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# Prescription of Drugs in Children with Impaired Renal Function

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**Introduction:**

Paediatric nephrologist often needs to consider multiple factors to drug dosing for children with impaired renal function. They usually convert adult dosing guidelines into paediatric doses and adjust them to the patient's renal function, a procedure that is time-consuming and error-prone. It is said that drug absorption, distribution, metabolism and excretion is different in children than adults.[1] In newborn, the elimination of drugs is low because of insufficient drug metabolizing capacity of the liver and immaturity of kidney function. These alterations of drug metabolism are correlated to age-adjusted hormonal changes.[2] In this review, dosing tables of some important and commonly used antimicrobials are provided for easy and quick reference in order to facilitate prescription for children with impaired renal function.

**Effects of impaired kidney function on pharmacokinetics & pharmacodynamics of drug:**

Kidney is one of the major regulators of internal fluid environment. So any disease in kidney not only alters it's function but can also affect multiple organ systems. Therefore, physiological changes that can be induced by the reduced renal function, can have pronounced effects on the pharmacokinetics (PK) and the pharmacodynamics (PD) of many drugs[3,4]. Pharmacokinetics is defined by the individual patient's ability to absorb, distribute, metabolize and eliminate the drug from the body. On the other hand, pharmacodynamics is characterized by how drugs affect the body. Clinicians must have a basic understanding of the PK and PD as well as biochemical and physiologic effects of drugs in patients with renal disease. Therefore, it is essential to have a basic understanding on the fundamental principles of pharmacology.

The amount of drug absorbed into the systemic circulation is primarily affected by the route of administration. When the drug is given intravenously, its absorption is considered complete with exception of some prodrugs (e.g. fosphenytoin)[5]. On the other hand, drugs that are administered by the oral route or other extravascular sites are absorbed only a fraction of the total dose. In the gastrintestinal tract drugs are absorbed across the intestinal epithelium, a tissue rich in drug-metabolizing enzymes (e.g. cytochromes P-450) and transporters (e.g. P-glycoprotein). After oral administration, most drugs cross the intestinal epithelium by passive diffusion along a concentration gradient in unbound (free) and non-ionized form[5].

The movement of drugs may be affected by the pH gradient. High gastric pH may be responsible for impairment of drug absorption. At birth until age 2-3 yr the gastric pH remain high approximately 6-8. So medications that require acid milieu for drug absorption (phenytoin and phenobarbital) cannot be absorbed completely at these age groups[6]. In children with kidney disease, drug absorption may be altered by a number of mechanisms, including *genetic factors* (e.g. polymorphisms of drug-metabolizing enzymes or drug transporters), *disease-induced changes* in the structure and physiology of the absorptive site (e.g. first-pass effect) and *interactions* among drugs (e.g. phosphate binders with antibiotics or iron-containing supplements)[5,7]. Common causes of impairment of drug absorption occur due to uraemia induced delayed gastric emptying or vomiting or oedema of the gastrointestinal tract[8]. Bioavailability of some drugs is limited by intestinal metabolism via the cytochrome P-450 (CYP) enzymes (mainly CYP3A4/5). For example, administration of strong CYP3A inhibitors, such as ketoconazole or diltiazem, can decrease the metabolism of cyclosporine or tacrolimus in the gut and increase the amount of active drug reaching the systemic circulation[9,10]. The enhanced absorption of active drug can result in an increase in blood concentrations and toxicity. That is why; in developing countries diltiazem/ketoconazole-cyclosporine[11] or diltiazem/ketoconazole-tacrolimus[12] interaction has been used to decrease the treatment costs of immunosuppressive agents among transplant patient.

Children with kidney dysfunction have decreased protein synthesis and increased protein elimination, which can increase drug toxicities. For example, about 97% of mycophenolate in the plasma is bound to

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albumin while 2-3% is free. Hypoalbuminaemia (<2.5 gm/dl) causes increased risk of toxicities due to an increased concentration of free mycophenolate in the plasma[13]. Beside these, uraemia can induce changes in the albumin structure. So that mycophenolate like acidic drugs can bind less avidly, this can misinterpret the measurement of the drug concentrations. Because most drug assays reflect sum of the bound and active unbound species.

Quantitatively, the liver and gastrointestinal tracts are the most important organs of drug metabolism. However, for some drugs, kidney is the primary site of drug metabolism and kidney disease can impact the biotransformation profile. For example, imipenem is a â-lactam antibiotic that is rapidly hydrolyzed by dipeptidases located on the brush border or the proximal renal tubule. Kidney failure impairs the normal metabolism and results in an accumulation of imipenem and an increased risk of seizures[14]. In general, microsomal enzyme systems are immature in infants and neonates. It has been shown that drug metabolism is slower in the children than adult at this stage of life.[15]

Drugs and drug metabolites are eliminated from the body through various excretory pathways, including kidney, biliary, salivary, mammary, sweat, lung and intestinal. Among them kidney is the most important route of drug excretion. Drug removal rate is typically expressed as elimination half-life (t½), the time required for the plasma concentration to decrease by 50%. The half-life is dependent on volume of distribution (Vd) and clearance (renal, hepatic or other) as expressed by the following formula-

$$t½ = 0.693 \times Vd / clearance$$

As the renal clearance decreases, t½ will increase (assuming that Vd is unchanged). It should be noted that active drug metabolites may also be excreted by the kidney and therefore have a prolonged half-life in renal failure.[16]

**Assessment of kidney function:**

Renal function should be measured before prescribing any drug. Because the rate of elimination of drugs excreted by the kidneys is proportional to glomerular filtration rate (GFR).[17]The measurement of GFR can be accomplished by using some exogenous substances. Urinary clearance of inulin, which is the gold standard, is rarely performed except for research purposes because of the limited availability of the substance and the labor intensity of the procedure and the assay.[18] Measurement of GFR can also be possible by utilizing endogenous compound like creatinine or cystatine C. Creatinine clearance is calculated by measuring the amount of creatinine in an accurately timed urine collection and a midcollection plasma creatinine. Dosages of drugs cleared by the kidney should usually be adjusted according to creatinine clearance.[19] It can be quickly estimated by measuring the child‘s serum creatinine and length.[20]

CCr = Length(cm) × k/ Plasma Cr(mg/dl)

**Different constant values(k) for schwartz formula for the estimation of GFR**

| | Cr mg/dl | Cr μmol/L |
|---|---|---|
| Low birth wt infants(<1 yr) | 0.33 | 29.2 |
| Full term infants (>1 yr) | 0.45 | 39.8 |
| Children (2-12 yrs) | 0.55 | 48.6 |
| Females (13-21 yrs) | 0.55 | 48.6 |
| Males (13-21 yrs) | 0.70 | 61.9 |

It is important to understand that the normal relationship among serum creatinine, length and GFR is altered in disturbances of creatinine biosynthesis (e.g. muscular disease and malnutrition) and in clinical settings where the serum creatinine is rapidly changing (e.g. acute renal failure and dialysis). In these situations, a timed urine collection is required for an accurate estimate of GFR.

**Aspects of drug dosing in children with reduced renal function:**

Adjustment of dosage and frequency of a drug in children with impaired renal function is often delicate to calculate. Several factors and issues should take under consideration for prescribing drugs during impaired renal function of a child. Most studies on drug dosage in patients with renal failure are performed in adults. Thus, off-label use is common in paediatrics. To overcome these problems and improve the safety and efficacy of pharmaceuticals for children, Senate and House of Representatives of the United States of America enacted the “Best Pharmaceuticals for Children Act” in January 4, 2002 (Public Law 107-109).[21] Similar legislation is also initiated in Europe for clearing the way for appropriate clinical trials in children.[22] In one study (1999) over 90% of neonates and 70% of paediatric patients were receiving a drug which was not approved in the paediatric population.[23] Most drug dosing are based on `targeted effects` or `concentration effects`. Children even in good renal function metabolize drugs differently than adults. Renal dysfunction adds a further level of complexity to drug dosing.

**Basic principles of drug dosing**

Following basic principles of drug dosing are needed to be considered in patients with impaired renal function:

1. Drug therapy should be limited to the smallest possible number of substances to reduce accumulation of toxic metabolites that may result in unknown or unexpected interactions.[24]
2. Modification of drug doses in renal disease is usually necessary only when the glomerular filtration rate (GFR) is less than 30–40 ml/min/ 1.73m$^2$.[25]
3. Drugs with long plasma half-lives need to extend the dosing interval. This may help to improve the patient's compliance by simplifying drug schedules but can fluctuate the plasma concentration. For example, glycopeptide antibiotic, Vancomycin.[26]
4. Drugs with a narrow therapeutic range need to reduce the dosage size instead of the interval. Because prescription of these drugs in impaired renal function may result in toxic or nontherapeutic levels. So these drugs dose should be reduced proportionally to the predicted reduction in drug clearance. This may be advantageous for drugs in which a relatively constant steady-state level is desired, such as antibiotics or antiarrhythmic drugs with short plasma half-lives.[24]
5. Though most published guidelines do not recommend a loading dose but the volume of distribution of many drugs, especially hydrophilic antibiotics, including â-lactams, cephalosporins, and penems, are significantly increased in the presence of reduced kidney function, the administration of aggressive loading doses (25–50% greater than normal) are highly recommended specially the drug with long half-life.[27]
6. Drug monitoring should be performed in reduced renal function if facilities are available. Drugs such as aminoglycoside antibiotics or certain cardiac glycosides have a narrow therapeutic range and almost entirely depend on renal excretion for their elimination. Regular monitoring of plasma levels is imperative for these drugs.

**Effects of dialysis on drugs:**

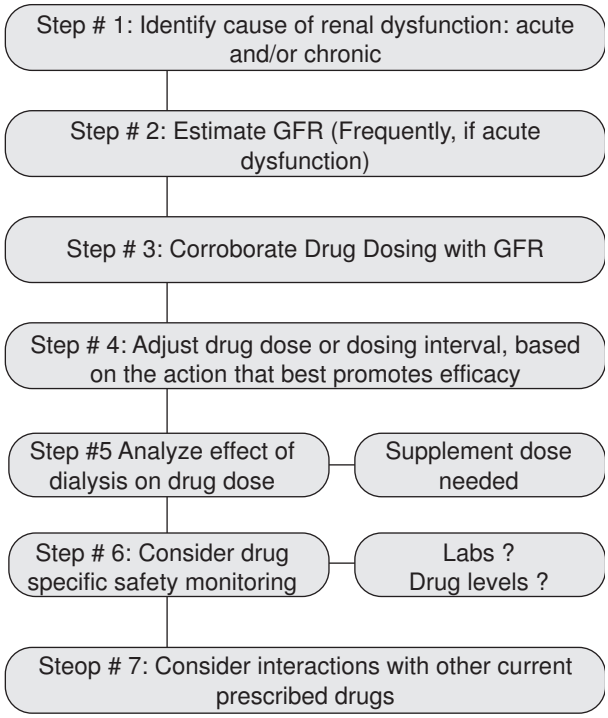
Drug removal during dialysis is an important factor to consider when prescribing drug therapy for the patient with ESRD. Among variety of factors, dialyzer pore size or flux, surface area, ultrafiltration rate and blood flow rate are probably the most important. During dialysis drug clearance occurs by the processes of diffusion and convection. Drugs with small molecular weights are removed mainly by diffusion, whereas drugs with middle or large molecular weights are removed by convection.

Drug removal during haemodialysis is a function of the dialysis dose, (Kt/V), 'K' being the dialyzer clearance, 't' the time on dialysis and 'V' the urea volume of distribution which is equivalent to total body water. Since total body water is smaller in children, some authors suggested that dialytic drug should be higher in children than in adults, if 'K' and 't' are the same.[28,29]

Some drug characteristics also affect drug dialyzability. These are:

1. Molecular weight and size: Drugs with small molecular size or volume (<500 D) are more readily dialyzable than larger one.
2. Drugs that are highly protein bound (>80%), are poorly dialyzable whereas low protein bound drugs are more readily dialyzable.[30]
3. The volume of distribution of drugs also affects dialyzability. Drugs with low volume of distribution (â-lactam antibiotics, aminoglycosides and glycopeptides), are usually confined to the intravascular and extracellular spaces and therefore are effectively removed by dialysis. On the other hand, drugs with large volume of distribution are usually highly tissue bound and cannot be removed by the dialysis.[31,32,33,34]

**Drug Dosing Strategy in Renal Dysfunction**



## Recommendation for dosage of antimicrobials for children with normal and reduced kidney Function:

## Antibacterial Antibiotics[35-40]

### Aminoglycoside Antibiotics

| Drug | Dose for normal renal function | Adjusment for renal failure GFR *ml/min/1.73m²* | | |
|---|---|---|---|---|
| | | 30-50 | 10-29 | <10 |
| Amikacin | 5-7.5 mg/kg/dose q8h | q12-18h | q18-24h | q48-72h |
| Gentamicin | 2.5 mg/kg/dose q8h | q12-18h | q18-24h | q48-72h |
| Streptomycin | 20-40 mg/kg/dose q24h | 7.5 mg/kg/dose q24h | 7.5 mg/kg/dose q48h | 7.5 mg/kg/dose q72-96h |

### Cephalosporine Antibiotics

| Drug | Dose for normal renal function | Adjusment for renal failure GFR *ml/min/1.73m²* | | |
|---|---|---|---|---|
| | | 30-50 | 10-29 | <10 |
| Cefaclor | 20-40 mg/kg/day q8-12h | 100% | 100% | 50% |
| Cefadroxil | 30 mg/kg/day q12h | 100% | 15mg/kg q24 h | 15mg/kg q36h |
| Cefazolin | 50-100 mg/kg/day q8h | 100% | 25mg/kg/dose q12 h | 25mg/kg/dose q24h |
| Cefepime | 50 mg/kg/dose q8-12h | 50mg/kg/dose q24h | 50mg/kg/dose q24h | 50mg/kg/dose q48h |
| Cefotaxime | 100-200 mg/kg/day q8h | 35-70 mg /kg /dose q8-12h | 35-70 mg /kg /dose q12h | 35-70mg / kg / dose q24h |
| Ceftazidime | 75-150 mg/kg/day q8h | 50mg/kg/dose q12h | 50mg/kg/dose q24h | 50mg/kg/dose q48h |
| Ceftriaxone | 50-100 mg/kg/day q12-24h | 100% | 100% | All doses q24h |
| Cefuroxime Axetil | 30 mg/kg/day q12h | 100% | 15mg/kg/ dose q12 h | 15mg/kg/ dose q24h |
| Cefuroxime Sodium | 75-150 mg/kg/day q8h | 100% | 25-50 mg/kg/ dose q12 h | 25-50 mg/kg/ dose q24h |
| Cephalexin | 25-50 mg/kg/day q6h | 5-10 mg/kg/ dose q8h | 5-10mg/kg/dose q12h | 5-10 mg/kg/ dose q24h |
| Cephradine | 25-50 mg/kg/day q6-12h;For OM:75-100 mg/kg/ day q6-12h | 12.5-50 mg/ kg/dose q12h | 12.5-50 mg/ kg/dose q24h | 12.5-50 mg/kg/dose q36h |

### Miscealneous Antibacterial Antibiotics

| Drug | Dose for normal renal function | Adjusment for renal failure GFR *ml/min/1.73m²* | | |
|---|---|---|---|---|
| | | 30-50 | 10-29 | <10 |
| Azythromycin | 10 mg/kg once, then 5 mg/kg/day q24h | 100% | 100% | 100% |
| Clarithromycin | 15 mg/kg/day q12h | 100% | 4 mg/kg/dose q12h | 4 mg/kg/dose q24h |
| Clinndamycin | Oral: 10-30 mg/kg/day q6-8h; IV: 25-40 mg/kg/day q6h | 100% | 100% | 100% |
| Dapsone | 1-2 mg/kg/day q24h | 100% | 100% | 100% |
| Erythromycin | 30-50 mg/kg/day q6-8h | 100% | 100% | 10-17 mg/kg/dose q8h |
| Imipenem/Cilastatin | 60-100 mg/kg/day q6h | 7-13 mg/kg/dose q8h | 7.5-12.5 mg/kg/dose q12h | 7.5-12.5 mg/kg/dose q24h |
| Meropenem | 60-120 mg/kg/day q8h | 20-40 mg/kg/dose q12h | 10-20 mg/kg/dose q12h | 10-20 mg/kg/dose q24h |
| Metronidazole | 15-30 mg/kg/day q6-8h | 100% | 100% | 4 mg/kg/dose q6h |
| Rifampin | 10-20 mg/kg/day q12-24h | 100% | 100% | 100% |
| Trimethoprim / Sulfamethoxazole | 5-20 mg/kg/day q6-12h | 5-7.5 mg/kg/dose q8h | 5-10 mg/kg/dose q12h | Not recommended, but if need5-10 mg/kg/dose q24h |
| Vancomycin | 10-15 mg/kg/dose q6-8h | 10 mg/kg/dose q12h | 10 mg/kg/dose q18-24h | 10 mg/kg/dose as needed per serum conc. |

### Penicillins

| Drug | Dose for normal renal function | Adjusment for renal failure GFR *ml/min/1.73m²* | | |
|---|---|---|---|---|
| | | 30-50 | 10-29 | <10 |
| Amoxicillin | 25-50 mg/kg/day q8h | 100% | 8-20 mg/kg/dose q12h | 8-20 mg/kg/dose q24h |
| Amoxicillin / Clavulanate | 20-40 mg/kg/day q8h | 100% | 8-20 mg/kg/dose q12h | 8-20 mg/kg/dose q24h |
| Ampicillin | 100-200 mg/kg/day q6h | 35-50 mg/kg/dose q6h | 35-50 mg/kg/dose q8-12h | 35-50 mg/kg/dose q12h |
| Piperacillin | 200-300 mg/kg/day q6h | 50-75 mg/kg/dose q8h | 50-75 mg/kg/dose q12h | 50-75 mg/kg/dose q12h |
| Piperacillin / Tazobactam | 200-300 mg/kg/day q6h | 35-50 mg/kg/dose q6h | 35-50 mg/kg/dose q8h | 35-50 mg/kg/dose q8h |

### Qulnolone Antibiotics

| Drug | Dose for normal renal function | Adjusment for renal failure GFR *ml/min/1.73m²* | | |
|---|---|---|---|---|
| | | 30-50 | 10-29 | <10 |
| Ciprofloxacin | 20-30 mg/kg/day q12h | 100% | 10-15 mg/kg/dose q18h | 10-15 mg/kg/dose q24h |
| Levofloxacin | <5 yr: 5-10 mg/kg/dose q12h >5 yr: 5-10 mg/kg/dose q24h | 100% | All ages: 5-10 mg/kg/dose q24h | All ages: 5-10 mg/kg/dose q48h |
| Oflaxacin | 15 mg/kg/day q12h | 7.5 mg/kg/dose q24h | 7.5 mg/kg/dose q24h | 7.5 mg/kg/dose q48h |
| Doxycyline | >8 yr: 2-4 mg/kg/day q12-24h | 100% | 100% | 1 mg/kg/dose q12h |

**Conclusion:**

In general, dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate. Recommended methods for maintenance dose adjustments are dose reduction, lengthening the dose interval, or both. Usually fluctuations of GFR occur in children with impaired renal function especially in acute kidney injury. So nephrotoxic drugs should be avoided in these situations. Physicians should be familiar with commonly used medications that require dose adjustments.

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