DISEASE"/ OR *"CONTRAST INDUCED NEPHROPATHY"/ OR *TOXICITY/ OR *NEPHROTOXICITY/ OR *"ACUTE TOXICITY"/ OR *"DRUG TOXICITY"/ OR *"ACUTE TUBULAR NECROSIS"/ OR *"DRUG TOXICITY AND INTOXICATION"/ OR (("drug-induced disease" OR "contrast induced nephro*" OR "contrast induced renal dysfunction" OR "contrast induced renal failure" OR "contrast media induced nephro*" OR "contrast agent induced nephro*" OR "contrast induced acute renal failure" OR "contrast media induced renal failure" OR "contrast medium induced nephro*" OR "contrast medium induced renal failure" OR "contrast nephro*" OR "contrast agent-inducing nephro*" OR "radio-contrast nephro*" OR "radio-contrast-induced nephro*" OR "radiocontrast

	nephro*" OR "radiocontrast-induced nephro*" OR "RC-induced nephro*" OR nephro* OR "kidney toxicity" OR "nephro toxicity" OR "renal toxicity" OR hypertoxicity OR "subacute toxicity" OR "tissue toxicity" OR "toxic actions" OR "toxic effect" OR toxigenicity OR "acute tubular necrosis" OR pharmacotoxicity OR "toxicity, drug") NOT review*).ti)) AND (*PEDIATRICS/ OR (*ADOLESCENT/ OR *"HOSPITALIZED ADOLESCENT"/ OR *JUVENILE/ OR *"HOSPITALIZED CHILD"/ OR *"HOSPITALIZED INFANT"/ OR *"HOSPITALIZED PATIENT"/ OR *"HOSPITALIZED PATIENTS"/ OR *"HOSPITALIZED TEENAGER"/ OR *INFANT/ OR *BABY/ OR *CHILD/ OR *BOY/ OR *GIRL/ OR *"PRESCHOOL CHILD"/ OR *"SCHOOL CHILD"/ OR *TODDLER/) OR ((paediatric* OR pediatric* OR "paediatric aspect" OR "paediatric care" OR "paediatric practice" OR "paediatric research" OR "paediatric service" OR "pediatric aspect" OR "pediatric care" OR "pediatric practice" OR "pediatric research" OR "pediatric service" OR adolescen* OR teen* OR "hospitalised adolescen*" OR "hospitalized teen*" OR "adolescen*, hospitalized" OR "hospitalised teen*" OR "hospitalised child*" OR "child*, hospitalized" OR "hospitalised infant*" OR infant* OR baby OR babies OR juvenil* OR youth* OR child* OR girl* OR "female child*" OR "female infant*" OR "infant female*" OR boy* OR "infant male*" OR "male child*" OR "male infant*" OR "preschool child*" OR preschool* OR "child*, preschool*" OR "pre-school child*" OR "pre-school going child*" OR pre-school* OR "school child*" OR "child*, school*" OR "school boy*" OR "school girl*" OR "school-going (boy*)" OR "school-going (child*)" OR "school-going (girl*)" OR school* OR "schoolgoing (child*)" OR toddler*) NOT review*).ti)) [DT 2000-2020] [English language]
MEDLINE	((*"ACUTE KIDNEY INJURY"/ OR *"KIDNEY TUBULAR NECROSIS, ACUTE"/ OR (("Acute Kidney Injury" OR "Acute Kidney Failure" OR "Acute Kidney Insufficiency" OR "Acute Renal Failure" OR "Acute Renal Injury" OR "Acute Renal Insufficiency" OR "Kidney Failure, Acute" OR "Kidney

	Insufficiency, Acute" OR "Renal Failure, Acute" OR "Renal Insufficiency, Acute" OR "Acute Kidney Tubular Necrosis" OR "Lower Nephron Nephrosis") NOT review*).ti) AND (*"ABNORMALITIES, DRUG-INDUCED"/ OR ((Nephro* OR "drug-induced" OR "contrast-induced") NOT review*).ti)) [DT 2000-2020] [Human age groups Infant,newborn OR Infant OR Child,preschool OR Child OR Adolescent] [Languages English]
CINAHL	(((*"KIDNEY FAILURE, ACUTE"/ OR *"RENAL INSUFFICIENCY"/ OR (("acute kidney injury" OR "kidney failure, acute" OR "renal insufficiency") NOT review*).ti) AND (*NEPHROTOXICITY/ OR *"DRUG TOXICITY"/ OR ((drug-induced OR nephro* OR "drug toxic*") NOT review*).ti)) AND (*PEDIATRICS/ OR (*CHILD/ OR *"CHILD, HOSPITALIZED"/ OR *"CHILD, PRESCHOOL"/ OR *INFANT/ OR *ADOLESCENCE/ OR *"MINORS (LEGAL)"/ OR *"INFANT, DRUG-EXPOSED"/ OR *"INFANT, HOSPITALIZED"/ OR *"INFANT, NEWBORN"/) OR ((pediatric* OR paediatric* OR child* OR "child*, hopsitalized" OR "child*, preschool*" OR infant* OR adolescen* OR minor* OR "minor* (legal)" OR "infant*, drug-exposed" OR "infant*, hospitalized" OR "infant*, newborn") NOT review*).ti)) [DT 2000-2020] [Languages eng]"

Appendix 4 – Table of excluded studies in systematic review after full text assessment

Study	Authors	Reason for Exclusion
The spectrum of acute renal failure in IgA nephropathy	Wen, Chen, 2010	Inappropriate patient population (study of adults not paediatrics)
Impact of acute kidney injury at the onset of idiopathic nephrotic syndrome in Japanese children	Fujinaga, Kusaba, 2019	Inappropriate intervention (no nephrotoxins)
Assessment of nephrotoxic medication associated acute kidney injury at a tertiary paediatric hospital	Hendry et al, 2019	Full text could not be obtained (abstract publication only)
Prognosis and acute complications at the first onset of idiopathic nephrotic syndrome in children: a nationwide survey in Japan (JP-SHINE study)	Sato et al, 2019	Inappropriate intervention (no nephrotoxins)
Impact of cumulative nephrotoxin exposure on acute kidney injury in the pediatric critically ill patients	Akcan-Arikan, Kennedy, 2016	Full text could not be obtained (abstract publication only)
Paediatric acute kidney injury is poorly recognised in the hospital setting – on behalf of the British association for paediatric nephrology	Bhojani et al, 2016	Full text could not be obtained (abstract publication only)
Acute renal failure (ARF) in the course of nephrotic syndrome (NS) in children	Zaniew et al, 2010	Full text could not be obtained (abstract publication only)

Appendix 5 – risk of bias assessment of included studies within systematic review, adapted from JBI checklists[37, 38]

Study	Study design	Recruitment of cases and controls from same population?	Exposures measured similarly to assign cases and controls?	Exposure measured in a valid and reliable way?	Confounding factors identified and accounted for?	Were groups free of the outcome at the start of the study?*	Outcome measured in a valid and reliable way?	Follow up length reported and long enough for outcomes (aims of the study) to occur?†	Follow up complete, and reasons to loss to follow up described and explore?†	Strategies to address incomplete follow up stated?†	Was appropriate statistical analysis used?
Sharma 2018[51]	Retrospective cohort study	Yes	Yes	Yes	Unclear – states multivariate logistic regression was applied, however also states "it was not possible to control for additional risk factors in patients with AKI"	No	Yes	N/A – aims of study were just short-term outcomes and were reported during admission	N?A	No	Yes

Yang 2020[56]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	Unclear – length of follow-up unclear however all patients accounted for and aims of study were just short-term outcomes	Yes	No	Yes
Prasad 2019[45]	Prospective observational study	Yes	Yes	Yes	Yes	No	Yes	No – outcomes observed at discharge	N/A	No	Yes
Uber 2018[54]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	Yes – followed up 3 months after AKI	Unclear	No	Yes
McGregor 2016[44]	Retrospective cohort study	Yes	Yes	Yes	Unclear	No	Yes – but comparison difficult due to reporting	Yes – sufficient for aims of study	Unclear	Unclear	Yes
Kim 2018[42]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	Unclear – follow-up length not stated however aims of study did not include short or long-term outcomes	Unclear – one patient lost to follow up (no more information)	No	Yes

Shalaby 2015[50]	Retrospective cohort study	Yes	Yes	Unclear	Yes	No	Yes – but comparison difficult due to reporting	Unclear – average (type not stated) follow up time 16 days	Unclear	No	yes
Rheault 2015[46]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	N/A – aims of study were just short-term outcomes and were reported during admission	N/A	No	Yes
Rhone 2014[47]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	N/A – aims of study were not to report patient outcomes (just risk factors) and were reported during admission	N/A	No	Yes
Xiong 2020[55]	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	N/A – study was designed to determine in-hospital outcomes	N/A	No	Yes
Tresa 2017[53]	Prospective observational study	Yes	Yes	Unclear	No – or not stated	No	Yes – but comparison difficult due to reporting	Yes – 3 month follow up	Yes	Yes	Yes

Yaseen 2017[57]	Prospective observational study	Yes	Yes	Unclear	No – or not stated	No	Yes – but comparison difficult due to reporting	Yes – 3 month follow up	Yes	N/A (all patients followed up/accounted for)	Yes
Safder 2020[48]	Prospective observational study	Yes	Yes	Unclear	Yes	No	Yes – but comparison difficult due to reporting	Yes – sufficient for aims of study	Unclear	No	Yes
Goldstein 2020[29]	Prospective interventional study	Yes	Yes	Yes	Yes	No	Yes	Yes – long-term follow up sufficient for aims of study	Unclear	No	Yes
Kirkley 2018[43]	Retrospective cohort analysis	Yes	Yes	Yes	Yes	No	Yes	Yes – sufficient for aims of study	Unclear	No	Yes
Benoit 2019[41].	Prospective interventional study	Yes	Yes	Yes	Yes	No	Yes	Yes – sufficient for aims of study	Unclear	No	Yes
Schaffzin 2014[49]	Retrospective cohort study	Yes	Yes	Yes	Unclear – recognised but not accounted for	No	Yes – however purpose of	N/A – study purposely did not consider long-term outcomes, short-term outcomes and	N/A	No	Yes

							paper was to compare two systems of defining AKI	were reported during admission			
Stoops 2019[52]	Prospective interventional study	Yes	Yes	Yes	Yes	No	Yes	N/A – defined when a patient encounter was closed and was not designed to capture long-term outcomes	N/A	No	Yes
Young 2020[58].	Prospective interventional study	Yes	Yes	Yes	Yes	No	Yes	Yes – sufficient for aims of study	Unclear	No	Yes
Goldstein 2016[28]	Prospective interventional study	Yes	Yes	Yes	Yes	No	Yes	Yes – long-term follow up sufficient for aims of study	Unclear	No	Yes

*This column was not relied on so much in the appraisal due to the nature of our systematic review. Many eligible reviews included children with vs without AKI, not necessarily all without AKI at the start of the study – which was not a requirement for our review. Prospective studies reported changes in AKI rates post-intervention, so recognised that a proportion of patients already had an AKI at the start of the study.

†The columns regarding follow up were not relied on so much in the appraisal due to the nature of available literature. Although we wanted to describe and analyse data regarding short and long-term outcomes, we have learnt that it this has been difficult to report in the majority of studies as this would require a long follow-up period. Many of the studies were retrospective in nature and did not plan to perform a future follow up over a long time period.

Study	Study design	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were cases and controls matched appropriately?	Were the same criteria used for the identification of cases and controls?	Exposure measured in a valid and reliable way?	Exposure measured in the same way for cases and controls?	Confounding factors identified and accounted for?	Outcome assessed in a standard, valid and reliable way for cases and controls?	Was exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?
Moffett 2011[21]	Retrospective case control study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 6 – Drug-induced Acute Kidney Injury in non-critically ill, hospitalised children: A systematic review and meta-analysis (RCPCH abstract and E-Poster)

Authors: Charlotte Hankinson[1], Dr Louise Oni[1], Prof Andrea Jorgensen[2], Dr Stephen McWilliam[1]

Affiliations:

1. Department of Women's and Children's Health, University of Liverpool, Institute in the Park, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP
2. Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background: Nephrotoxic medication associated Acute Kidney Injury (NTMx-AKI) is a potentially preventable cause of AKI.

Objectives: We conducted a systematic review to appraise the epidemiology of AKI in children, and here present results of a sub-review in non-critically ill, hospitalised children.

Methods: Two reviewers searched three electronic databases (EMBASE, MEDLINE and CINAHL) from January 2000 until November 2020. Eligible studies for this sub-review included in-hospital exposure to NTMx in non-critically ill children (0 to <18 years of age) with no diagnosis of kidney pathology, and reported AKI as an outcome.

Results: Of 205 publications identified, 21 met the inclusion criteria for the main systematic review, and five[21, 28, 29, 44, 49] were included in this sub-review. Of these, two[21, 44] report AKI outcomes in all non-critically ill hospitalised patients (with and without nephrotoxin exposure), and three[28, 29, 49] report outcomes only in those with nephrotoxin exposure.

The pooled incidence of AKI in all non-critically ill, hospitalised children was 32% (p<0.00001, 95% CI 29-35%, pooled data from two papers[21, 44] (n=3088 patients)). Children with AKI were younger than those without (p=0.14, mean difference 3.10 years, 95% CI -7.22-1.01, pooled

data from two papers[21, 44] (n=3088 patients)), however this association was not statistically significant.

The pooled incidence of AKI in nephrotoxin-exposed, non-critically ill, hospitalised children was 17% (p<0.00001, 95% CI 15-19%, pooled data from three papers[28, 29, 49] (n=747 patients[49] combined with n=7756 nephrotoxin exposures[28, 29])). All papers considered nephrotoxin exposure as a risk factor for the development of AKI. However, there was insufficient homogeneity for meta-analysis.

The data suggest that AKI prolongs hospital stay (p=0.14, mean difference 3.07 days, 95% CI -1.05-7.18, pooled data from two papers[21, 44] (n=3088 patients)), although this was not statistically significant. Mortality was only reported in one paper[44]. In-hospital mortality was higher in those with AKI (0.6%) than without (0.06%).

Conclusions: AKI is common in non-critically ill, hospitalised children. Whilst meta-analysis did not produce significant findings, the data suggest that nephrotoxin exposure and younger age are risk factors for AKI. Children with AKI also had longer hospital stays and increased mortality.

DRUG-INDUCED ACUTE KIDNEY INJURY IN NON-CRITICALLY ILL, HOSPITALISED CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Authors: Charlotte Hankinson[1], Dr Louise Oni[1], Prof Andrea Jorgensen[2], Dr Stephen McWilliam[1]

[1]Department of Women's and Children's Health, University of Liverpool, Institute in the Park, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP; [2]Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background

- Nephrotoxic medication associated Acute Kidney Injury (NTMx-AKI) is a potentially preventable cause of AKI.
- We conducted a systematic review to appraise the epidemiology in children, and here present results of a sub-review in non-critically ill, hospitalised children.

Methods

- Two reviewers searched three electronic databases (EMBASE, MEDLINE and CINAHL) from January 2000 until November 2020.
- Eligible studies for this sub-review included in-hospital exposure to NTMx in non-critically ill, hospitalised children (0 to <18 years of age) with no diagnosis of kidney pathology, and reported AKI as an outcome.

Results

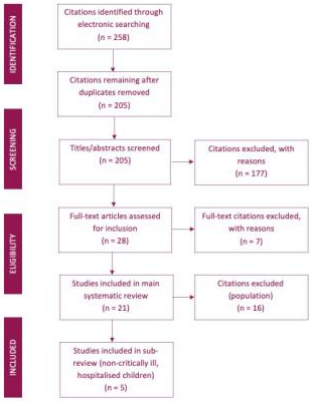

Figure 1: PRISMA flow diagram displaying the identification of included studies in the systematic review

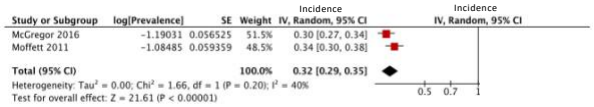

Figure 2: Overall incidence of AKI

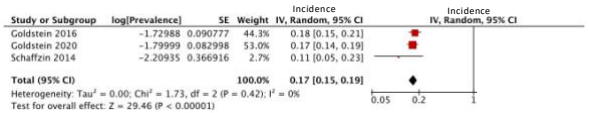

Figure 3: Overall incidence of AKI in cohort of non-critically ill patients exposed to nephrotoxins

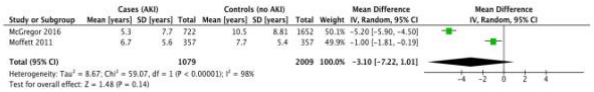

Figure 4: Mean age (years) in cases vs controls

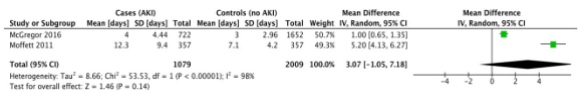

Figure 5: Mean length of stay (days) in cases vs controls

References

1. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, et al. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. American Journal of Kidney Diseases. 2016;67(3):384-90.
2. Schaffzin JK, Dodd CN, Nguyen H, Schondelmeyer A, Campanella S, Goldstein SL. Administrative Data Misclassifies and Fails to Identify Nephrotoxin-Associated Acute Kidney Injury in Hospitalized Children. Hospital Pediatrics. 2014;4(3):159-66.
3. Goldstein SL, Dahale D, Kirkendall ES, Mottes T, Kaplan H, Muething S, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. Kidney International. 2020;97(3):580-8.
4. Goldstein SL, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney International. 2016;90(1):212-21.
5. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clinical journal of the American Society of Nephrology : CJASN. 2011;6(4):856-63.

The pooled **incidence of AKI** in all non-critically ill, hospitalised children was **32%** (pooled data from two papers[1, 5]).

Conclusions

AKI is common in non-critically ill, hospitalised children. Whilst meta-analysis did not produce significant findings, the data suggest that **nephrotoxin exposure and younger age are risk factors for AKI.**

Children with AKI also had **longer hospital stays and increased risk of mortality.**

Appendix 7 – Drug-induced Acute Kidney injury in children with Nephrotic Syndrome: A systematic review and meta-analysis (BAPN abstract and E-Poster)

Authors: Charlotte Hankinson[1], Dr Louise Oni[1], Prof Andrea Jorgensen[2], Dr Stephen McWilliam[1]

Affiliations:

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4. Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background: Nephrotoxic medication associated Acute Kidney Injury (NTMx-AKI) is a potentially preventable cause of AKI. We conducted a systematic review to appraise the epidemiology in children, and here present results of a sub-review in children with Nephrotic Syndrome (NS).

Methods: Two reviewers searched three electronic databases (EMBASE, MEDLINE and CINAHL) from January 2000 until November 2020. Eligible studies for this sub-review included in-hospital exposure to NTMx in children (0 to <18 years of age) with NS, and reported AKI as an outcome.

Results: Of the 205 publications identified, 21 met the inclusion criteria for the main systematic review, six[42, 45, 46, 51, 56, 57] were included in the sub-review, of which five[42, 45, 46, 51, 56] could be included in the meta-analysis.

The included papers report a range of incidence of AKI from 16%[45, 56] to 51%[46].The pooled incidence of AKI in children with NS was 29% of all hospitalisations (p<0.0001, 95% CI 16-52%, pooled data from five papers[42, 45, 46, 51, 56] (n=1715 hospitalisations)).

Children with AKI were older than those without (p=0.02, mean difference 1.86 years, 95% CI 0.35-3.37, pooled data from three papers[42, 45, 56] (n=745 hospitalisations)). All papers demonstrated nephrotoxin exposure as a risk factor for the development of AKI, although the pooled data did not reach statistical significance (P=0.11, odds ratio 3.51, 95% CI 0.76-16.25, pooled data from two papers[51, 56] (n=929 hospitalisations)).

AKI was associated with prolonged hospital stay (p=0.003, mean difference 5.42 days, 95% CI 1.87-8.98, pooled data from three papers[42, 45, 56] (n=745 hospitalisations)), but an association with mortality did not reach statistical significance (p=0.12, odds ratio 9.72, 95% CI 0.54-173.64, pooled data from two papers[45, 46] (n=409 patients, 4 deaths)).

Conclusions: Children with NS exposed to nephrotoxins and of an older age are at increased risk of developing AKI, than non-exposed and younger children. Children with AKI also had longer hospital stays and increased risk of mortality.

DRUG-INDUCED ACUTE KIDNEY INJURY IN CHILDREN WITH NEPHROTIC SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

Authors: Charlotte Hankinson[1], Dr Louise Oni[1], Prof Andrea Jorgensen[2], Dr Stephen McWilliam[1]

[1]Department of Women's and Children's Health, University of Liverpool, Institute in the Park, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP; [2]Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background:
- Nephrotoxic medication associated Acute Kidney Injury (NTMx-AKI) is a potentially preventable cause of AKI.
- We conducted a systematic review to appraise the epidemiology in children, and here present results of a sub-review in children with Nephrotic Syndrome (NS).

Methods:
- Two reviewers searched three electronic databases (EMBASE, MEDLINE and CINAHL) from January 2000 until November 2020.
- Eligible studies for this sub-review included in-hospital exposure to NTMx in children (0 to <18 years of age) with NS, and reported AKI as an outcome.

Results:

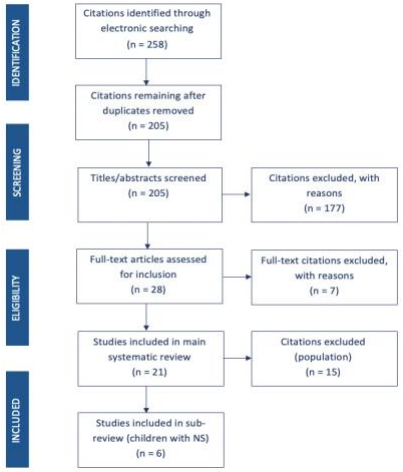


Figure 1: PRISMA flow diagram displaying the identification of included studies in the systematic review

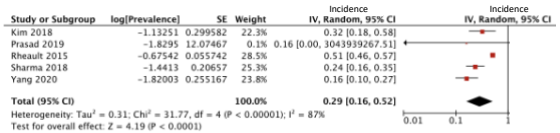


Figure 2: Overall incidence of AKI

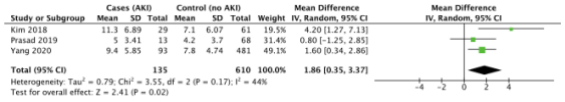


Figure 3: Mean age (years) in cases vs controls

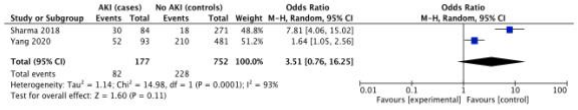


Figure 4: NTMx exposure in cases vs controls

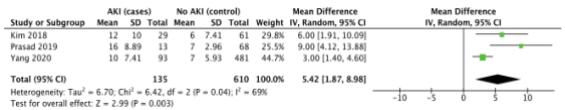


Figure 5: Length of stay (days) in cases vs controls

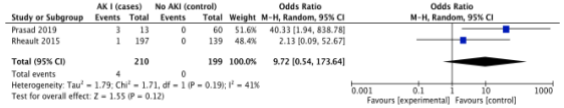


Figure 6: Mortality in cases vs controls

Conclusions:
- Children with NS exposed to nephrotoxins and of an older age are at increased risk of developing AKI, than non-exposed and younger children.
- Children with AKI also had longer hospital stays and increased risk of mortality.

References

1. Kim MY, Cho MH, Kim JH, Ahn YH, Choi HJ, Ha IS, et al. Acute kidney injury in childhood-onset nephrotic syndrome: Incidence and risk factors in hospitalized patients. Kidney Res Clin Pract. 2018;37(4):347-55.
2. Prasad BS, Kumar M, Dabas A, Mishra K. Profile of Acute Kidney Injury in Hospitalized Children with Idiopathic Nephrotic Syndrome. Indian pediatrics. 2019;56(2):119-22.
3. Yang EM, Yoo KH, Ahn YH, Kim SH, Lee JW, Chung WY, et al. Lower albumin level and longer disease duration are risk factors of acute kidney injury in hospitalized children with nephrotic syndrome. Pediatric Nephrology. 2020.
4. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL, Seamon M, et al. AKI in Children Hospitalized with Nephrotic Syndrome. Clinical Journal of the American Society of Nephrology. 2015;10(12):2110-8.
5. Sharma M, Mahanta A, Barman AK, Mahanta PJ. Acute kidney injury in children with nephrotic syndrome: a single-center study. Clinical Kidney Journal. 2018;11(5):655-8.
6. Yaseen A, Tresa V, Lanewala AA, Hashmi S, Ali I, Khatri S, et al. Acute kidney injury in idiopathic nephrotic syndrome of childhood is a major risk factor for the development of chronic kidney disease. Ren Fail. 2017;39(1):323-7.

This poster was presented with a one-minute narration which can be viewed on YouTube via:

https://www.youtube.com/watch?v=ApITFjq6LxA

Appendix 8 – AHCH study protocol

Protocol: What is the epidemiology of drug-induced Acute Kidney Injury in children at Alder Hey Children's Hospital?

Team Information

Project Lead	Charlotte Hankinson[1]
Research Team Members	Charlotte Hankinson[1], Dr Louise Oni[1], Professor Andrea Jorgensen[2], Dr Stephen McWilliam[1]
Date	08/01/2021
Institution(s)	3. Department of Women's and Children's Health, University of Liverpool, Institute in the Park, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP, UK 4. Department of Health Data Science, University of Liverpool, United Kingdom, L69 3GL

Background

Nephrotoxic medication associated Acute kidney injury (NTMx-AKI) is a common and potentially preventable cause of AKI in children[1, 17, 20, 21], accounting for some part of AKI in 20 -30% of patients[1]. Despite this, comprehensive research around the topic remains limited. Studies to date have conveyed the association of AKI with poor short- and long-term outcomes[14-18], such as residual kidney damage following an acute deterioration in kidney function – highlighting the importance of increasing understanding around the subject area.

Objective

Through our sub-review of nephrotoxic AKI in non-critically ill children we studied papers both in a non-critically ill population, and also in non-critically ill children exposed to nephrotoxins. This has allowed us to guide this data analysis in terms of determining what data we need to capture and how to define our outcomes, in a way to allow us to best analyse the available data. There is good evidence currently that suggests monitoring nephrotoxin exposures in hospitalised children can have a positive effect on reducing AKI rates. Having access to the data outlined below will allow us to analyse the exposures and AKI rates in children at Alder Hey Children's Hospital (AHCH), hopefully laying the foundations to able to build on this in the future. The long-term aim would be to incorporate an alert system into the existing AKI dashboard, to flag patients who would benefit from

a medication review or more frequent monitoring – ultimately reducing AKI rates and thus improving patient's outcomes.

Question

Full Question: What is the epidemiology of Acute Kidney Injury in non-critically ill children at Alder Hey Children's Hospital (AHCH)?

Primary objectives:

- Describe the incidence of AKI in non-critically ill children at AHCH
- Describe the incidence of AKI in nephrotoxin-exposed non-critically ill children at AHCH

Secondary objectives: In addition to the primary outcome, we will:

- Identify risk factors (primarily nephrotoxins) for the development of AKI in non-critically ill children
- Describe outcome measures to report AKI epidemiology in non-critically ill children
- Describe identified risk factors for the development of AKI in non-critically ill children
- Describe outcomes (including length of stay and mortality) in non-critically ill children with AKI

Population	Non-critically ill children admitted to/treated as inpatients at AHCH
Intervention	No intervention
Comparator	Children with AKI compared to children without AKI Children with nephrotoxin exposure compared to children without nephrotoxin exposure
Outcomes	Diagnosis of AKI Length of hospital stay Mortality

Eligibility Criteria

PICO	Inclusion Criteria	Exclusion Criteria
Population	Non-critically ill children admitted to/treated as inpatients at AHCH	Non-human Critically ill Outpatients Over the age of 18 Renal patients at time of admission
Intervention	N/A	N/A
Comparator	Children with AKI compared to children without AKI Children with nephrotoxin exposure compared to children without nephrotoxin exposure	N/A
Outcomes	Diagnosis of AKI Length of hospital stay Mortality	N/A

Data Extraction

Data of identified patients will be conducted by one reviewer (CH), taking into account the inclusion and exclusion criteria. We aim to extract data from a time period of 2 years, from 1st January 2019 to 31st December 2020 to hopefully compare pre-pandemic data to data collecting during 2020.

The data extracted for synthesis will be finalised after piloting with a select list of patients.

The hope to be able to collect the following data from patients meeting the eligibility criteria. In order to begin work on this project as soon as possible, the data would ideally be prioritised in the following order:

1. Number of patients in the hospital
2. Number of patients in the hospital exposed to nephrotoxins
    a. Included in this: which nephrotoxin(s); number of nephrotoxins exposed to at any one time; duration of exposure (with a 2-day window post-exposure to class as NTMx-AKI); when nephrotoxin was given in relation to AKI alert

3. Number of patients in the hospital that develop AKI (both nephrotoxin exposed and unexposed)
    a. This can be done using the pre-existing AKI alert system. Included in this: AKI alert or not; number of alerts; date of alert; peak AKI stage; stage of AKI when alert flagged
4. Patient demographics (anything available including age at admission, gender, ethnicity, most recent weight prior to admission (or first weight done during admission if no previous data), height (however we anticipate this will not be consistently recorded))
5. Patient outcomes: length of hospital stay, mortality, subsequent CKD

We will define nephrotoxin exposure as per the Goldstein Cininnati group's approach[28, 29], defined as receipt of an intravenous aminoglycoside on ≥3 consecutive days or ≥3 nephrotoxic medications on the same calendar day. Data will also be collected on diuretics and vancomycin. The current list of nephrotoxins developed for the use of the current AKI alert system will be used to do this. Patients will be considered exposed during the time of exposure and for the 2 days after exposure ended. As above, the data we will collect in relation to nephrotoxins will be which nephrotoxins, number of nephrotoxins, duration of exposure, and timing of exposure in relation to AKI alert.

We will define mortality as death within 28 days of the final AKI alert.

We will define AKI and baseline Serum Creatinine (SCr) using the AKI alert system and Electronic Medical Record (EMR) already in place at AHCH. The AKI alert system is currently in place for children ≥6 months of age. For this reason, we will consider other methods to look at data in children <6 months old in order to include this population. Baseline serum creatinine from the EMR is defined as:

- The lowest value compared to the previous 7-day average
- If no SCr measurement in the previous 7 days, an average is obtained from the previous year
- If no SCr measurement in the previous year, AKI alerts are not flagged

Data Synthesis

The aim is to quantify results as much as possible, such as comparing risk factors and outcomes in children with AKI compared to children without AKI, and children exposed to nephrotoxins against those not exposed.

For the analysis of data, we aim to be able to compare our data as directly as possible to the data from the Goldstein papers, so for this reason our outcomes are guided by their criteria.

Data synthesis will aim to include:

6. A summary of data extracted from eligible participants (compare children with and without AKI), displayed in a table to include:
    a. Patient demographics (anything available including age at admission; gender; ethnicity; most recent weight prior to admission (or first weight done during admission if no previous data); height (however we anticipate this will not be consistently recorded))
    b. Inpatient details (AKI alerts; Peak AKI stage; Stages of AKI when alert flagged; Exposure to nephrotoxins; Length of hospital stay; Mortality; Reason for admission)
7. A summary of data extracted from eligible participants (children with AKI – compare exposed to non-exposed), displayed in a table to include:
    a. Patient demographics (anything available including age at admission; gender; ethnicity; most recent weight prior to admission (or first weight done during admission if no previous data); height (however we anticipate this will not be consistently recorded))
    b. Inpatient details (AKI alerts; Peak AKI stage; Stages of AKI when alert flagged; Exposure to nephrotoxins; Length of hospital stay; Mortality; Reason for admission)
8. If data is available, we aim to conduct a quantitative analysis of the primary outcomes to include:
    a. The overall incidence of AKI in non-critically ill children at AHCH
    b. The overall incidence of NTMx-AKI in non-critically ill children at AHCH
    c. Risk factors for development of AKI (primarily nephrotoxins) in non-critically ill children
    d. Outcomes (including length of stay and mortality) in non-critically children with AKI

Project Timeline

	January	February	March	April	May	June
Preparation						

Piloting of protocol						
Selection of included participants and application of eligibility criteria						
Data extraction						
Data synthesis and analysis						
Write up and editing						

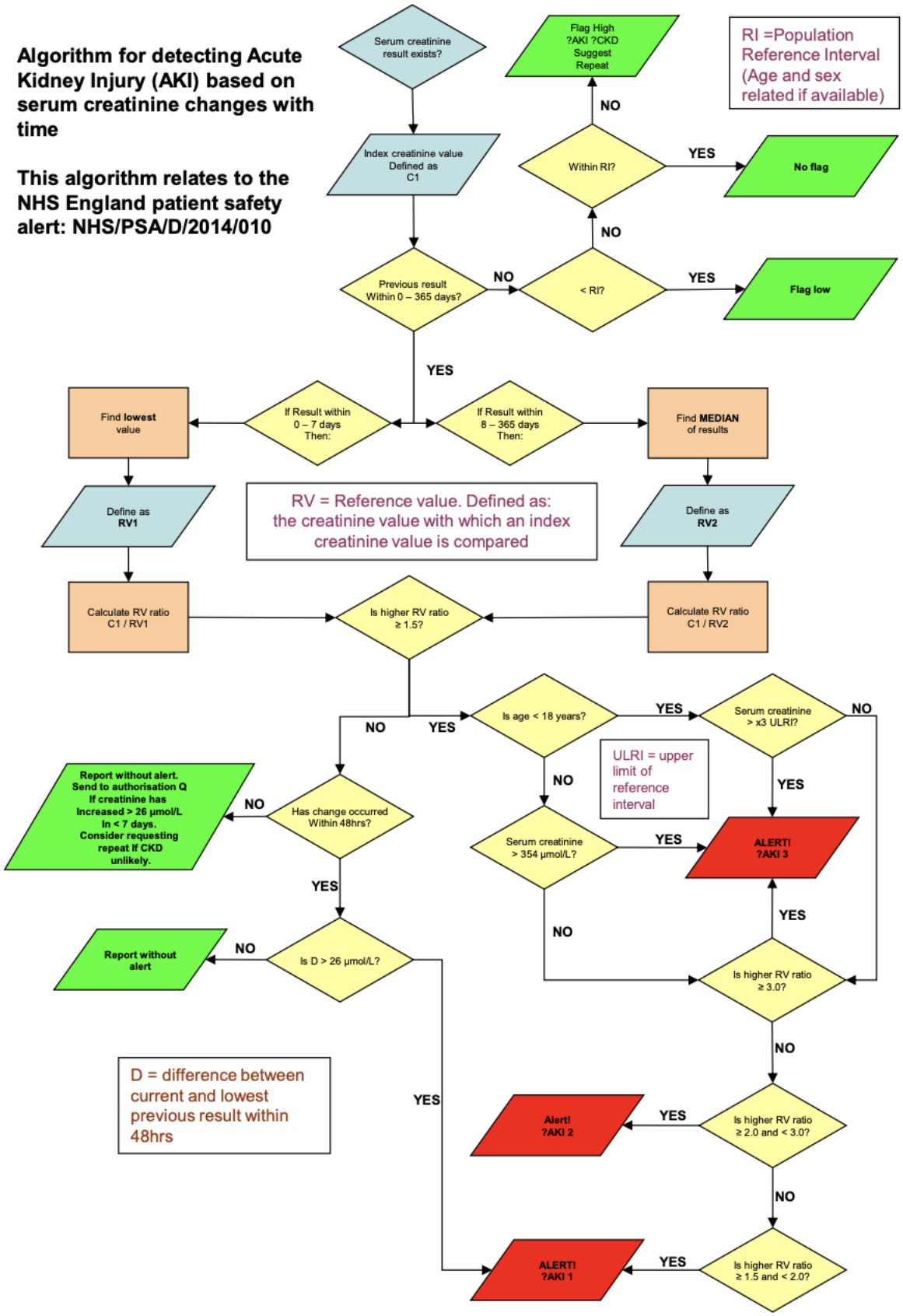
Research Team Member Roles

Task	Description	Team Member Responsible
Preparation	Contact necessary people to plan what information would be needed to extract and how this can be done.	SM
Piloting of protocol	Manually extract one week's worth of data to understand what data is recorded	CH
Identification of eligible patients, data extraction and analysis/synthesis	Extract and record relevant information form included participants.	CH
Write up and editing	Publish the study in a peer reviewed journal.	CH, SM, LO

Appendix 9 – AHCH Nephrotoxin list

Aciclovir	Lithium
Alendronic Acid	Losartan
Amikacin	Mesalazine
Amphotericin	Methotrexate
Captopril	Pamidronate
Cefotaxime	Piperacillin/tazobactam
Ceftazidime	Risedronate
Cefuroxime	Sirolimus
Ciclosporin	Spironolactone
Cidofovir	Sulfasalazine
Colistimethate	Tacrolimus
Co-trimoxazole	Teicoplanin
Dapsone	Trimethoprim
Diclofenac	Tobramycin
Enalapril	Topiramate
Furosemide	Valaciclovir
Ganciclovir	Valganciclovir
Gentamicin	Vancomycin
Ibuprofen	Zonisamide
Lisinopril	

Appendix 10 – AHCH AKI alert algorithm



Acknowledgements

Algorithm for detecting Acute Kidney Injury (AKI) based on serum creatinine changes with time

This algorithm relates to the NHS England patient safety alert: NHS/PSA/D/2014/010

Conceptual design: Members of the consensus group whose names and meeting report can be accessed on:

http://www.acb.org.uk/docs/E-Alerts_for_AKI_meeting_statement

Graphic design: Robert Desborough, Mike Bosomworth, Robert Hill