What factors need to be considered when dosing patients on renal replacement therapies?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

Renal replacement therapy (RRT) is indicated when renal function is so poor that the kidneys are barely operational. RRT is used in the management of acute renal failure to remove toxins, excess fluid and to correct biochemical disturbances (1). It also forms part of ongoing regular care in patients with end-stage chronic kidney disease (CKD) where the glomerular filtration rate (GFR) is <15mL/min (1,2).

The main types of RRT are (2):
- intermittent haemodialysis (HD)
- peritoneal dialysis (PD) [automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD)]
- haemodiafiltration (HDF) [may be intermittent or continuous]
- continuous renal replacement therapy (includes continuous arteriovenous haemofiltration (CAVHF)/continuous venovenous haemofiltration (CVVHF),continuous arteriovenous haemodialysis (CAVHD)/continuous venovenous haemodialysis(CVVHD),continuous arteriovenous haemodiafiltration (CAVHDF)/continuous venovenous haemodiafiltration (CVVHDF)

HD and PD are used in the treatment of CKD. Continuous renal replacement therapies are typically seen in intensive care patients with acute kidney injury (AKI). Some intermittent therapies - intermittent haemodialysis, intermittent haemofiltration, intermittent haemodiafiltration, and intermittent high-flux dialysis may also be prescribed for patients in intensive care (3). There are several other 'hybrid' therapies which are outside the scope of this Q&A.

RRT technologies and practices have evolved significantly in recent years. In industrialised societies, the vast majority of continuous renal replacement therapy (CRRT) is now provided using pumped, veno-venous methods (4), whereby blood is driven by a pump through a filter via an extracorporeal circuit, originating from a vein and returning to the same vein (3). In most cases, these have resulted in greater drug clearances (5). Pharmacokinetic studies that formed the basis for many of the drug dosing recommendations used today were performed in the 1980s and 1990s using RRT techniques, such as CAVHF, that are no longer used in current practice (5). In CAVHF filtration is maintained by the patient’s arterial pressure, as blood is supplied from an artery and feeds back to a vein. This achieves a lower drug clearance than current methods of CRRT which use higher ultrafiltration/dialysate flow rates and more efficient filters and avoid the potential hazards of the acute arterio-venous access used historically (4-6). These older studies varied in design, using different haemofilters, blood and dialysate flow rates and ultrafiltration rates; and drug clearance was calculated by various methods. Dosing recommendations based on this older data may result in underdosing of drugs e.g. antibiotics (5). Advice on drug dosage in RRT from the literature may no longer apply to modern RRT (7) and should therefore be interpreted cautiously.

A detailed discussion of these techniques is beyond the scope of this Q&A.

Answer

The factors that need to be considered when dosing patients on RRT are:-
- The drug being used

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**Drug factors**

Drugs which are cleared by the kidneys are usually dialysed, and vice versa, although there are some anomalies (1).

Factors affecting the removal of a drug from the blood by RRT include:

- **Renal clearance as a proportion of total body clearance** – If the renal clearance of a drug is normally less than 25-30% of total body clearance, impaired renal function is unlikely to have a clinically important effect on drug removal (with some exceptions - see note below on non-renal clearance). Similarly, drug removal by RRT will have little influence on total body clearance and dosing adjustments do not have to be considered. However, drugs eliminated by the kidney often undergo substantial removal during RRT and dosing adjustments are frequently needed (8). The higher the degree of drug clearance by the kidneys, the more the RRT affects drug clearance (9).

- **Protein binding** – Highly protein bound drugs (>80%) are not generally removed by RRT because the drug-protein complex is too large (>50,000 Da) for the pore size of the filter membrane (3, 9, 10). However, if protein binding is approximately 50% or less, removal may be significant (6). In critically ill patients with AKI, protein binding values derived from studies in healthy volunteers may not apply. Therefore predictions of drug removal based on protein-binding estimates from healthy subjects will result in inaccurate predictions of drug clearance by CRRT (6). Critically ill patients with AKI often have low albumin values, which may result in an increase in the unbound fraction of many drugs e.g. phenytoin (8).

- **Volume of distribution (Vd) and water / lipid solubility** – A large Vd reflects a drug that is highly tissue bound and lipid soluble. Consequently only a small amount is present in the plasma and available for clearance (1,8). Drugs with a high Vd (>1L/kg) will therefore be removed to a limited extent (6). CRRT may be more effective than intermittent RRT in removing drugs with a high Vd because the equilibrium between the plasma and tissue levels will be constantly changing (8,11). Drugs with a small Vd (<1L/kg) are generally hydrophilic and confined to the vascular space as they are unable to pass through plasma membranes (3). As solutions used in RRT are aqueous, these water-soluble drugs will be cleared by RRT (1,3,6,11). In critically ill patients with AKI the Vd may differ from values obtained in healthy volunteers or may show greater inter- and intra-individual variation e.g. the Vd of aminoglycosides increases by approximately 25% in such patients (8). The Vd of water soluble drugs will increase in patients with oedema or ascites, and decrease in patients with muscle wasting or volume depletion (12).

- **Molecular weight (MW)** Most drugs are small molecules with a MW ≤ 500 Da (13). Examples of middle (500-15,000 Da) and large (>15,000 Da) molecules include vancomycin and infliximab, respectively (14). Small molecules (≤ 500 Da) are readily removed by passive diffusion of solutes across a across a concentration gradient. Larger molecules are removed by convection (see below).

- **Steric hindrance** – Even if a molecule appears small enough to be removed by the RRT process the atomic arrangement of the drug molecule may affect its ability to pass through the RRT membrane (11).

- **Timing of administration** – HD is intermittent and results in rapid drug clearance. In practice this is most important for once-daily drugs – especially antibiotics. These should be given after the HD session, otherwise a proportion of the drug may be removed and its duration of action reduced (1,11,15). However in practice for drugs dosed more frequently dose timing may be left unchanged as complex dosing regimens may reduce adherence to therapy (15). Supplementary doses may be considered for drugs with a low Vd and a narrow therapeutic
range. However, it is preferable to adjust the timing of regular doses in patients receiving HD, rather than adding extra doses, as suggested by some texts (11). For CRRT and CAPD, since these are continuous processes, there is no need to schedule doses around RRT sessions (1).

**RRT factors**

Dose adjustment for RRT is normally only necessary for drugs that require dose adjustment because of the presence of renal failure (but see note below on non-renal clearance). Removal by RRT only replaces glomerular filtration (10), and RRT is usually less effective than the normal kidney (1). Some drugs also undergo renal tubular secretion or reabsorption (10,16). A clinically important example of this is fluconazole, which undergoes substantial tubular reabsorption in the normal kidney. Therefore in a patient on CRRT, the total fluconazole clearance may even be higher than in patients with normal kidney function, as RRT does not replace tubular function; therefore the drug is not reabsorbed (16).

Factors affecting drug removal include (3,6,10,11,12,13,17):

- Dialysate flow rate
- Blood flow rate
- Ultrafiltration rate (plasma water with solutes removed per unit of time)
- Type of membrane used - membrane composition, surface area, electrostatic charge, permeability to water and solutes
- Composition of dialysis fluid
- Administration of pre- or post-dilution replacement solutions and replacement solution flow rate and location (pre- or post- filter)
- Type of vascular access, mechanism of solute clearance

**Filter membrane properties** - The type of membrane used has a major role to play in drug removal. Membrane permeability differs on the basis of the type of RRT used. Conventional low-flux intermittent HD hemodialyzers have smaller pore sizes and are inefficient at removing molecules larger than 500 Da (3). In recent years high-flux dialysis has been introduced into practice and Renal Association guidelines recommend the use of high-flux HD membranes (18). These membranes are made of a semi-permeable biosynthetic material (e.g. polysulfone, polyacrylonitrile) and have large pore-sizes (5,000 -20,000 Da), thus allowing the removal of larger molecules (10). Some drugs e.g. vancomycin, cisplatin, are cleared during high-flux dialysis but not during conventional haemodialysis (19). Filters that are used in CRRT have increased pore size and are effective in removing molecules up to 50,000 Da (3). Some membranes may adsorb significant amounts of drugs to their surface. Adsorption is subject to saturation, and the influence on drug removal will depend on the frequency of filter changes. Solute removal may decrease with an increase in age of the filter, resulting from protein clogging or clotting that occurs over time (3,8,10).

Haemofilters are filters designed to work predominantly in convection mode. In general, these filters have high-flux membranes with high permeability to water and to low- and middle- molecular weight solutes (1000– 12,000 Da) and have high "biocompatibility." Newer designs allow the achievement of powerful, simultaneous convection and diffusion (high-flux HD, HDF). With current CRRT machines, solute exchange can be obtained by convection, diffusion or both, with easier and more precise control over each component of the therapy. Blood, dialysate, and ultrafiltrate flow rates can be controlled accurately with integrated pumps, and greater dialysate or convective flows, and therefore greater diffusive and convective solute fluxes, can be achieved (3).

**Flow Rates** - Although variation exists depending on which mode of therapy and which membranes are used, in general, higher flow rates (blood flow, dialysate flow, ultrafiltration flow) result in increased solute removal (3).
### Table 1. Definitions of terms used (2)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion</td>
<td>The movement of solutes from fluid with a high to a low concentration across a semi-permeable membrane</td>
</tr>
<tr>
<td>Convection</td>
<td>The movement of solutes in fluid across a membrane under pressure</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>The movement of fluid under pressure across a semi-permeable membrane</td>
</tr>
</tbody>
</table>

### Haemodialysis

HD is used in the treatment of CKD and is performed intermittently (e.g. three times a week). In HD, blood is presented to one side of a membrane, and a dialysis solution is presented to the other side (1). Blood and dialysate solution flow in opposite directions ('counter-current') or in the same direction ('co-current'), separated by a semi-permeable membrane. A counter-current configuration is preferred because the average concentration gradient is kept higher along the whole length of the dialyzer (3). Excess fluid is removed by ultrafiltration (see Table 1) and waste products leave the patient's blood and enter the solution by diffusion (1,2). Only molecules of small molecular weight (<500 Da) are readily removed during diffusion. Replacement fluid is not required (3). Increasing blood and dialysate flow rates increases solute clearance. However the efficiency of diffusion is reduced as flow rates increase, so the increased efficiency is not proportional to the increase in flow rates (12). The composition of the dialysate will also affect the diffusion process (11).

### Peritoneal Dialysis

There are two kinds of PD. CAPD involves regularly instilling fluid into the peritoneal cavity during the day, and later draining it. The patient's peritoneum acts as a semi-permeable membrane. APD is the same basic process except that a machine delivers and then drains the fluid at night while sleeping (1). Diffusion and convection of solutes occurs between capillary blood and the dialysis solution in the peritoneal cavity, and osmosis removes excess fluid (2). Factors affecting drug removal include:

- Composition of the dialysate
- Pathology of the peritoneum – peritonitis increases the permeability of the membrane
- Volume and exchange rate of dialysate in the peritoneum
- Molecular weight of drug (see above)
- Osmotic concentration gradient between plasma and dialysate (11).

### Haemofiltration

CAVHF/CVVHF is a continuous, slow process using a highly permeable membrane with larger pores than in HD (1). Water and solutes (including drugs) are removed by convection from the blood as it flows past the membrane (20). Blood is presented to one side of a membrane but there is no solution on the other side; pressure is used to push water and solutes through the membrane and this ultrafiltrate is then removed (20). Large volumes of ultrafiltrate are formed which are replaced partially or completely with appropriate replacement fluids to achieve solute clearance and volume control (3). When replacement fluid is added to blood before the haemofilter this is known as pre-dilution. If replacement fluid is added after the haemofilter this is post-dilution. Pre-dilution results in decreased clearance of drugs, because the drug concentration in the plasma entering the haemofilter is lower than the plasma drug concentration in the patient’s circulation due to dilution by the replacement fluid (13).

### Haemodiafiltration

HDF is a hybrid of HD and HF (simultaneous diffusion, ultrafiltration and convection). This gives clearance of small, middle and large molecules. Blood is withdrawn as for HD and passes through a high-flux dialyser. This has the ability to remove large volumes of extracellular fluid and molecules up to 50,000 Da requiring the infusion of replacement fluid which can be added pre- or post- filter (2,3).
Dosing in different types of RRT in the absence of specific guidelines

In this scenario the patient can be dosed in accordance with the theoretical glomerular filtration rate (GFR) achieved by that particular mode of RRT. It is important to know the type of RRT and membrane used as clearances will vary (11), as outlined above. If there are no specific guidelines on how to dose a drug in a particular RRT system then for HD and CAPD use a dose as would be used for a GFR of less than 10mL/min. In practice, although it is recognised that haemofiltration is worse at drug clearance than haemodiafiltration, renal units tend to dose patients on either as if they have a GFR of about 15-25 mL/min (1).

Solute removal and drug clearance are most effective with CVVHDF, followed by CVVHD, CVVHF and then intermittent renal replacement therapies (3,9).

Table 2. Dosing schedule in different types of RRT (11,14)

<table>
<thead>
<tr>
<th>Renal replacement therapy</th>
<th>Typical theoretical GFR achieved during therapy (mL/min)</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent HD</td>
<td>150-200 during dialysis (0-10 between dialysis periods)</td>
<td>If a drug is likely to be removed by HD it should be given after the procedure and not before (11).</td>
</tr>
<tr>
<td>Intermittent HDF</td>
<td>Intermittent HDF removes drugs more efficiently than HD, although there is limited information in this area. The Renal Drug Handbook /Database (RDH) gives guidance on dosing in HDF for some drugs where published information is available (14).</td>
<td></td>
</tr>
<tr>
<td>CAPD (4 exchanges daily)</td>
<td>5-10</td>
<td>See above</td>
</tr>
<tr>
<td>CAVHF</td>
<td>0-15</td>
<td>The RDH does not give many specific guidelines for CAVHF/CVVHF, but comments that dosing schedules will be similar to CAVHD/CVVHD even though the drug clearance capacity of CAVHF/CVVHF may be lower (14).</td>
</tr>
<tr>
<td>CVVHF</td>
<td>15-25</td>
<td></td>
</tr>
<tr>
<td>CAVHDF</td>
<td>20</td>
<td>See above</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>30-40</td>
<td>Certain drugs e.g. antibiotics may undergo removal to a considerable degree by CVVHDF (2). The RDH gives guidance on dosing in CVVHDF for some drugs where published information is available (14).</td>
</tr>
</tbody>
</table>

Patient factors affecting choice of dose in RRT

- **Condition being treated**

In many situations it is important not to underdose the patient, e.g. in the treatment of severe infections, there is a risk of sub-therapeutic antibiotic plasma levels resulting in therapeutic failure and the emergence of resistant organisms (6, 21). Considerable inter-individual variability in antibiotic clearance by CRRT has been demonstrated, which cannot always be explained by differences in effluent (dialysate plus ultrafiltrate) flow rates (22). Therefore caution has to be exercised when using data from studies and case reports to guide dosing of antibiotics in patients on CRRT (21).
Individualised dosing of antibiotics with therapeutic drug monitoring, if feasible, has been suggested (22). The pharmacokinetics of drugs will be affected by the critical illness that is associated with the patient’s renal impairment. For example patients with septic shock may exhibit higher $V_d$ due to capillary leakage and aggressive fluid resuscitation. However, cardiogenic shock involves peripheral vasoconstriction which should have no effect on the $V_d$ (23).

- **Residual renal function**
  Patients may have some residual renal function, which will contribute to drug excretion. This has to be accounted for in adjusting the dose. However their serum creatinine may fluctuate markedly and should not be used to estimate GFR (15). Drugs eliminated predominantly by the renal route will be removed by both kidneys and CRRT, with the greater role being played by the kidneys. As kidney function improves, the percentage of drug eliminated by CRRT declines (6).

- **Pharmacokinetic changes induced by renal failure**
  - **Protein binding** – see above - ‘Drug factors’
  - **Volume of distribution** – see above - ‘Drug factors’
  - **Non-renal clearance and presence of active and/or toxic metabolites** – The pharmacokinetics of some drugs which undergo hepatic clearance via CYP3A4 and via drug transporters such as OATP and P-gp are altered by renal impairment. This may result in the accumulation of active or toxic water-soluble metabolites, which would normally be renally excreted (3,24). These metabolites may be removed by RRT, but often data are lacking on the amounts removed and their activity or toxicity (19,24). For some drugs with multiple elimination pathways (e.g. renal plus biliary for piperacillin) the presence of AKI appears to cause a relative upregulation of non-renal pathways. This causes the antibiotic concentration to be lower than predicted by the reduction in renal function (25).

**Drug factors affecting choice of dose in RRT**
- **Therapeutic index** – Most drugs have a broad therapeutic index, therefore a rigorous adjustment of doses in patients undergoing RRT is unnecessary. However, for drugs with a narrow therapeutic index e.g. aminoglycosides, dosage adjustment and where available, serum drug level monitoring are essential (20).
- **Chronic administration versus single and loading doses** – Single and loading doses do not usually need to be altered in renal failure (12,26) even if the drug has a narrow therapeutic index, because accumulation is unlikely (19). Initial doses of a course of a drug e.g. antibiotic, that requires an immediate therapeutic effect should not be reduced, as the time to reach therapeutic levels may otherwise be prolonged (26 ). Maintenance doses and frequency will depend on the type of RRT and the drug being used (11).

**Summary**
- There are a number of inter-dependent factors that need to be considered when dosing patients on RRT. Consider the drug, the patient and the type of RRT.
- Alteration of drug dosage is usually only necessary if renal clearance exceeds 25% of total body clearance.
- Drugs which are cleared by the kidneys are usually dialysed, and vice versa, although there are some anomalies.
- Dose adjustment for RRT is normally only necessary for drugs that require dose adjustment because of the presence of renal failure. No RRT is as effective as the normal kidney – so for most drugs, doses used will never be larger than those recommended in normal renal function.
- Physicochemical drug characteristics affecting drug removal include protein binding, volume of distribution, water/lipid solubility, and molecular weight. Drugs that are highly protein bound (>80%) and/or have a large $V_d$ (>1L/kg), are unlikely to be removed to a significant degree. In general, very large molecules are less likely to be removed than smaller ones.
- Pharmacokinetic studies that formed the basis for many of the drug dosing recommendations used today were performed in the 1980s and 1990s using less efficient
techniques of RRT than those employed currently. These studies varied in design, used different haemofilters, blood, dialysate and ultrafiltration rates and calculated drug clearance by different methods. Advice on drug dosage in CRRT from the literature should therefore be applied cautiously to individual patients. Dosing recommendations based on this older data may result in underdosing of drugs e.g. antibiotics.

- In patients on HD, dose after the dialysis session otherwise a proportion of the drug may be removed during the HD session and its duration of action reduced. For CRRT and CAPD, since these are continuous processes, there is no need to schedule doses around RRT sessions.
- For toxic drugs, and for drugs with a narrow therapeutic index, drug monitoring with measurements of plasma concentrations, where available, and monitoring of the patient for therapeutic response and adverse effects, are essential.

**Limitations**

- A detailed discussion of the main types of RRT is beyond the scope of this Q&A.
- Other techniques of RRT in use, such as slow continuous ultrafiltration (SCUF) or sustained low efficiency dialysis (SLED) and various hybrid therapies, are not discussed here.
- Please see Q&A https://www.sps.nhs.uk/articles/what-factors-need-to-be-considered-when-dosing-patients-with-renal-impairment-2/ for factors to be considered when dosing patients with renal impairment.

**References**

24. Bailie GR, Mason NA. Bailie and Mason’s 2014 Dialysis of Drugs. Renal Pharmacy Consultants, LLC. Saline, Michigan, USA. p. 3.

Quality Assurance

Prepared by
Julia Kuczynska, South West Medicines information and Training, Bristol (based on earlier work by Richard Leung and Julia Kuczynska)

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Checked by
Michèle Skipp, South West Medicines Information and Training, Bristol

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Search strategy

- Medline (PubMed): [exp *RENAL INSUFFICIENCY or “KIDNEY FAILURE” or “RENAL FAILURE” or exp*RENAL REPLACEMENT THERAPY] and [exp*DRUG ADMINISTRATION SCHEDULE or exp *PHARMACOKINETICS] [Limit to: Publication Year 2015 – current (2017) and HUMAN]
- Embase: [exp*KIDNEY FAILURE or exp *ACUTE KIDNEY FAILURE or exp *CHRONIC KIDNEY FAILURE or exp *CONTINUOUS RENAL REPLACEMENT THERAPY/ or exp *HEMOFILTRATION/ or exp *RENAL REPLACEMENT THERAPY/ ] and [exp *DRUG ADMINISTRATION or exp *PHARMACOKINETICS] [Limit to: Publication year 2015 – current (2017) and HUMAN]
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