Pharmacology & Therapeutics xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Optimising the use of medicines to reduce acute kidney injury in children and babies

L Oni [a,b,*], DB Hawcutt [a,c], MA Turner [a,d], MW Beresford [a,e], S McWilliam [f], C Barton [f,g], BK Park [f], P Murray [f,h], B Wilm [f,h], I Copple [f], R Floyd [h], M Peak [i], A Sharma [j], DJ Antoine [f]

[a] Department of Women's & Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[b] Department of Paediatric Nephrology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[c] Department of Paediatric Pharmacology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[d] Centre for Better Births, Liverpool Women's Hospital, Liverpool, UK
[e] Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[f] Department of Molecular and Clinical Pharmacology, MRC Centre for Drug Safety Science, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[g] Department of Paediatric Oncology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[h] Department of Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[i] Department of Research and Development, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[j] Department of Nephrology, The Royal Liverpool and Broadgreen University Hospitals NHS Foundation Trust, Liverpool, UK

ARTICLE INFO

Keywords:
Acute kidney injury
Nephrotoxic
Children

ABSTRACT

The majority of medications in children are administered in an unlicensed or off-label manner. Paediatricians are obliged to prescribe using the limited evidence available. The 2007 EU regulation on the use of paediatric drugs means pharmaceutical companies are now obliged to (and receive incentives for) contributing to paediatric drug data and carrying out paediatric clinical trials. This is important, as the efficacy and adverse effect profiles of medicines vary across childhood. Additionally, there are significant age-related changes in the pharmacodynamic and pharmacokinetic activity of many drugs. This may be related to physiological (differential expressions of cytochrome P450 enzymes or variable glomerular filtration rates at different ages for example) and psychological (increasing autonomy and risk perception in teenage years) changes.

Increasing numbers of children are surviving life-threatening childhood conditions due to medical advances. This means there is an increasing population who are at risk of the consequences of the long-term, early exposure to nephrotoxic agents. The kidney is an organ that is particularly vulnerable to damage as a consequence of drugs. Drug-induced acute kidney injury (AKI) episodes in children and babies are principally due to non-steroidal anti-inflammatory drugs, antibiotics or chemotherapeutic agents. The renal tubules are vulnerable to injury because of their concentrating ability and high-energy hypoxic environment.

This review focuses on drug-induced AKI and the methods to minimise its effect, including general management plus the role of child-specific pharmacokinetic data, the use of pharmacogenomics and early detection of AKI using urinary biomarkers and electronic triggers.

Contents

Abbreviations: AKI, acute kidney injury; TIN, tubulointerstitial nephritis; EU, European Union; CF, cystic fibrosis; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; COX inhibitors, cyclooxygenase inhibitors.

* Corresponding author at: NIHR Academic Clinical Lecturer in Paediatric Nephrology, Department of Women's & Children's Health (University of Liverpool), Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK.
E-mail address: louise.oni@liverpool.ac.uk (L. Oni).

http://dx.doi.org/10.1016/j.pharmthera.2017.02.018
0163-7258/

1. Introduction

The majority of prescribed medications in children are administered in an "off-label" or unlicensed manner. This means that they are prescribed for either an unapproved indication, age group, formulation or dosage due to a lack of regulatory approval to meet the acceptable standards of efficacy, safety and quality (Frattarelli et al., 2014). Paediatricians therefore prescribe most medicines using the best available evidence in the best interests of their patients. The reason for medications having to be prescribed in this manner is due to the lack of evidence to inform regulatory bodies, as previously there were no financial incentives to undertake the necessary studies.

The pharmaceutical industry is no longer permitted to develop new medicines for use in adults only. In 2007 the European (EU) Union introduced a new regulation concerning medicinal products that are indicated for use in paediatric populations (Hawcutt & Smyth, 2008). Parallel legislation exists in the US (Turner, Catapano, Hirschfeld, & Giaquinto, 2014). The EU Paediatric Drug Regulation aims to encourage more high quality ethically sound research in children and adolescents to promote the achievement of marketing authorisation in a greater number of medicines. This was achieved through the introduction of Paediatric Investigation Plans (PIPs), offering substantial funding incentives to the pharmaceutical industry for contributing to paediatric pharmacology research (van Riet-Nales et al., 2014). Pharmaceutical companies who now complete a PIP can be rewarded with a six-month extension to the patent of their product. Furthermore so called 'orphan drugs', those that have been developed to treat a rare condition in children, are now rewarded with two years market exclusivity, and any off patent drug designed for children will get an eight-year data and ten-year market exclusivity for that indication (Paci & Vassal, 2012). Since the introduction of these EU incentives, there has been an increase in the proportion of clinical trials that include children (Turner et al., 2014).

Child-specific data is very important. Children are distinct from adults and even differ across infancy and childhood as they are undergoing extensive physiological and psychological changes during growth and development. In children the bioavailability, volume of distribution, metabolism and clearance of drugs differs from adults. Differences exist in gastric pH, intestinal emptying and bile and pancreatic acids in children together with increased total body water and alterations in membrane permeability affecting drug distribution (Fernandez et al., 2011). The hepatic blood flow and metabolising enzymes are decreased with implications for drug metabolism; excretion is affected by the immature glomerular filtration, renal tubular secretion and tubular reabsorption of children, especially babies. These changes are particularly true in the younger population such as the neonate (de Wildt, Tibboel, & Leeder, 2014), during critical illness or in children with co-morbidities (Liborio, Branco, & Torres de Melo Bezerra, 2014). In a similar manner to adults, drug interactions and genetic variations may also exist. Using adult data to directly guide the use of drugs in children therefore has its limitations, and it is for this reason that they deserve dedicated pharmacological research using a translational approach (Fig. 1).

In addition to differences in drug handling in children, the consequences of childhood drug exposure on organs including the kidney may only become apparent once the child grows into an adult. Due to advances in medical management, many children are now surviving previously life-threatening conditions: for example, the survival rate of extreme prematurity (those infants born <27 weeks gestation) has improved from 62% to 81% over the past 20 years (Bode et al., 2009), and death from multi-organ failure has halved (Joffe, Anton, & Burkholder, 2011). Survival rates from childhood leukaemia have dramatically improved from 28% in 1968 to current rates of 81% (in 2005) and 0.1% of all adults are now survivors of childhood cancer (Basta, James, Gomez-Pozo, Craft, & McNally, 2011; Mariotto et al., 2009). This pattern is seen in chronic disease states too: the life expectancy of patients with cystic fibrosis (CF) is now around 40 years of age (Harness-Brumley, Elliott, Rosenbluth, Raghavan, & Jain, 2014). With this increased survival long-term renal morbidity associated with treatment in childhood is now being identified in adults. For prematurity, childhood cancer and cystic fibrosis chronic kidney disease (CKD) in later life is now recognised (Mulder et al., 2013; Quon, Mayer-Hamblett, Aitken, Smyth, & Goss, 2011; Rodriguez-Soriano, Aguirre, Oliveros, & Vallo, 2005); furthermore, adult patients with CF have an annual prevalence of CKD of over 2%. In each of these patient groups the CKD risk is directly related to the earlier exposure of nephrotoxic agents and perhaps even acute kidney injury (AKI) episodes. Previous studies demonstrate that even with normal baseline renal function, a single AKI episode increases the risk of CKD by up to 1.9–13 times (dependent on the definition of severity used) when compared to a matched non-AKI population, even after a short follow up period (Belayev & Palevsky, 2014). Although it should be noted that the findings described in all of these studies are merely proposed causal associations.

Thus, it is important to note that as a consequence of medical advances, where intensive treatment with antibiotics improves outcomes and acute organ injury can be managed, and as life expectancy rises, the burden of CKD due to nephrotoxic drug exposure causing AKI in childhood is likely to increase. This increasing risk emphasises the importance of preventing AKI through a person-centred approach to ensure patients obtain the best possible outcome from their medicines in a safe and effective way. This is termed medicines optimisation (NICE, 2015). The aim of this review is to illustrate and discuss ways in which the use of nephrotoxic medications in children could be optimised in order to reduce AKI episodes and subsequently minimise the long-term risk of CKD.

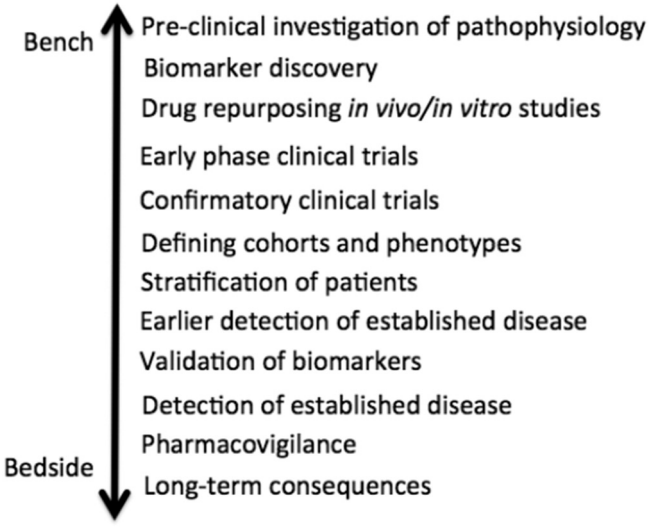

Fig. 1. The translational pathway (from 'bench' to 'bedside' and back again) illustrating the clinical and research requirements in order to reduce drug-induced kidney injury.

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

1.1. Defining acute kidney injury (AKI)

Internationally agreed definitions of AKI exist. Due to its low cost and ease of measurement, creatinine-based assessments of AKI are generally adopted and allow for comparison between international studies (Askenazi, 2011). The most common creatinine-based tools used in children are the pRIFLE (paediatric risk, injury, failure, loss and end stage renal disease) or the acute kidney injury network (AKIN) criteria (Akcan-Arikan et al., 2007; Mehta et al., 2007), both of which have been modified from the original adult derived classification to include parameters suitable for childhood patients (Kavaz et al., 2012). Both tools have limitations, since for example the use of creatinine in patients with low muscle mass states is unreliable and their use in preterm neonates is problematic. Creatinine levels in preterm neonates are much higher than can be expected for their body size; one proposed explanation for this is that the immature kidney is able to reabsorb creatinine during the slow urinary flow that occurs along immature renal tubules (Matos, Duarte-Silva, Drukker, & Guignard, 1998). Another limitation is the variation in measurements used in different laboratories that will especially influence patients such as neonates who have a creatinine value at the lower end of the spectrum and where a difference from 15 μmol/L to 30 μmol/L may represent clinical significance. Despite these limitations the pRIFLE and AKIN are generally accepted as the most suitable tool for the classification and comparison of AKI in children.

1.2. Incidence of drug-induced AKI in children

AKI is thought to occur in up to 30% of children in intensive care (Faught, Greff, Rieder, & Gideon, 2014). In all types of AKI, prescribed medications are the causative agents in >25% of patients (Bentley, Corwin, & Dasta, 2010). The majority of drug-induced AKI episodes are due to non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics or chemotherapeutic agents. Children receiving these drugs are typically acutely unwell and thus they will have confounding factors, such as hypovolaemia, hypotension, that increase their propensity to develop AKI. One of the most common classes of nephrotoxic antibacterial drugs used in children is the aminoglycosides (Sinclair et al., 2014). Around 20–30% of all children treated with an aminoglycoside for >5 days develop AKI (Zappitelli, Moffett, Hyder, & Goldstein, 2011). A study assessing 175 children with previously normal renal function, demonstrated that after 48 h of vancomycin treatment AKI occurred in 14% of patients and was related to the dose used, the length of therapy and the additional use of concomitant drugs (Sinclair et al., 2014). Our in-house data (unpublished, courtesy of author DH) has demonstrated that over a two-year period from December 2009 to November 2011, 754 children received treatment with aminoglycoside antibiotics at Alder Hey Children's NHS Foundation Trust, Liverpool, UK. Sixty-three children (8.4% of those treated) developed AKI (defined by the AKIN criteria) during or shortly after treatment, and 21 (2.8% of those treated) had severe AKI (AKIN stage 2 or 3). Obviously in a tertiary care setting AKI may be multifactorial but this data demonstrates that AKI is a common, often severe, clinical condition seen in everyday practice.

2. Pathophysiology of nephrotoxic AKI

Understanding the mechanism leading to AKI is crucial to developing improved methods of detection or novel treatment options in the future. The kidney is exposed to a large number of drugs because it receives one quarter of cardiac output. Drug-induced AKI typically involves renal tubular cells as they exist in a predominantly hypoxic environment in order to cope with the high metabolic demands required in the day to day task of management of electrolyte reabsorption and controlling hydration. The proximal renal tubules are presented with highly concentrated drugs making them particularly vulnerable to injury. More specifically, drugs can either have the requisite charge and size for filtration at the glomerulus or be taken up by the apical membrane of the renal tubular cells or transported across the basolateral membrane through transporters such as the human organic anion transporter (OAT) and the human organic cation transporter (OCT). Both OATs and OCTs transport drugs including tenofovir or cisplatin, respectively, and thus increase the risk of injury in the proximal tubules and adjacent tissues (Perazella, 2009). Biotransformation of drugs also produces local metabolites and reactive oxygen species (ROS), that can cause cytoplasmic accumulation and local toxicity with ultimate necrosis or apoptosis of the renal tubular cells (Izzedine, Launay-Vacher, & Deray, 2005). Thus, the pathophysiology of drug-induced AKI varies according to the individual drug. Here, we shall focus on the main drugs responsible for AKI in children. These include: NSAIDs, antibiotics (mainly the aminoglycosides) and immunosuppressant and chemotherapeutic agents (mainly calcineurin inhibitors, ifosfamide, cisplatin) (Misurac et al., 2013). In some patients the diagnosis or likely causative agent may not always be that obvious.

2.1. Non steroid anti-inflammatory drug-induced AKI

The predominant NSAID prescribed in paediatric practice (Misurac et al., 2013) is ibuprofen, a widely available and commonly used drug in children as a simple analgesic, antipyretic or anti-inflammatory agent. In addition, ibuprofen is often used in neonates in an attempt to close a patent ductus arteriosus. NSAIDs are believed to have two main AKI mechanisms. Firstly, they can insult the kidney by altering the renal haemodynamic status, and secondly, they can cause acute tubular interstitial nephritis (TIN). NSAID agents reduce cyclooxygenase (COX) activity. In health, COX activity causes vasodilation throughout the body, including in the afferent glomerular arteriole, by the synthesis of prostaglandin PG (predominantly PGE2 and prostacyclin). The NSAIDs therefore cause vasoconstriction as a result of decreased prostaglandin production arising from COX suppression. In normovolaemic and normotensive children the vasoconstrictor effect of NSAIDs is unlikely to cause significant vasoconstriction and/or reduced renal perfusion. However, in a child who is intravascularly deplete, for example due to acute gastroenteritis, the vasoconstrictor effect can lead to the development of AKI by reducing renal perfusion, increasing hypoxia and subsequently causing acute tubular necrosis (ATN) of varying degree. The second method of injury is TIN since NSAIDs are responsible for 20% of all cases of TIN (Valluri et al., 2014). Acute TIN occurs as the pathways responsible for the breakdown of arachidonic acid are disrupted due to NSAID-induced COX inhibition, resulting in the local production of leukotrienes that can cause a local inflammatory response within the tubulointerstitium.

2.2. Aminoglycoside induced AKI

Antibiotics, mainly the aminoglycosides (AG) such as gentamicin, amikacin and tobramycin, are nephrotoxic (Wargo & Edwards, 2014). AG-induced nephrotoxicity is characterized by selective targeting of proximal tubule cells. Accumulation of the drug within the proximal tubule cells, is thought to be the key determining mechanism for the development of toxicity (Mathews & Bailie, 1987). Endocytosis via the multi-ligand receptor megalin has been demonstrated to be the principal pathway for this accumulation. This is supported by the fact that megalin knock-out mice do not exhibit renal accumulation of AGs (Schmitz et al., 2002). Intracellular aminoglycoside can result in apoptosis or necrosis of proximal tubule cells by a variety of pathways (mitochondrial dysfunction and the release of reactive oxygen species) (Servais et al., 2005; Servais et al., 2008). AG-induced nephrotoxicity is described as non-oliguric renal failure with a varying degree of renal tubular dysfunction (Begg & Barclay, 1995). A reduction in GFR is reported to be a late event, occurring between 5 and 10 days after the start of treatment (Taber & Pasko, 2008). The renal impairment is reported to be completely reversible in most patients upon early

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

withdrawal of the AG (Luft, 1984), although there is increasing recognition that repeated episodes of AKI or AG exposure may contribute to later chronic damage (Belayev & Palevsky, 2014).

2.3. Immunosuppressant and chemotherapy induced AKI

The main nephrotoxic immunosuppressive agents are the calcineurin inhibitors (CNI's) that are used for solid organ transplantation and contribute to vascular dysfunction resulting from an increase in vasoconstrictor factors, endothelin and thromboxane, and activation of the renin-angiotensin system (RAS). A reduction of vasodilator factors prostacyclin, prostaglandin E2, and nitric oxide (NO) also occurs together with free radical formation and sympathetic nerve activation. Finally, reversible tubular dysfunction is recognised as a feature of acute CNI nephrotoxicity. The two most common CNI agents, ciclosporin and tacrolimus, which have a completely different molecular structure and intracellular binding site but a similar toxicity profile, suggest that these effects are related to calcineurin/NFAT-dependent mechanisms (Naesens, Kuypers, & Sarwal, 2009).

There are many chemotherapeutic agents that can cause kidney injury. The most commonly prescribed in children are ifosfamide and cisplatin. Ifosfamide is a nitrogen mustard-alkylating agent which is metabolised by the enzyme CYP3A into chloroacetaldehyde; it affects both the glomerulus and renal tubules and causes proximal tubular dysfunction in all patients and AKI in up to 30% of children (Knijnenburg et al., 2013); this incidence is greater than in adult equivalent cohorts (Oberlin et al., 2009; Skinner et al., 2010). Younger children seem to be at a particular risk. One explanation for this may be due to the higher expression of hepatic CYP3A in the younger population (Aleksa, Halachmi, Ito, & Koren, 2004; Aleksa et al., 2005), ifosfamide is metabolised by CYP3A producing toxic levels of chloroacetaldehyde. This leads to a cascade of events, where the proximal renal tubular cells undergo oxidative stress, followed by impaired solute reabsorption and cell necrosis, and subsequently a depletion of glutathione. The kidney is dependent on glutathione to maintain its redox status and thus influences susceptibility to cytotoxicity induced by oxidants and electrophiles (Lash, 2005). Cisplatin is believed to contribute to nephrotoxicity through a completely different mechanism, which occurs following its uptake by the basolateral OCT, hence uptake from the blood stream. It primarily targets DNA, producing ROS and activating signalling pathways such as the mitogen-activated protein kinase (MAPK), P53 and P21. Local proximal tubule cell death occurs together with an inflammatory response from the production of tumour necrosis factor (TNF)-alpha and TNF-alpha receptor 2 (Hanigan & Devarajan, 2003). The overwhelming oxidative stress response appears to be the damaging insult to the kidney in cisplatin nephrotoxicity.

Despite differing pathophysiological mechanisms of injury, using nephrotoxic agents in combination increases the risk of developing AKI. Additionally, existing renal insufficiency, prolonged therapy, high drug concentrations and dehydration can increase this risk further.

3. Patient susceptibility to drug-induced AKI

3.1. Host factors

Host factors can influence the risk of developing nephrotoxicity, explaining the variability often seen in its occurrence. In adults, females are at a greater risk of drug-induced AKI when compared to males due to their reduced body size and reduced total body water volume. Underestimation of GFR also occurs in females due to a lower mean body weight and lack of recognition of creatinine changes from a baseline that may be lower than that of males. Gender differences in the activity of cytochrome P450 and uridine diphosphate glucuronosyltransferase (UGT) enzymes result in differences in the drug clearance (Anderson, 2008). Accurate drug dosing is made difficult by the complexities of changing body size, underestimation of GFR and body composition during growth combined with changing enzyme expression levels and a lack of reliable pharmacokinetic (PK) data These all contribute to the risk of AKI (de Wildt et al., 2014). Preterm infants born before 34 weeks gestation are at particular risk of AKI as the kidney is still developing new nephrons, with fetal nephrogenesis not being completed until 34–36 weeks gestation. Offsetting this however, neonates may not have some of the other risk factors described above as the concentrating ability of the neonatal tubules is poor and energy-dependent processes are less prominent. Therefore the preterm neonate especially those born at the limits of viability, represent a complex childhood population in terms of drug handling and toxicity (Kent, Turner, Sharland, & Heath, 2014; Zaffanello et al., 2010). Maternal health during pregnancy may also affect in utero nephrogenesis for the child, for example babies exposed to poor nutrition or infants of diabetic mothers may have fewer nephrons and thus be more susceptible to kidney injury (Benz & Amann, 2010; Gross, Amann, & Ritz, 2005).

Other patient susceptibility factors include specific disease states, for example volume depletion due to intercurrent illness, a low circulating plasma albumin, liver cirrhosis, obstructive jaundice and pre-existing acute or chronic kidney disease (Perazella, 2009).

3.2. Pharmacogenomics

Predicting how an individual may respond to a particular drug is possible through the appropriate use of pharmacogenomics, which can explain some of the person specific variability. Pharmacogenomics is a method of explaining the individual pharmacodynamic and PK drug responses and how they differ according to a patient's genotype. It is estimated that 10–20% of ADRs are genetically determined (Ingelman-Sundberg, 2004). A good example of the use of pharmacogenomics is through the identification of genes that cause tenofovir-induced renal Fanconi syndrome. In patients exposed to tenofovir, a single nucleotide polymorphism was found to be present in the gene encoding the multidrug-resistant protein-2 (MRP2) efflux transporter in those who developed Fanconi syndrome. This gene is usually responsible for transporting tenofovir out of the cell (Izzedine et al., 2006). Therefore, testing for this genotype prior to treatment may identify patients at risk of developing its nephrotoxic adverse effects. Within our Centre, the search for genes responsible for cisplatin and AG induced renal tubular damage is currently underway (Hawcutt, 2011).

4. Consequences of drug-induced AKI

It has been recognised that the presence of AKI, of any aetiology, independently correlates acutely with a longer hospital stay, with greater mortality and in the long-term, a worse renal outcome (Askenazi, 2011). The acute complications are mainly associated with the fluid overload resulting from AKI and in the longer term, incomplete renal recovery or accelerated progression to CKD.

Due to the increase in overall life expectancy, the kidney is a susceptible organ to the impact of co-morbidities, such as diabetes and ischaemic vascular disease; therefore CKD is emerging as an important healthcare problem in the general population (Imran et al., 2015). As many patients with drug-induced AKI have additional co-morbidities, it is difficult to determine the precise long-term risk of CKD from use of the drug in question. However, in a large study by Goldstein's group, 70% of children who were exposed to either >3 days of AG or >3 nephrotoxic agents, and who developed AKI, demonstrated features of residual kidney damage as early as 6 months post AKI (Menon, Kirkendall, Nguyen, & Goldstein, 2014). Longer-term studies are required to confirm these findings, however, this is in keeping with the earlier described studies on the cumulative effect of AG in patients with CF. Reducing the long-term consequence of kidney injury and inflammation associated with drugs administered during childhood is therefore an important healthcare priority.

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

5. Management of drug-induced AKI

5.1. Current management

The current detection of AKI is based on serum creatinine, urea and urine output, with the mainstay of management being supportive care and reducing any further renal insults. National initiatives are in place to enhance the early detection of AKI and include reporting estimated GFR values and methods to alert clinicians to rising creatinine measurements (England, Date accessed 20.6.15). Whilst these are more complicated to introduce in a childhood population due to variations in the creatinine values according to age and body size, strategies have been developed to overcome this.

In general, management should involve;

- Identification
- informing the patient
- reducing further nephrotoxic insults
- assessing and supporting adequate hydration
- identifying the need for senior and/or specialist input (e.g.: nephrologist review)
- monitoring electrolytes to initiate renal replacement therapy if required
- ensuring resolution of renal function
- screening for risk factors for CKD (hypertension and proteinuria).

In drug-induced renal inflammation such as acute TIN, a short course of oral corticosteroids may improve the renal outcome, however, the supporting evidence is weak, and robust clinical trials are needed (Gonzalez et al., 2008).

5.2. Prevention of AKI

Avoidance, cautious and/or judicious use of nephrotoxic agents could help to reduce or prevent drug-induced AKI, although in clinical practice this is often challenging. Other methods include using extended dosing intervals and short-term therapy with adequate therapeutic monitoring.

5.2.1. Optimal dosing

Although there has been an improving trend since the introduction of the EU regulation on the use of paediatric drugs in 2007, there remains a significant paucity of appropriate information to guide the optimal medication dosing in infants and children. A priority in drug administration is to adjust for the patients eGFR and in cases of AKI to adjust this on a daily basis. Guidance on appropriate drug dosing in patients with established renal impairment is difficult to find and limited, this is especially true in the cohort of children who are exposed to multi-organ supportive measures as part of intensive care management. PK data in neonates demonstrate variability according to maturity, postnatal age and adjunctive medications (De Cock et al., 2012; Vucicevic, Rakonjac, Miljkovic, Jankovic, & Prostran, 2014). Furthermore, there is very little guidance on how to dose many drugs used in children or neonates who undergo extra-corporeal membrane oxygenation (ECMO), continuous veno-venous haemofiltration, haemodialysis or acute peritoneal dialysis. A recent study has demonstrated that modes of dialysis influence the clearance of drugs that are not even metabolised by the kidney, through alteration of hepatic enzyme levels (Thomson et al., 2015). In each of these situations the kidney is already insulted; therefore, minimising further harm whilst achieving maximum drug efficacy to increase the chance of overall recovery is a clinical conundrum, which emphasises the importance of specific PK studies in children of differing ages but also in differing circumstances. This is an overwhelming challenge driving the need to design multi-centre studies due to the small number of eligible patients and the severity of their illness.

5.2.2. Pharmacovigilance

Monitoring the pharmacovigilance of drugs after their licensed use is an important aspect of ensuring safety. Reporting and recording adverse drug events through local and national systems should be a routine part of clinical care, although under-reporting is common (Hawcutt, O'Connor, & Turner, 2014). In the UK, the MHRA Yellow Card system provides a united way of monitoring drug safety, with the median number of ADRs reported per annum between 2000 and 2009 in children being 2146 (Hawcutt, Mainie, Riordan, Smyth, & Pirmohamed, 2012). Encouragingly, reports of drug-induced nephrotoxicity and electrolyte disturbances have been detected through such reporting systems, thus highlighting their role in the longer-term monitoring of medications (Ramirez, Jimenez, et al., 2013; Ramirez, Rossignoli, et al., 2013; Riva et al., 2013).

5.2.3. Improved detection of AKI

AKI is currently detected late in the disease process. In case an obvious precipitating agent fails to be identified, the optimal method of determining the extent of AKI is by renal biopsy. However, this is rarely undertaken as the risks are likely to be greater than the benefits, and a clinical history, together with renal symptoms or signs, may assist with determining the probable cause.

Recent studies have demonstrated that the establishment of novel biomarkers allows an earlier detection of renal injury (Fuchs & Hewitt, 2011; Khan, Batuman, & Lertora, 2010). The most promising biomarkers in all forms of childhood AKI incorporate clinical propensity scoring, perhaps highlighting the multifactorial aetiology (Constance et al., 2016; Menon et al., 2016). Our group have undertaken proof-of-concept studies to investigate the role of biomarkers in detecting AG nephrotoxicity in neonates (McWilliam et al., 2012). The most promising biomarkers to be discovered in the earlier detection of drug-induced AKI are cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), *N*-acetyl-B-D-glucosaminidase (NAG) and low molecular weight proteins such as B2 microglobulin and retinol binding protein (RBP) (Fuchs & Hewitt, 2011; Khan et al., 2010). Table 1 summarises their mechanism of release and the type of drug injury they detect. Most of these biomarkers are more accurately measured in the urine as this likely represents the kidney better than blood concentrations. None of these biomarkers have yet to be routinely measured within the clinical setting but reference intervals for children (for KIM-1 and NGAL) are reported (McWilliam et al., 2014). Members of our group have been actively involved in the qualification of a number of these urinary biomarkers for use in children (McWilliam et al., 2012; McWilliam et al., 2014).

Healthcare alerts using electronic triggers to identify high-risk patients may reduce the incidence of nephrotoxic AKI, by allowing better recognition and earlier intervention (Kirkendall et al., 2014). These systems can be passive, interrupted (requiring an action to the prompt) or active, such as where an early intervention team are activated (Thomas et al., 2015). Those with active interventions are believed to be more effective and avoid clinician 'alert fatigue' that may occur with electronic systems. An electronic system developed to identify patients at high-risk of nephrotoxicity has been described in the literature, detailing that the system sends emails to the appropriate nephrologist with key clinical information (Kirkendall et al., 2014). Other methods to detect established AKI earlier include measuring daily serum creatinine levels in patients at risk (Downes et al., 2015; Zappitelli et al., 2011). In a study assessing >100 children with CF who received intravenous AG for >3 days, daily serum creatinine measurement promoted earlier detection of AKI but did not prevent its onset (Downes et al., 2014).

5.2.4. Drugs that induce biological systems

Understanding the pharmacology of drug toxicity allows the use of novel methods to prevent drug-induced AKI through the manipulation of biological pathways that directly contribute to kidney injury. Many of these methods use drug repurposing i.e.: using a drug already

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

Table 1
Biomarkers associated with drug-induced kidney injury.

Urinary biomarker	Source	Mechanism of release	Drugs
Kim-1	Urine	Expressed by tubular epithelial cells in response to injury	Cisplatin, aminoglycosides, ciclosporin
Cystatin C	Blood	Expressed by nucleated cells, inhibitor of extracellular cysteine proteinase, glomerular filtration, reabsorption and degradation by proximal tubular cells	Cisplatin, aminoglycosides, carbapenem, doxorubicin, calcineurin inhibitors
Beta 2 microglobulin	Urine	Found in all nucleated cells, glomerular filtration, reabsorption by proximal tubular cells	Aminoglycosides, cisplatin, tenofovir
NGAL	Urine	Protein that belongs to the lipocalin family and is expressed by the tubules during injury	Aminoglycosides, cisplatin, ciclosporin, radiocontrast dye
NAG	Urine	Proximal tubular lysosomal enzyme, increased expression in injury	Ciclosporin, tacrolimus, aminoglycosides, cisplatin
RBP	Urine	Synthesised in the liver and filtered by the glomerulus, reabsorbed by proximal tubular cells	Aminoglycosides, cisplatin, tenofovir

Abbreviations: Kim-1, kidney injury molecule 1; NGAL neutrophil gelatinase associated lipocalin; IL interleukin; NAG *N*-acetyl-B-D-glucosaminidase; RBP retinol binding protein.

available for a different purpose. This has the advantage of gaining more market opportunities for the pharmaceutical manufacturer. A good example of this is the combined use of phenytoin as an enzyme inducer, with corticosteroids to induce p-glycoprotein since both drugs have been shown to synergistically reduce tacrolimus nephrotoxicity (Bax, Tijssen, Rieder, & Filler, 2014). Another example currently being evaluated is the inhibition of the mevalonate pathway using statins to prevent AG nephrotoxicity by reducing renal tubular cell cytotoxicity (Antoine, Srivastava, Pirmohamed, & Park, 2010). The translation of these strategies into clinical practice is currently underway in children with CF by some of our authors. It has also been speculated that *N*-acetylcysteine (NAC) is able to prevent ifosfamide toxicity and clinical trials in this area are awaited (Hanly et al., 2012).

5.3. Novel treatments under evaluation

In patients with established AKI, cell-based regenerative medicine therapies offer a potential avenue for regeneration and repair of the damaged kidneys. In preclinical studies and phase 1 clinical trials, the administration of mesenchymal stem/stromal cells (MSC) to subjects with AKI led to significant improvements in renal health and renal function in rodents, especially when delivered intra-arterially (Wang, He, Pei, & Zhao, 2013). However, despite these beneficial effects, there are a number of safety issues associated with MSC therapy that need to be addressed. For instance, in animal models, MSCs have been shown to promote tumour growth (Djouad et al., 2003), generate sarcomas (Tasso et al., 2009), and form inappropriate cell types within the kidney (Kunter et al., 2007). A further concern is that the cells could cause intravascular thrombosis, as shown in a recent study where high doses of MSCs caused deterioration of renal function in rodents (Cai et al., 2014). The importance of defining the correct dose is further highlighted by the Phase 2 trial 'ACT-AKI' (NCT01602328) that evaluated MSCs for the treatment of AKI in cardiac bypass patients. In this trial, outcomes were worse in patients who received the therapy (Gooch & Westenfelder, 2016; Swaminathan et al., 2014), and this was likely due to the cells forming microthrombi within the renal vasculature. The therapeutic effects of MSCs, and indeed many other cell types, including kidney-derived cells (Bruce et al., 2015) and renal progenitor cells (Toyohara et al., 2015), are mediated by paracrine factors that suppress inflammation, promote tubular cell proliferation and prevent apoptosis (Geng et al., 2014; Sharkey et al., 2016). There is evidence to suggest that some of these effects are mediated by extracellular vesicles (EVs) (Bruno et al., 2009) modulating the immune system (Robbins & Morelli, 2014). Our increasing understanding of the mechanisms whereby cell therapies elicit their beneficial effects will facilitate the development of safer and more effective therapies in the future; for instance, the administration of EVs rather than the cells themselves would circumvent the potential risks of tumourigenesis, maldifferentiation and thrombosis.

6. Conclusion

Drug-induced AKI is a serious problem in children especially those who are now surviving previously life-threatening diseases and in whom we aspire to a life expectancy that matches the general population with minimum co-morbidity. Avoiding these drugs completely is impractical, rather innovative methods to inhibit or detect the consequences of these agents should be prioritised. An awareness of the mechanism of nephrotoxicity of these drugs is important as it facilitates understanding of novel biomarkers and allows exploration into potential adjuncts to combat the toxicity. Due to the healthcare costs and consequences associated with drug-induced AKI, it is likely that these strategies will become a part of routine prescribing in the future.

Conflict of interest statement

The University of Liverpool receives income from Chiesi, Shire and Janssen, Grunenthal and Quintiles for consultancy services conducted by author MAT. None of these consultancies are relevant to this review and MAT derives no personal benefit from them.

References

Akcan-Arikan, A., Zappitelli, M., Loftis, L. L., Washburn, K. K., Jefferson, L. S., & Goldstein, S. L. (2007). Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney International 71*, 1028–1035.
Aleksa, K., Halachmi, N., Ito, S., & Koren, G. (2004). Renal ontogeny of ifosfamide nephrotoxicity. *The Journal of Laboratory and Clinical Medicine 144*, 285–293.
Aleksa, K., Matsell, D., Krausz, K., Gelboin, H., Ito, S., & Koren, G. (2005). Cytochrome P450 3A and 2B6 in the developing kidney: Implications for ifosfamide nephrotoxicity. *Pediatric Nephrology 20*, 872–885.
Anderson, G. D. (2008). Gender differences in pharmacological response. *International Review of Neurobiology 83*, 1–10.
Antoine, D. J., Srivastava, A., Pirmohamed, M., & Park, B. K. (2010). Statins inhibit aminoglycoside accumulation and cytotoxicity to renal proximal tubule cells. *Biochemical Pharmacology 79*, 647–654.
Askenazi, D. (2011). Evaluation and management of critically ill children with acute kidney injury. *Current Opinion in Pediatrics 23*, 201–207.
Basta, N. O., James, P. W., Gomez-Pozo, B., Craft, A. W., & McNally, R. J. (2011). Survival from childhood cancer in northern England, 1968–2005. *British Journal of Cancer 105*, 1402–1408.
Bax, K., Tijssen, J., Rieder, M. J., & Filler, G. (2014). Rapid resolution of tacrolimus intoxication-induced AKI with a corticosteroid and phenytoin. *The Annals of Pharmacotherapy 48*, 1525–1528.
Begg, E. J., & Barclay, M. L. (1995). Aminoglycosides–50 years on. *British Journal of Clinical Pharmacology 39*, 597–603.
Belayev, L. Y., & Palevsky, P. M. (2014). The link between acute kidney injury and chronic kidney disease. *Current Opinion in Nephrology and Hypertension 23*, 149–154.
Bentley, M. L., Corwin, H. L., & Dasta, J. (2010). Drug-induced acute kidney injury in the critically ill adult: Recognition and prevention strategies. *Critical Care Medicine 38*, S169–S174.
Benz, K., & Amann, K. (2010). Maternal nutrition, low nephron number and arterial hypertension in later life. *Biochimica et Biophysica Acta 1802*, 1309–1317.
Bode, M. M., D'Eugenio, D. B., Forsyth, N., Coleman, J., Gross, C. R., & Gross, S. J. (2009). Outcome of extreme prematurity: A prospective comparison of 2 regional cohorts born 20 years apart. *Pediatrics 124*, 866–874.
Bruce, A. T., Ilagan, R. M., Guthrie, K. I., Rivera, E., Choudhury, S., Sangha, N., ... Basu, J. (2015). Selected renal cells modulate disease progression in rodent models of chronic kidney disease via NF-kappaB and TGF-beta1 pathways. *Regenerative Medicine 10*, 815–839.

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

Bruno, S., Grange, C., Deregibus, M. C., Calogero, R. A., Saviozzi, S., Collino, F., ... Camussi, G. (2009). Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *Journal of the American Society of Nephrology: JASN 20*, 1053–1067.

Cai, J., Yu, X., Xu, R., Fang, Y., Qian, X., Liu, S., ... Ding, X. (2014). Maximum efficacy of mesenchymal stem cells in rat model of renal ischemia-reperfusion injury: Renal artery administration with optimal numbers. *PLoS One 9*, e92347.

Constance, J. E., Balch, A. H., Stockmann, C., Linakis, M. W., Korgenski, E. K., Roberts, J. K., ... Spigarelli, M. G. (2016). A propensity-matched cohort study of vancomycin-associated nephrotoxicity in neonates. *Archives of Disease in Childhood. Fetal and Neonatal Edition 101*, F236–F243.

De Cock, R. F., Allegaert, K., Schreuder, M. F., Sherwin, C. M., de Hoog, M., van den Anker, J. N., ... Knibbe, C. A. (2012). Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. *Clinical Pharmacokinetics 51*, 105–117.

de Wildt, S. N., Tibboel, D., & Leeder, J. S. (2014). Drug metabolism for the paediatrician. *Archives of Disease in Childhood 99*, 1137–1142.

Djouad, F., Plence, P., Bony, C., Tropel, P., Apparailly, F., Sany, J., ... Jorgensen, C. (2003). Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. *Blood 102*, 3837–3844.

Downes, K. J., Rao, M. B., Kahill, L., Nguyen, H., Clancy, J. P., & Goldstein, S. L. (2014). Daily serum creatinine monitoring promotes earlier detection of acute kidney injury in children and adolescents with cystic fibrosis. *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society 13*, 435–441.

Downes, K. J., Patil, N. R., Rao, M. B., Koralkar, R., Harris, W. T., Clancy, J. P., ... Askenazi, D. J. (2015). Risk factors for acute kidney injury during aminoglycoside therapy in patients with cystic fibrosis. *Pediatric Nephrology 30*, 1879–1888.

England, N. (Date accessed 20.6.15).

Faught, L. N., Greff, M. J., Rieder, M. J., & Gideon, K. (2014). Drug-induced acute kidney injury in children. *British Journal of Clinical Pharmacology 80*, 901–909.

Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics 3*, 53–72.

Frattarelli, D. A., Galinkin, J. L., Green, T. P., Johnson, T. D., Neville, K. A., Paul, I. M., & Van Den Anker, J. N. (2014). Off-label use of drugs in children. *Pediatrics 133*, 563–567.

Fuchs, T. C., & Hewitt, P. (2011). Biomarkers for drug-induced renal damage and nephrotoxicity-an overview for applied toxicology. *The AAPS Journal 13*, 615–631.

Geng, Y., Zhang, L., Fu, B., Zhang, J., Hong, Q., Hu, J., ... Chen, X. (2014). Mesenchymal stem cells ameliorate rhabdomyolysis-induced acute kidney injury via the activation of M2 macrophages. *Stem Cell Research & Therapy 5*, 80.

Gonzalez, E., Gutierrez, E., Galeano, C., Chevia, C., de Sequera, P., Bernis, C., ... Praga, M. (2008). Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney International 73*, 940–946.

Gooch, A., & Westenfelder, C. (2016). Modified hydrogels to enhance cellular therapy for AKI: A translational challenge. *Journal of the American Society of Nephrology: JASN*.

Gross, M. L., Amann, K., & Ritz, E. (2005). Nephron number and renal risk in hypertension and diabetes. *Journal of the American Society of Nephrology: JASN 16*(Suppl. 1), S27–S29.

Hanigan, M. H., & Devarajan, P. (2003). Cisplatin nephrotoxicity: Molecular mechanisms. *Cancer Therapy 1*, 47–61.

Hanly, L. N., Chen, N., Aleksa, K., Cutler, M., Bajcetic, M., Palassery, R., ... Koren, G. (2012). *N*-acetylcysteine as a novel prophylactic treatment for ifosfamide-induced nephrotoxicity in children: Translational pharmacokinetics. *Journal of Clinical Pharmacology 52*, 55–64.

Harness-Brumley, C. L., Elliott, A. C., Rosenbluth, D. B., Raghavan, D., & Jain, R. (2014). Gender differences in outcomes of patients with cystic fibrosis. *Journal of Women's Health 23*, 1012–1020.

Hawcutt, D. (2011). *Molecular genetics of adverse drug reactions in children Vol. 2016.* (In).

Hawcutt, D. B., & Smyth, R. L. (2008). The new European regulation on pediatric medicines: Regulatory perspective. *Paediatric Drugs 10*, 143–146.

Hawcutt, D. B., Mainie, P., Riordan, A., Smyth, R. L., & Pirmohamed, M. (2012). Reported paediatric adverse drug reactions in the UK 2000–2009. *British Journal of Clinical Pharmacology 73*, 437–446.

Hawcutt, D. B., O'Connor, O., & Turner, M. A. (2014). Adverse drug reactions in neonates: Could we be documenting more? *Expert Review of Clinical Pharmacology 7*, 807–820.

Imran, S., Sheikh, A., Saeed, Z., Khan, S. A., Malik, A. O., Patel, J., ... Hussain, A. (2015). Burden of chronic kidney disease in an urban city of Pakistan, a cross-sectional study. *JPMA. The Journal of the Pakistan Medical Association 65*, 366–369.

Ingelman-Sundberg, M. (2004). Pharmacogenetics of cytochrome P450 and its applications in drug therapy: The past, present and future. *Trends in Pharmacological Sciences 25*, 193–200.

Izzedine, H., Launay-Vacher, V., & Deray, G. (2005). Renal tubular transporters and antiviral drugs: An update. *AIDS 19*, 455–462.

Izzedine, H., Hulot, J. S., Villard, E., Goyenvalle, C., Dominguez, S., Ghosn, J., ... Deray, A. G. (2006). Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy. *The Journal of Infectious Diseases 194*, 1481–1491.

Joffe, A. R., Anton, N. R., & Burkholder, S. C. (2011). Reduction in hospital mortality over time in a hospital without a pediatric medical emergency team: Limitations of before-and-after study designs. *Archives of Pediatrics & Adolescent Medicine 165*, 419–423.

Kavaz, A., Ozcakar, Z. B., Kendirli, T., Ozturk, B. B., Ekim, M., & Yalcinkaya, F. (2012). Acute kidney injury in a paediatric intensive care unit: Comparison of the pRIFLE and AKIN criteria. *Acta Paediatrica 101*, e126–e129.

Kent, A., Turner, M. A., Sharland, M., & Heath, P. T. (2014). Aminoglycoside toxicity in neonates: Something to worry about? *Expert Review of Anti-Infective Therapy 12*, 319–331.

Khan, E., Batuman, V., & Lertora, J. J. (2010). Emergence of biomarkers in nephropharmacology. *Biomarkers in Medicine 4*, 805–814.

Kirkendall, E. S., Spires, W. L., Mottes, T. A., Schaffzin, J. K., Barclay, C., & Goldstein, S. L. (2014). Development and performance of electronic acute kidney injury triggers to identify pediatric patients at risk for nephrotoxic medication-associated harm. *Applied Clinical Informatics 5*, 313–333.

Knijnenburg, S. L., Mulder, R. L., Schouten-Van Meeteren, A. Y., Bokenkamp, A., Blufpand, H., van Dulmen-den Broeder, E., ... Jaspers, M. W. (2013). Early and late renal adverse effects after potentially nephrotoxic treatment for childhood cancer. *The Cochrane Database of Systematic Reviews 10*, CD008944.

Kunter, U., Rong, S., Boor, P., Eitner, F., Muller-Newen, G., Djuric, Z., ... Floege, J. (2007). Mesenchymal stem cells prevent progressive experimental renal failure but maldifferentiate into glomerular adipocytes. *Journal of the American Society of Nephrology: JASN 18*, 1754–1764.

Lash, L. H. (2005). Role of glutathione transport processes in kidney function. *Toxicology and Applied Pharmacology 204*, 329–342.

Liborio, A. B., Branco, K. M., & Torres de Melo Bezerra, C. (2014). Acute kidney injury in neonates: From urine output to new biomarkers. *BioMed Research International 2014*, 601568.

Luft, F. C. (1984). Clinical significance of renal changes engendered by aminoglycosides in man. *Journal of Antimicrobial Chemotherapy 13*, 23–28.

Mariotto, A. B., Rowland, J. H., Yabroff, K. R., Scoppa, S., Hachey, M., Ries, L., & Feuer, E. J. (2009). Long-term survivors of childhood cancers in the United States. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 18*, 1033–1040.

Mathews, A., & Bailie, G. R. (1987). Clinical pharmacokinetics, toxicity and cost effectiveness analysis of aminoglycosides and aminoglycoside dosing services. *Journal of Clinical Pharmacy and Therapeutics 12*, 273–291.

Matos, P., Duarte-Silva, M., Drukker, A., & Guignard, J. P. (1998). Creatinine reabsorption by the newborn rabbit kidney. *Pediatric Research 44*, 639–641.

McWilliam, S. J., Antoine, D. J., Sabbisetti, V., Turner, M. A., Farragher, T., Bonventre, J. V., ... Pirmohamed, M. (2012). Mechanism-based urinary biomarkers to identify the potential for aminoglycoside-induced nephrotoxicity in premature neonates: A proof-of-concept study. *PLoS One 7*, e43809.

McWilliam, S. J., Antoine, D. J., Sabbisetti, V., Pearce, R. E., Jorgensen, A. L., Lin, Y., ... Pirmohamed, M. (2014). Reference intervals for urinary renal injury biomarkers KIM-1 and NGAL in healthy children. *Biomarkers in Medicine 8*, 1189–1197.

Mehta, R. L., Kellum, J. A., Shah, S. V., Molitoris, B. A., Ronco, C., Warnock, D. G., & Levin, A. (2007). Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Critical Care 11*, R31.

Menon, S., Kirkendall, E. S., Nguyen, H., & Goldstein, S. L. (2014). Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. *The Journal of Pediatrics 165*(522–527), e522.

Menon, S., Goldstein, S. L., Mottes, T., Fei, L., Kaddourah, A., Terrell, T., ... Basu, R. K. (2016). Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: A prospective cohort study. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association 31*, 586–594.

Misurac, J. M., Knoderer, C. A., Leiser, J. D., Nailescu, C., Wilson, A. C., & Andreoli, S. P. (2013). Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. *The Journal of Pediatrics 162*, 1153–1159 (1159 e1151).

Mulder, R. L., Knijnenburg, S. L., Geskus, R. B., van Dalen, E. C., van der Pal, H. J., Koning, C. C., ... Kremer, L. C. (2013). Glomerular function time trends in long-term survivors of childhood cancer: A longitudinal study. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 22*, 1736–1746.

Naesens, M., Kuypers, D. R., & Sarwal, M. (2009). Calcineurin inhibitor nephrotoxicity. *Clinical Journal of the American Society of Nephrology: CJASN 4*, 481–508.

NICE (2015). *Medicines optimisation: The safe and effective use of medicines to enable the best possible outcomes.*

Oberlin, O., Fawaz, O., Rey, A., Niaudet, P., Ridola, V., Orbach, D., ... de Vathaire, F. (2009). Long-term evaluation of ifosfamide-related nephrotoxicity in children. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 27*, 5350–5355.

Paci, A., & Vassal, G. (2012). Off-patent oral oncology drugs for kids (O3K FP7-project): From bedside to PUMA. *International Journal of Pharmaceutics 435*, 148–150.

Perazella, M. A. (2009). Renal vulnerability to drug toxicity. *Clinical Journal of the American Society of Nephrology: CJASN 4*, 1275–1283.

Quon, B. S., Mayer-Hamblett, N., Aitken, M. L., Smyth, A. R., & Goss, C. H. (2011). Risk factors for chronic kidney disease in adults with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine 184*, 1147–1152.

Ramirez, E., Jimenez, C., Borobia, A. M., Tong, H. Y., Medrano, N., Krauel-Bidwell, L., ... Frias, J. (2013a). Vancomycin-induced acute kidney injury detected by a prospective pharmacovigilance program from laboratory signals. *Therapeutic Drug Monitoring 35*, 360–366.

Ramirez, E., Rossignoli, T., Campos, A. J., Munoz, R., Zegarra, C., Tong, H., ... Frias, J. (2013b). Drug-induced life-threatening potassium disturbances detected by a pharmacovigilance program from laboratory signals. *European Journal of Clinical Pharmacology 69*, 97–110.

Riva, N., Caceres Guido, P., Rousseau, M., Dip, M., Monteverde, M., Imventarza, O., ... Schaiquevich, P. (2013). Pharmacovigilance of calcineurin inhibitor in peidatric kidney and liver transplantation. *Farmacia Hospitalaria: Organo Oficial de Expresion Cientifica de la Sociedad Espanola de Farmacia Hospitalaria 37*, 441–449.

Robbins, P. D., & Morelli, A. E. (2014). Regulation of immune responses by extracellular vesicles. *Nature Reviews. Immunology 14*, 195–208.

Rodriguez-Soriano, J., Aguirre, M., Oliveros, R., & Vallo, A. (2005). Long-term renal follow-up of extremely low birth weight infants. *Pediatric Nephrology 20*, 579–584.

Schmitz, C., Hilpert, J., Jacobsen, C., Boensch, C., Christensen, E. I., Luft, F. C., & Willnow, T. E. (2002). Megalin deficiency offers protection from renal aminoglycoside accumulation. *Journal of Biological Chemistry 277*, 618–622.

Servais, H., Van Der Smissen, P., Thirion, G., Van der Essen, G., Van, B. F., Tulkens, P. M., & Mingeot-Leclercq, M. P. (2005). Gentamicin-induced apoptosis in LLC-PK1 cells: Involvement of lysosomes and mitochondria. *Toxicology and Applied Pharmacology 206*, 321–333.

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018

Servais, H., Ortiz, A., Devuyst, O., Denamur, S., Tulkens, P. M., & Mingeot-Leclercq, M. P. (2008). Renal cell apoptosis induced by nephrotoxic drugs: Cellular and molecular mechanisms and potential approaches to modulation. *Apoptosis: An International Journal on Programmed Cell Death 13*, 11–32.

Sharkey, J., Scarfe, L., Santeramo, I., Garcia-Finana, M., Park, B. K., Poptani, H., ... Murray, P. (2016). Imaging technologies for monitoring the safety, efficacy and mechanisms of action of cell-based regenerative medicine therapies in models of kidney disease. *European Journal of Pharmacology 790*, 74–82.

Sinclair, E. A., Yenokyan, G., McMunn, A., Fadrowski, J. J., Milstone, A. M., & Lee, C. K. (2014). Factors associated with acute kidney injury in children receiving vancomycin. *The Annals of Pharmacotherapy 48*, 1555–1562.

Skinner, R., Parry, A., Price, L., Cole, M., Craft, A. W., & Pearson, A. D. (2010). Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. *Pediatric Blood & Cancer 54*, 983–989.

Swaminathan, M., Mazer, D., Chertow, G. M., Warnock, D. G., Paragamian, V., & Brenner, R. M. (2014). ACT-AKI: A phase 2 multicenter, randomized, double-blind, placebo controlled trial of AC607 for the treatment of acute kidney injury in cardiac surgery subjects. *The American Society of Nephrology kidney week Vol. B3 HI-OR09*. (Philadelphia, PA).

Taber, S. S., & Pasko, D. A. (2008). The epidemiology of drug-induced disorders: The kidney. *Expert Opinion on Drug Safety 7*, 679–690.

Tasso, R., Augello, A., Carida, M., Postiglione, F., Tibiletti, M. G., Bernasconi, B., ... Pennesi, G. (2009). Development of sarcomas in mice implanted with mesenchymal stem cells seeded onto bioscaffolds. *Carcinogenesis 30*, 150–157.

Thomas, M. E., Blaine, C., Dawnay, A., Devonald, M. A., Ftouh, S., Laing, C., ... Ostermann, M. (2015). The definition of acute kidney injury and its use in practice. *Kidney International 87*, 62–73.

Thomson, B. K., Nolin, T. D., Velenosi, T. J., Feere, D. A., Knauer, M. J., Asher, L. J., ... Urquhart, B. L. (2015). Effect of CKD and dialysis modality on exposure to drugs cleared by nonrenal mechanisms. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 65*, 574–582.

Toyohara, T., Mae, S., Sueta, S., Inoue, T., Yamagishi, Y., Kawamoto, T., ... Osafune, K. (2015). Cell therapy using human induced pluripotent stem cell-derived renal progenitors ameliorates acute kidney injury in mice. *Stem Cells Translational Medicine 4*, 980–992.

Turner, M. A., Catapano, M., Hirschfeld, S., & Giaquinto, C. (2014). Paediatric drug development: The impact of evolving regulations. *Advanced Drug Delivery Reviews 73*, 2–13.

Valluri, A., Hetherington, L., McQuarrie, E., Fleming, S., Kipgen, D., Geddes, C. C., ... Bell, S. (2014). Acute tubulointerstitial nephritis in Scotland. *QJM: Monthly Journal of the Association of Physicians 108*, 527–532.

van Riet-Nales, D. A., Romkens, E. G., Saint-Raymond, A., Kozarewicz, P., Schobben, A. F., Egberts, T. C., & Rademaker, C. M. (2014). Oral medicines for children in the European paediatric investigation plans. *PLoS One 9*, e98348.

Vucicevic, K., Rakonjac, Z., Miljkovic, B., Jankovic, B., & Prostran, M. (2014). Pharmacokinetic variability of amikacin after once-daily and twice-daily dosing regimen in full-term neonates. *Journal of Pharmacological Sciences 124*, 138–143.

Wang, Y., He, J., Pei, X., & Zhao, W. (2013). Systematic review and meta-analysis of mesenchymal stem/stromal cells therapy for impaired renal function in small animal models. *Nephrology 18*, 201–208.

Wargo, K. A., & Edwards, J. D. (2014). Aminoglycoside-induced nephrotoxicity. *Journal of Pharmacy Practice 27*, 573–577.

Zaffanello, M., Bassareo, P. P., Cataldi, L., Antonucci, R., Biban, P., & Fanos, V. (2010). Long-term effects of neonatal drugs on the kidney. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, The Federation of Asia and Oceania Perinatal Societies, The International Society of Perinatal Obstetricians 23*(Suppl. 3), 87–89.

Zappitelli, M., Moffett, B. S., Hyder, A., & Goldstein, S. L. (2011). Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: A retrospective cohort study. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association 26*, 144–150.

Please cite this article as: Oni, L., et al., Optimising the use of medicines to reduce acute kidney injury in children and babies, *Pharmacology & Therapeutics* (2017), http://dx.doi.org/10.1016/j.pharmthera.2017.02.018