**Prescribing in paediatric kidney impairment**

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**INTRODUCTION**

Kidney impairment is common in the paediatric population. This includes patients with an acute deterioration in kidney function during an episode of Acute Kidney Injury (AKI), patients with Chronic Kidney Disease (CKD) and patients undergoing renal replacement therapy (RRT) or with kidney transplants. Patients with kidney impairment are at increased risk of adverse events associated with errors in drug prescribing and administration.[1] This article aims to highlight several key principles prescribers should be aware of when managing these patients, with a particular focus on management in secondary care.

**DRUG HANDLING IN THE HEALTHY KIDNEY**

A person’s response to a drug is determined by a combination of pharmacokinetics and pharmacodynamics [2]. Pharmacodynamics is concerned with the **effect of the drug on the body**. Pharmacokinetics is best described as **the effect of the body on the drug** and reflects the physiologic processes of **absorption, distribution, metabolism and elimination;**[2–4] it is important to remember that each of these processes may be altered in kidney disease. Unfortuntely there are no agreed national guidelines on how to adjust doses in kidney impairment. Pharmacists have specialist knowledge which should be utilised within the MDT to advise the necessary dosage adjustments.

**Absorption** may be reduced in patients with kidney impairment for numerous reasons including nausea and vomiting associated with uraemia and oedema of the gastrointestinal tract due to hypoproteinaemia.[2,4] Drug doses are not routinely altered to allow for these factors but must be considered when assessing the efficacy of treatment. An example could be switching from oral prednisolone to intravenous (IV) methylprednisolone if there was a concern regarding the absorption of the oral medication.

**Distribution** of drugs is affected as a result of changes affecting protein binding, primarily hypoalbuminemia. This is particularly important for highly protein-bound drugs, for example, tacrolimus. A higher proportion of unbound drug, due to hypoproteinaemia, can result in accumulation of active drug in the plasma. [2,4] However this effect is usually of little significance due to a compensatory increase in clearance.[5] With tacrolimus such an effect can be accounted for by monitoring therapeutic levels.

Phase I and phase II **metabolism** usually results in the formation of inactive metabolic products. This action can be prolonged in kidney disease, which could result in higher plasma concentrations of the parent drug and potential for toxicity.[4] The kidney itself is the site of metabolism for certain medications, including vitamin D. It converts 25-hydroxycholecalciferol to 1,25-dihydroxyvitamin D, which is the active form of vitamin D. Abnormalities in vitamin D metabolism play a major role in the pathogensis of secondary hyperparathyroidism.[6]

The kidney is involved in the **elimination** of drugs and metabolites by glomerular filtration, tubular secretion and re-absorption, all of which are reduced in kidney disease.[4] The impact of kidney disease on elimination is the most relevant for prescribing, and examples of important medicines affected are given later.

**DEFINING KIDNEY** **IMPAIRMENT**

Kidney impairment is recognised by detecting a fall in glomerular filtration rate (GFR). Formal GFR measurements rely on the administration of a filtration marker and the subsequent measurement of its clearance over time.[7] This is not routinely performed and is not a practical method for assessing a patient’s kidney function for prescribers. GFR measurements can be estimated (eGFR) using several methods.[7] In paediatrics, the most commonly used method to calculate eGFR is the ‘Bedside Schwartz’ equation which is validated for children from 1-18 years:[8]

Whilst other calculations exist, this method calculates eGFR using height and serum creatinine (SCr) levels, data that is routinely available in paediatric patients, allowing clinicians to easily identify patients with reduced kidney function before making prescribing decisions in a contemporaneous manner. It is currently felt to be the most accurate bedside equation for use in patients with and without CKD.[9]

The CKD in children (CKiD) study derived a calculation involving both Cystatin C and SCr levels, alongside other basic clinical parameters.[10] This equation has been shown to increase the accuracy of predicting GFR in children with CKD. However for ease of use this requires a validated online calculator which can be found in the key resources below.

As with any estimation, there are limitations to these methods. These include not being validated for children less than 1 year old and the requirement for tests to be measured using validated methods. It is now a requirement for UK laboratories to measure SCr using a validated enzymatic method. The importance of accurate height/length measurements cannot be underestimated in ensuring optimal estimations. Local centres should consider the most appropriate equation based on the evidence in the literature and ease of use for staff.

**Acute Kidney Injury**

AKI is defined as a sudden decline in kidney function. It is reported to occur in 5% of hospitalised children, with this figure rising to almost 30% in those who are critically unwell.[11] It may not have any symptoms and is detected by the rise in SCr noted on blood sampling.[12] It is associated with increased mortality and length of hospital stay alongside a higher risk of developing chronic kidney disease in the future.[13] The severity of AKI can be assessed using the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 1).[12] Early recognition of AKI, and subsequent changes in management that prevent further kidney injury, have been shown to improve outcomes in hospitalised children.[14] Many drugs commonly prescribed in paediatric practice can cause and contribute to AKI. Others may have unwanted or toxic side effects secondary to the inability of the poorly functioning kidney to handle the medication or its metabolites.

**Chronic Kidney Disease**

CKD is defined as an abnormality in the function or structure of the kidneys that persists for more than 3 months. This can be categorised into stages of severity using the patient’s GFR and degree of proteinuria (Table 1). In milder stages, CKD is often asymptomatic. As severity increases patients are at higher risk of electrolyte abnormalities, anaemia, renal osteodystrophy and long-term cardiovascular complications. RRT, in the form of dialysis, or kidney transplantation is required when the kidneys can no longer function to a level to keep fluid and electrolytes within safe limits. This is referred to as CKD stage 5. The degree of chronic impairment has a significant impact on the kidneys’ ability to handle drugs safely. Paediatricians need to be aware of the challenges of prescribing in CKD to ensure they prescribe safely.[15]

Table 1: Severity of kidney impairment (adapted from [12,16])

|  |  |  |  |
| --- | --- | --- | --- |
| Stage | **AKI**  KDIGO Criteria | | **CKD**  Based on eGFR (ml/min/1.73m2) |
| 1 | * 1.5 x increase in serum creatinine (SCr) * SCr Rise of > 26umol/L | Urine output (UO) < 0.5 ml/kg/hr for 6-12 hr | Greater than 90 |
| 2 | * 2-3x rise in baseline SCr | UO <0.5 ml/kg/hr for > 12 hr | 60-89 |
| 3 | * 3 x rise in baseline SCr * Initiation of RRT * eGFR <35 ml/min/1.73m2 * SCr rise to > 354 umol/L | UO < 0.3 ml/kg/hr for > 24 hrs  Or  Anuria for > 12 hrs | 3a 45-69  3b 30-44 |
| 4 |  | | 15-29 |
| 5 |  | | Less than 15 or RRT |

**SAFE PRESCRIBING IN KIDNEY IMPAIRMENT**

Kidney impairment has been associated with an increased risk of adverse effects with medication; the majority due to inappropriate dosing of medication primarily eliminated by the kidney. Practitioners should be routinely educated in methods for ensuring safe prescribing practices in kidney impairment.

Prescribing safely in AKI requires the early identification and calculation of a patient’s level of kidney function using an appropriate eGFR calculation. All current medications should be reviewed and amended based on the most recent eGFR. A diagnosis of AKI and the current degree of kidney impairment should be documented in a patient’s notes so that prescribers are aware of this before starting any new medication. Medications should be reviewed daily and adjusted based on changes in kidney function; an aspect which can be led by the ward pharmacist [17]. In acutely unwell patients, particularly in those with suspected sepsis and no previous history of kidney impairment, it is important to promptly and appropriately treat the acute illness to prevent further kidney damage. This includes administration of antibiotics in a timely manner. Adjustments can then be made for subsequent doses.[18]

Preserving kidney function and delaying progression to dialysis is the primary aim in the management of CKD.[19] To accomplish this it is important to have knowledge of potential toxicities and interactions of prescribed medication, consider alternative therapies and individualise drug therapy depending on the level of kidney impairment. CKD is also under-recognised in patients and there is limited published data on drug dosing for these children, which contributes to an increased frequency of medication errors.

Certain medications may further impair kidney function, cause unwanted adverse effects or dangerous electrolyte abnormalities when used in kidney impairment. The clinical team should consider whether these medications should be deprescribed or used wth caution, seeking advice from pharmacists or used under expert guidance. Common medications included in this group are listed in Table 2

E-prescribing provides the opportunity to develop automated alerts that could prompt prescribers to consider a patient’s kidney function before initiating nephrotoxic medications, and may help to improve outcomes.[20] Prescribers should also be encouraged to use electronic resources such as the online British National Formularly (BNF) or the BNF app, which ensure the most up to date guidance is being accessed.

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug Examples** | **Pharmacology and other information** | **Impact of kidney impairment** | **Action** |
| **Anti-infectives** | | | |
| Aminoglycosides   * Gentamicin * Tobramycin * Amikacin | * Concentration-dependent, bactericidal agents * Inhibit bacterial protein synthesis * Elimination mainly by glomerular filtration * 50-60% of the dose excreted within 24 hours | * Reduced clearance * Rapid accumulation * Nephrotoxicity * Ototoxicity | * Avoid if possible * Dosing based on eGFR with input from pharmacist * Monitor plasma concentrations (pre-dose levels) * Await results before giving next dose * Adjust dose or dosing interval accordingly[21,22] |
| Vancomycin | * Glycopeptide active against the majority of gram-positive bacteria including methicillin-resistant staphylococcus aureus (MRSA) * Predominantly renal clearance * 80-90% recovered unchanged in the urine | * Reduced clearance * Rapid accumulation * Nephrotoxicity * Ototoxicity | * Dosing based on eGFR with input from pharmacist * Monitor plasma concentrations (pre-dose levels) * Await results before giving next dose * Adjust dose or dosing interval accordingly[21,22] |
| *β*-lactam antibiotics   * Penicillins * Cephalosporins * Carbapenems | * Time-dependent pharmacodynamics | * Reduced clearance and protein binding leads to higher plasma concentrations. * Central nervous system disturbances including confusion, myoclonus and seizures | * Dosing based on eGFR with input from pharmacist * Reduce the dose and/or dosing interval |
| Aciclovir | * Predominantly renal clearance | * Increased risk of toxicity including nephrotoxicity and neurotoxicity | * Dosing based on eGFR with input from pharmacist * Reduce the dose and/or dosing interval[23] |
| **Antifungals** | | | |
| Conventional amphotericin B | * Exhibits concentration-dependent fungicidal activity | * Highly nephrotoxic, permanent kidney impairment may occur in patients including those receiving doses of more than 1mg/kg/day, those with pre-exisiting kidney impairment or on concurrent nephrotoxic drugs. | * Use with caution in kidney impairment * Seek input from pharmacist and/or infectious diseases team * Consider using liposomal amphotericin or an alternative antifungal. Please note although liposomal amphotericin is less nephrotoxic the risk of kidney impairment still exists. |
| **Analgesics** | | | |
| Opioids   * Morphine * Tramadol * Codeine | * This varies for individual opioids therefore it is important to understand the pharmacokinetics of each drug to minimise the risk of toxicity. * Morphine, tramadol and codeine have significant renal clearance. | * Reduced clearance * Accumulation of toxic/active metabolites * Central nervous system and respiratory depression | * Caution in CKD 4 or 5 * Dose reduction in earlier stages of impairment (e.g. reduction of 50-75% for morphine and codeine) * Avoid slow-release preparations * Consider using opiates with lower dependence on renal excretion such as oxycodone and fentanyl[21]. Fentanyl should only be used under the direction of a specialist team. * Consider nurse or parent/patient controlled analgesia rather than continuous infusion |
| Non-sterodal anti-inflammatory drugs (NSAIDs) e.g:   * Ibuprofen * Diclofenac * Celecoxib | * Inhibit prostaglandin synthesis which may result in sodium retention and reduced kidney blood flow | * Increased impact on kidney blood flow, causing further decline of kidney function | * Avoid if possible * If an NSAID is required liaise with a nephrologist and/or specialist pharmacist [24] |
| **Diurectics** | | | |
| * Furosemide * Spironolactone (potassium sparing diuretic) | * Varies with different diuretics however the ultimate aim is to increase the amount of water in the urine | * Can cause a reduction in GFR if their use results in hypovolaemia. | * Use with caution * Increased risk of hyperkalaemia with potassium sparing diuretics |
| **Angiotensin-converting enzyme (ACE) and Angiotensin receptor blockers (ARBs) Inhibitors** | | | |
| Examples include:   * Lisinopril * Captopril * Losartan | * ACE inhibitors and ARBs inhibit the renin-angiotension-aldosterone system | * May increase the risk of AKI by reducing glomerular perfusion. | * Close monitoring of renal function during therapy. * Monitor for hyperkalaemia * If an episode of AKI occurs– consider omitting treatment until AKI resolves/liaise with a nephrologist |
| **Specialist medications** | | | |
| Calcineurin inhibitors   * Tacrolimus * Ciclosporin | * Immunosuppressants * Used in several kidney conditions as well as post-kidney transplant | * Associated with potential for nephrotoxicity | * Discuss with specialist team/pharmacist[2] |
| Anti-epileptics | * Varies for individual medications | * Accumulation * Increased CNS effects | * Dose adjustment based on GFR * Discuss with specialist team/pharmacist |
| Contrast media | * Various compounds for different radiological procedures | * Some associated with potential for nephrotoxicity * gadolinium-based contrast agents associated with nephrogenic systemic fibrosis in kidney impairment | * Avoid if possible in severe kidney impairment. * Discuss with radiologist if suitable alternative imaging modality available * Consider risks and benefits on an individual patient basis. * Consider pre-hydration |

Table 2: Selected medications to use with caution or avoid in kidney impairment. Please note medications listed in this table are those most commonly used in daily practice, this list is not exhaustive. Please refer to the BNFc, renal drug handbook and discuss with a pharmacist for specific advice on dosing adjustments.

**CKD 5, Renal Replacement Therapy and Kidney Transplants**

Prescribing in patients with CKD5 is a complex area and specialist advice should be sought in the vast majority of cases. For patients on dialysis, drug administration and plasma concentration levels may need to be timed around their dialysis sessions depending on the molecular properties of the drug. Transplant patients are on multiple other drugs and the likelihood of drug interactions needs to be checked carefully. Liaising with clinicians or pharmacists with a specialist interest in nephrology is recommended.

**SUMMARY**

Extra care needs to be taken when prescribing in patients with both AKI and CKD. This review has covered some basic principles regarding prescribing in these patients. Additional information should be obtained from a specialist or other appropriate resources (Table 3).

Table 3: Prescribing in Kidney Impairment – Useful resources

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| --- |
| * CKiD Online eGFR calculator - kidney.org/professionals/Kdoqi/gfr\_calculatorPed * BNF for children - [bnfc.nice.org.uk](https://bnfc.nice.org.uk/) * The Renal Drug Handbook or The Renal Drug Database – contact your pharmacist * ‘Think Kidneys’ - https://www.thinkkidneys.nhs.uk/aki/resources/paediatrics/ * Summary of Product Characteristics -   [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc) |

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