Principles of drug dosing during Sustained Low Efficiency Dialysis (SLED) and Sustained Low Efficiency Diafiltration (SLED-f) version 1

The information contained in this document has been compiled from a range of sources and from the clinical experience of the authors, all of whom are members of the UK Renal Pharmacy Group and are involved in the pharmaceutical care of renally-impaired patients. As such, some of the information contained in this document may not be in accordance with the licensed indications or use of the drug.
This document is not intended to offer definitive advice or guidance on how drugs should be used in patients on Sustained Low Efficiency Dialysis (SLED) and Sustained Low Efficiency Diafiltration (SLED-f). Due to the paucity of data there is limited evidence-based information available in this patient population. Dosing should always be adjusted according to the clinical situation and the patient.
This document contains no information on drug interactions or side-effect profiles. For information on these, users are advised to refer to the Summary of Product Characteristics, the British National Formulary, package inserts or other product data.

Terminology and acronyms

- CAVH - continuous arterio-venous haemofiltration. The precursor to CVVH, employing arterial pressure as the circuit pump.
- Convection ("solvent drag") - the movement of solutes in fluid across a semi-permeable membrane under pressure (associated with the fluid being removed during ultrafiltration). Convective transport is independent of solute concentration across the membrane. As long as the molecule can easily pass through the membrane pores, the rate of transfer by convection is independent of the molecule size therefore convection may remove larger molecule sizes than diffusion.
- CRRT - continuous renal replacement therapy. Generic term for continuous renal replacement therapy modalities used in the critical care setting, such as CVVHF, CVVHD.
- CVVH - continuous venous-venous haemofiltration. Relies solely on convection for solute clearance.

- CVVHD - continuous venous-venous haemodialysis. Relies on diffusion for solute clearance.
- CVVHDF - continuous venous-venous haemodiafiltration. Relies on diffusion and convection for solute clearance.
- Diffusion - the movement of solutes from a high concentration to a low concentration across a semi-permeable membrane. Clearance of solutes by diffusion is inversely proportional to the size of the molecule, hence diffusion is good for small molecule clearance. Diffusion is also influenced by molecular charge and protein binding.
- Haemofiltration fluid - a sterile, isotonic replacement fluid that is added to the blood to replace fluid volume and electrolytes during haemofiltration.
- HD – haemodialysis. Utilises diffusion as main mode of solute removal, with water removal by ultrafiltration. Requires ultrapure RO (reverse osmosis) water and ready-made concentrate to generate dialysate, or pre-mixed dialysate bags.
- HDF – haemodiafiltration. Combines diffusive and convective transport using a high-flux filter, a high ultrafiltration rate, countercurrent dialysate and replacement fluid. The combination is theoretically useful because it results in good removal of both large and small molecular weight solutes. Replacement fluid can be administered either pre or post filter.
- High flux dialyser/filter – synthetic membrane (e.g. polysulfone, polyacrylonitrile) with larger pore-sizes than low flux dialysers, allowing the removal of larger molecules up to 20,000 Daltons[6,9].
- HF – haemofiltration. No dialysate is used, a positive hydrostatic pressure drives water and solutes from the blood compartment across a highly permeable filter membrane to the filtrate compartment (ultrafiltration); solute movement is entirely dependent on convection.
- IHD - intermittent haemodialysis. Traditionally delivered during a 3-5-hour session 3 times a week.
- IHDF - intermittent haemodiafiltration.
- Low flux dialyser/filter – cellulose membrane with a small pore size only allowing clearance of molecules smaller than 500 Daltons[9].
- Online HDF – online haemodiafiltration. Sterile, isotonic haemofiltration replacement fluid is produced by the dialysis machine. Note online generation of haemofiltration fluid will require an ultrapure water source.
- PIRRT – prolonged intermittent renal replacement therapy. See SLED. PIRRT includes both convective (i.e. hemofiltration) and diffusive (i.e. haemodialysis) therapies, depending on the method of solute removal
- RO water - reverse osmosis water. Tap water that has undergone treatment to remove bacteria, endotoxins and impurities to render it safe for use with haemodialysis.
- RRT – renal replacement therapy. This includes all forms, such as IHD, CRRT, SLED and peritoneal dialysis.
- SLED – sustained low efficiency dialysis. Also known as slow low efficiency dialysis/slow extended daily dialysis.
- SLEDD - sustained low efficiency daily dialysis
- SLED-f – sustained low efficiency haemodiafiltration. Combines SLED with on-line hemodiafiltration.
- Ultrafiltration - the movement of fluid under pressure across a semi-permeable membrane.

Introduction

During the *Coronavirus* (*COVID*-19) pandemic 2020, the need to provide renal replacement therapy (RRT) to an increasing number of critically ill patients presented a number of challenges to renal and critical care units. RRT on the critical care unit is usually performed continuously (continuous renal replacement therapy/CRRT), however problems with supplies of CRRT consumables and haemofiltration fluid, and concerns over machine capacity led to critical care units looking at methods of providing intermittent RRT without the requirement for haemofiltration fluids and to allow treatment of multiple patients with one machine in a 24-hour period.

Summary of intermittent versus continuous renal replacement therapies

All forms of renal replacement therapy utilise a filter containing thousands of hollow fibres made of semipermeable membrane.

In intermittent haemodialysis (IHD), blood is removed from the patient via an arterial line and pumped through the dialysis circuit to the filter. A buffered crystalloid solution (dialysate) is pumped in the opposite direction outside the fibres. The concentration gradient produced by the opposing blood and dialysate flow directions facilitates movement of solutes across the membrane by diffusion from high to low concentration. Excess fluid is removed from the blood by ultrafiltration, with the dialysate compartment having a higher osmolality and being kept at a lower pressure relative to the blood compartment. The dialysed blood is then returned to the patient via a venous line. Systemic anticoagulation with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) is usually required for the duration of IHD to prevent clotting of the extracorporeal circuit. The machine can be run without the use of dialysate to provide isolated ultrafiltration (fluid removal).

As IHD is a relatively short intermittent process it requires high blood and dialysate flow rates in order to be effective. Standard flow rates for IHD are ≥300mL/min for blood and ≥500mL/min for dialysate[7]. Higher dialysate flow rates increase diffusive solute clearance but can cause disequilibrium due to rapid changes in electrolytes. Removal of large amounts of fluid in the short time frame of IHD can also increase haemodynamic instability.

The most common method of CRRT used in critical care units is continuous venous-venous haemofiltration (CVVH). Blood is removed from the patient via one lumen of a venous line and pumped through the dialysis circuit to the filter. The filters used for haemofiltration have larger pore sizes than in haemodialysis and are highly permeable to fluids and solutes. Unlike in IHD, dialysate is not used. Instead, a positive hydrostatic pressure created on the blood side of the filter drives water and solutes across the filter membrane into the filtrate compartment. Molecules that are small enough to pass through the membrane are dragged across the membrane with the water by the process of convection (“solvent drag”). The filtrate is discarded and to prevent hypovolaemia a sterile, isotonic replacement fluid (haemofiltration fluid) is added to the blood to replace fluid volume and electrolytes. The rate of fluid removal (ultrafiltration rate) is controlled by the blood pump speed. Hemofiltration rates of 1L/hr mean that 1L of fluid is removed from the patient's blood and eliminated as filtrate every

hour and 1L of replacement fluid is returned to the patient. Additional fluid removal parameters can be set on top of this. Different haemofiltration fluid compositions are available depending on the patient's requirements and can either be added before the filter (pre-dilution) or after (post-dilution). The post-dilution method is most common and allows a more accurate fluid balance, but has problems with clotting if the blood becomes too concentrated at the filter. Pre-dilution mode may prolong the filter life but reduces solute removal and requires increased haemofiltration fluid usage. The blood is then returned to the patient via the second lumen of the venous line. As with IHD, anticoagulation is often required to prevent clotting of the extracorporeal circuit. This can either be delivered systemically (i.e. heparin) or regionally (citrate) and is required continuously whilst on CRRT.

Advantages of CVVH over IHD include the ability to remove larger volumes of fluid per day as it is carried out over a longer time interval. The continuous nature of CVVH allows slower and better control of fluid balance, with reduced risk of hypovolaemia and hypotension. CVVH also allows a more gradual change in electrolytes with reduced risk of disequilibrium. Typical blood pump speeds used with CRRT are usually in the region of 100-250mL/min[8].

Disadvantages of CRRT compared to IHD include cost (largely due to pre-prepared haemofiltration fluid and consumables) and increased complexity and staff training.

Sustained Low Efficiency Dialysis (SLED) and Sustained Low Efficiency Diafiltration (SLED-f)

SLED is a hybrid of IHD and CRRT, consisting of prolonged haemodialysis utilising conventional IHD equipment, run at lower blood pump speeds and dialysate flow rates over a longer time period – typically 8-12 hours. This is often delivered daily as opposed to three times a week with IHD. Other terms used include prolonged intermittent renal replacement therapy (PIRRT), slow low efficiency dialysis, sustained low efficiency daily dialysis (SLEDD) and extended daily dialysis (EDD).
Note some references define PIRRT as using conventional CRRT machines running at higher prescribed clearances for intermittent durations (e.g. 8–12 hours). **It is therefore extremely important that healthcare professionals understand the modality being employed.**

The lower blood and dialysate flow rates used with SLED allow solute and fluid removal to occur at a slower rate over a longer duration compared to IHD. Typically blood and dialysate flow rates of 100-300 mL/min are used with SLED[3]. The blood pump speeds used with SLED are still higher than those used with CRRT.

As with IHD, SLED usually requires systemic anticoagulation with either UFH or LMWH to prevent blood from clotting in the extracorporeal circuit.

Some centres have utilised machines for intermittent haemodiafiltration (IHDF) to provide SLED-f (Sustained Low Efficiency Haemodiafiltration) which combines SLED with on-line haemodiafiltration. SLED-f utilises high flux membranes and therefore allows higher convective clearance of larger solutes[5], however is a more complex modality to run.

Advantages of SLED versus CRRT and IHD

- Reduced ultrafiltration (fluid removal) rate compared to IHD facilitates fluid removal in patients with haemodynamic instability who are unable to receive IHD due to hypotension or who require inotropic support.
- Reduced rates of solute removal compared to IHD minimises intradialytic solute disequilibrium.
- Extended treatment duration and increased treatment frequency allows a greater overall "dialysis dose" to be delivered compared to IHD.
- Intermittent nature of SLED compared to CRRT allows patients to undergo other procedures or investigations between sessions and facilitates the use of one machine for multiple patients in a 24-hour period.
- SLED requires intermittent anticoagulation compared to continuous anticoagulation with CRRT
- SLED uses conventional IHD machines, dialysers and dialysate concentrates rather than ultrafiltration fluids.
- SLED is reported to be cheaper to perform than CRRT[2, 3], largely due to the use of routine dialysate concentrates rather than expensive hemofiltration replacement solutions.

Disadvantages of SLED versus CRRT and IHD

- Staff training/unfamiliarity with process on the critical care unit.
- Lower clearance of middle and larger molecules/solutes compared to CVVH[2,4]
- Increased risk of extracorporeal circuit clotting compared to IHD due to reduced blood and dialysate flow rates. This may be of particular relevance in COVID-19 disease which is known to be associated with a hypercoagulable state. Use of SLED-f with replacement fluid administered pre-filter may overcome this issue.
- SLED modalities employing IHD machines may require a reverse osmosis (RO) ultrapure water supply for the dialysate – this may not always be readily available in some critical care units. Note there are some IHD machines that are able to create dialysate using tap water or use pre-mixed dialysate bags.

Drug clearance during RRT

Drug clearance during RRT is influenced by a number of factors. UK Medicines Information have produced a comprehensive guide on factors to consider for drug dosing in patients on RRT[9]. This is summarised below.

- Filter membrane permeability and properties

Historically IHD utilised “low-flux” filters with small pore sizes only allowing clearance of molecules smaller than 500 Daltons[9]. Nowadays many units employ the use of “high flux” filters for IHD which have larger pore sizes and allow the removal of solutes with a molecular size of up to 20,000 Daltons[6,9]. Filters used in CRRT have significantly increased pore sizes and are effective in removing molecules up to 50,000 Daltons[9]. When evaluating the literature around drug dosing with RRT and when making decisions for an individual patient in clinical practice it is therefore extremely important to understand the type of filter membrane being used.

- RRT modality/mechanism of solute removal.
  Most solute removal during IHD and SLED is by diffusion with some convection. Rates of diffusion of solutes across the membrane is dependent on molecular size and the concentration gradient of that solute across the membrane, which in turn is influenced by blood and dialysate flow rates. Usually diffusion is the most effective method for removal of small molecules (<500 Daltons[9]).

  Convective transport is independent of solute concentration across the membrane. As long as the molecule can easily pass through the membrane pores, the rate of transfer by convection is independent of the molecule size therefore convection may remove larger molecule sizes than diffusion. Rates of convection are dependent on the rate of ultrafiltration, which in turn is dependent on the pressure gradient across the dialysis membrane (transmembrane pressure) created by the blood and ultrafiltrate pumps in the machine. Because haemofiltration uses convection rather than diffusion for solute removal, it has a higher rate of removal of larger molecules compared to IHD and SLED.

- Flow rates
  Increasing blood, dialysate and/or ultrafiltration flow rates will generally increase the clearance of solutes. Although SLED uses lower blood and dialysate flow rates than IHD, the longer duration of SLED compared to IHD may result in equivalent or higher overall clearance rates[2,5].

- Molecular properties
  Molecular size, charge, degree of protein binding, volume of distribution, lipid or water solubility and degree of renal clearance all impact on the ability of a drug to be removed during RRT. Further details are available in the UKMi document on renal replacement therapy[9].

- Other factors
  Degree of residual renal function will determine the clearance of a renally eliminated drug.
  Dialysate composition may also impact on drug clearance, although in practice it is difficult to quantify this.

Drug clearance during SLED and SLED-f

It is likely that SLED will remove drugs to a different degree compared with IHD or CRRT.

During the time of dialysis, drug clearance of small molecules per hour is usually higher with SLED than CRRT[2] and lower than IHD[2,5]. However, because the duration of dialysis in SLED is usually 6 to 12 hours per day, the overall drug clearance per day may be the same or less than is seen with CRRT but greater than with IHD [2,5].

SLED has been suggested to remove less middle molecules in the range 1,000–10,000 Daltons compared to CVVH[4]. SLED-f is proposed to increase convective clearance of middle and larger molecules, but overall clearance remains less than with CRRT[1]

Based on the same principles as drug clearance during IHD, antimicrobials that are likely to have increased clearance by SLED are those with low protein binding, small molecular size, high water solubility and high dependence on renal clearance[9] – although there may be some anomalies.

Timing of drug administration

For medications administered intermittently that are cleared by SLED, the timing of drug administration in relation to the start and duration of SLED will influence overall drug exposure. For medications administrated as a continuous infusion that are removed by SLED, adjustment of the infusion rate for when the patient is on or off SLED needs to be considered.

It is therefore important to consider the timing of drug administration when interpreting or applying pharmacokinetic studies for patients receiving SLED.

Pharmacokinetics and pharmacodynamics

Many pharmacokinetic parameters are altered in critically ill patients with acute kidney injury (AKI) or pre-existing end stage renal disease (ESRD), therefore these parameters also need to be considered when making drug dosing adjustments in critically ill patients receiving SLED/SLED-f.
Oral absorption is often unreliable in critically ill patients and may necessitate parenteral administration of medications. Critically ill patients can have a significantly altered volume of distribution in the presence of sepsis, significant burns or aggressive fluid resuscitation, and the presence of hypoalbuminaemia can result in a higher fraction of unbound drug for highly protein bound dugs. In addition, overall drug elimination can change on a daily as a patient's residual renal function improves or declines, and can also be affected by changes to hepatic metabolism.

The pharmacodynamic profile of an antibiotic, whether its antimicrobial activity is concentration- or time-dependent, may influence the dosing regimen. For concentration-dependant antibiotics such as aminoglycosides, a higher concentration relative to the minimum inhibitory concentration (MIC) of the organism results in greater antimicrobial efficacy. Conversely for time-dependant antibiotics such a beta-lactams and vancomycin, efficacy is related to the time the drug concentration is maintained above the MIC of the organism. For some antimicrobials, such as fluoroquinolones, the ratio of the area under the curve to the MIC during a 24-h time period is important for efficacy.

Knowledge of the pharmacodynamic profile of an antimicrobial agent is therefore an important consideration when deciding on timing of administration relative to the initiation and duration of SLED, with the aim of maximising efficacy and minimising toxicity [5]. Therapeutic drug monitoring if available may be useful.

Adjusted body weight (AdjBW) is often used for dosing water soluble, critical dose medications in obese patients (body mass index [BMI]>30) and where actual body weight (ABW) is >20% above ideal body weight (IBW). Using IBW may result in significant underdosing which may put the patient at risk with critical dose medications. Many on-line calculators and apps are available to calculate BMI, IBW and AdjBW. More literature and dosing advice is being published in support of the use of AdjBW in obesity as for many drugs the licensed dosing information cites the use of IBW. Clinicians are advised to review the literature relevant to individual medications when deciding on the appropriate dosing weight to use . Therapeutic drug monitoring should be used to guide the dosing of antibiotics in obesity if available along with monitoring of clinical response and toxicity. Further studies are needed to provide guidance on how to dose antibiotics in obesity to achieve optimal efficacy and safety.

Summary table of individual agents

The following information has been compiled from the available literature or pharmacokinetics and dosing for other dialysis modalities. Within the literature there is significant variability in the frequency and duration of SLED/SLED-f sessions, blood and dialysate flow rates and type of filter used. For drugs that are dialysed, daily SLED/SLED-f sessions will result in more drug removal than with non-daily SLED/SLED-f. In the latter case, dose adjustment during non-SLED/SLED-f days may be required. Longer durations of sessions will result in more drug removal if a drug is dialysed. In the literature the duration of sessions varied from 5 to 12 hours, with many around 8 hours. Similarly, higher blood or dialysate flow rates will also increase drug removal.

Critically ill patients may require larger doses than those receiving SLED/SLED-f in the general ward setting. In some circumstances it may be appropriate to give normal doses for the first 24 to 48 hours of treatment to ensure rapid therapeutic concentrations and then adjust subsequent doses. **It is therefore extremely important that healthcare professionals consider modality-specific and patient-specific parameters including severity of illness and patient location when interpreting the information below and deciding on a dosing regime.**

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Amoxicillin	Dialysed	IV: 1g or 2g every 8 hours	IV: 1g or 2g every 8 hours	IV: Usual practice in the UK is to give 1g every 8 hours in GFR <10mL/min or IHD[35]. (Note: 1g every 12 hours was recommended in one paper[34])	Based upon limited data in SLED, pharmacokinetics and dosing for other dialysis modalities	2, 25, 34, 35
Anidulafungin	Unlikely	Normal dose: 200mg loading dose then 100mg daily	Normal dose: 200mg loading dose then 100mg daily	None	Limited data – single case report. Highly protein bound and unlikely to be removed by SLED/SLED-f	2, 11, 13, 30
Azithromycin	Unlikely	Normal dose: IV 500mg once daily	Normal dose: IV 500mg once daily	None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities.	30, 35

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Benzylpenicillin	Dialysed	1.8 g every 6 hours	1.8g every 6 hours	600mg - 1.2g every 6 hours depending on severity of infection		2, 35
Caspofungin	Unlikely	Normal dose: 70mg loading dose then 50mg daily (70mg daily if >80kg)	Normal dose: 70mg loading dose then 50mg daily (70 mg daily if >80kg)	None	No data. Recommendation based on pharmacokinetics and anidulafungin case report. Highly protein bound and unlikely to be removed by SLED/SLED-f.	11, 30
Ceftazidime	Dialysed	2g every 12 hours or 1g every 8 hours	2g every 12 hours or 1g every 8 hours	500mg - 1g every 24 hours depending on severity of infection	Higher dose of 2g every 8 hours has been used in critical care to ensure MIC is exceeded 100% of time	2, 5, 23, 30, 35
Ceftriaxone	Unlikely	Max 2g in 24 hours	Max 2g in 24 hours	Max 2g in 24 hours	Not removed by haemodialysis. One case report in PIRRT (haemodiafiltration) found no effect on drug clearance. Recommendation based on pharmacokinetics and dosing for other dialysis modalities	35, 36, 37
Ciprofloxacin	Dialysed	Normal dose	Normal dose	None		2, 11
Clarithromycin	Unlikely	Normal dose	Normal dose	None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities	35

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Co-amoxiclav	Possible	IV: 1.2g BD Oral: 625mg TDS	IV: 1.2g TDS Oral: 625mg TDS	IV: 1.2g BD Oral: None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities. SLED-f more likely to remove middle molecules	35
Colistin	Yes: >10% lost per hour on SLED via high flux filter	Loading dose: 6-10 million units (as per local Trust guidelines) Maintenance dose given 24 hours after loading dose: 3 million units TDS	Loading dose: 6-10 million units (as per local Trust guidelines) Maintenance dose given 24 hours after loading dose: 3 million units TDS	Loading dose: 6-10 million units (as per local Trust guidelines) Maintenance dose given 24 hours after loading dose: 1.5 million units BD	Dose should be given 1-2 hours before commencing SLED. Use therapeutic drug monitoring to optimise dosing	5, 28, 32
Co-trimoxazole	Yes: clearance in SLED higher than IHD, CVVHD, CVVHDF	For PCP treatment: can give up to 120mg/kg/day in 2 divided doses. After 72 hours reduce to 60mg/kg/day in 2 divided doses	For PCP treatment: can give up to 120mg/kg/day in 2 divided doses. After 72 hours reduce to 60mg/kg/day in 2 divided doses	60mg/kg/day in 2 divided doses[35]	Send sulfamethoxazole levels for prolonged courses where possible. Ideally avoid giving doses during SLED/SLED-f	5, 35
Daptomycin	Yes: 23.3% - 52% with high flux filter	6-8mg/kg/day	6-8mg/kg/day	Reduce to alternate day dosing (i.e. consider omitting on non-SLED/SLED-f day)	Doses up to 12mg/kg can be used. Give repeat doses after SLED/SLED-f. TDM can be performed	2, 4, 11, 21, 26

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Doxycycline	Unknown	Normal dose	Normal dose	None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities	35
Ertapenem	Yes	1g daily or 500mg pre and 500mg post SLED	1g daily or 500mg pre and 500mg post SLED-f	Reduce to alternate day dosing (i.e. consider omitting on non-SLED/SLED-f day)		2, 4, 5, 11, 24
Flucloxacillin	No	Normal dose	Normal dose	Maximum 4g/24hours	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities	35
Fluconazole	Yes	800mg loading dose then 400mg BD	800mg loading dose then 400mg BD	400mg once daily		2,10
Gentamicin	Yes	2-2.5mg/kg post SLED or 6mg/kg 1 hour before SLED as 30 min infusion Timing of subsequent doses guided by levels	2-2.5mg/kg post SLED-f or 6mg/kg 1 hour before SLED-f as 30 min infusion Timing of subsequent doses guided by levels	2-2.5mg/kg dependent on levels	Check levels daily. Only re-dose when level <1mg/L Local dosing regimes may differ	4, 5, 11
Levofloxacin	No	250mg-500mg daily	250mg-500mg daily	125mg daily	20% removed by SLED (high flux filter)	2,4,5,11,15, 26,30
Linezolid	Yes	Normal dose	Normal dose	None	30% removed during 8 hours of SLED via low-flux filter	2,4,5,11,15, 30,33

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Meropenem	Yes	1g every 8 hours	1g every 8 hours	1g od	50-78% removed during 6 hours of SLED via high-flux filter	2,4,5,11,12, 16,17,18, 26,29,30
Metronidazole	Yes	Normal dose	Normal dose	None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities	35
Moxifloxacin	Yes	Normal dose	Normal dose	None	Give post SLED 8-35% removed by SLED (high flux, 8 hours)	2,4,5,11,15, 30
Tazocin (piperacillin/ tazobactam)	Yes	4.5g TDS	4.5g TDS	4.5g BD	58% cleared	2,17,26,31
Teicoplanin	Yes (high flux) – although highly protein bound	Give normal loading dose, then reduce after 4th day to a third of the dose daily or normal dose every 72 hours.	Give normal loading dose, then reduce after 4th day to a third of the dose daily or normal dose every 72 hours.	None	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities. Give post SLED. Use therapeutic drug monitoring to optimise dosing where available	35
Temocillin	Yes	2g OD given post SLED	2g OD given post SLED-f	2g every 48 hours	No data – recommendation based on pharmacokinetics and dosing for other dialysis modalities.	35

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Vancomycin	Yes: 25-42% cleared in a 6-8 hour session with high flux filters, with majority in the first few hours	Loading dose 20mg/kg (range given 15–25mg/kg), then monitor levels daily BEFORE SLED. • If pre-SLED level 20–30mg/L give 500mg after 5 hours of SLED treatment • If pre-SLED level less than 20mg/L – give 1g after 5 hours of SLED treatment • If pre-SLED level more than 30mg/L do not give vancomycin BUT recheck level 3 hours after SLED finishes and redose as recommended above.	Loading dose 20mg/kg (range given 15–25mg/kg), then monitor levels daily BEFORE SLED-f. • If pre-SLED-f level 20–30mg/L give 500mg after 5 hours of SLED-f treatment • If pre-SLED-f level less than 20mg/L give 1g after 5 hours of SLED-f treatment • If pre-SLED-f level more than 30mg/L do not give vancomycin BUT recheck level 3 hours after SLED-f finishes and redose as recommended above.	Monitor levels DAILY on non-SLED/SLED-f days and dose according to local vancomycin guidelines.	Do not use continuous vancomycin infusions. Give a loading dose to achieve therapeutic levels quickly. Use therapeutic drug monitoring to optimise dose and avoid toxicity. Target concentrations as advised by microbiology.	5, 19, 20, 22, 29

Drug	Likely dialysability	Dosing during SLED	Dosing during SLED-f	Dose adjustment required for non-SLED/SLED-f days (Note - gaps in SLED/SLED-f of longer than 24 hours may require different advice)	Comments	References
Voriconazole	Yes	Normal dose	Normal dose	None	Accumulation of SBECD solubilising agent seen with IV preparation – use oral route unless benefit of IV outweighs risk. Consider therapeutic drug monitoring to optimise dosing.	10, 14, 30

Conclusion

Drug dosing in intermittent sustained modes of renal replacement therapies used in critically ill patients is highly challenging.

When evaluating and applying the literature on drug dosing during SLED or SLED-f, it is important to consider the renal replacement modality and type of membrane being employed, dialysate and blood flow rates, dialysis duration and frequency, the pharmacodynamic profile of the agent and the patient's clinical picture.

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Document prepared by a working party from the UK Renal Pharmacy Group by the following authors:

Caroline Ashley - Associate Professor UCL School of Pharmacy, Lead Pharmacist Renal Services, Royal Free London NHS Foundation Trust

Rachna Bedi – Senior Lead Renal Pharmacist, Imperial College Healthcare NHS Trust

Paul Clarke - Senior Specialist Renal Pharmacist, Oxford University Hospitals NHS Foundation Trust

Andrea Devaney - Consultant Pharmacist Transplantation and Renal Services, Oxford University Hospitals NHS Foundation Trust

Aileen Dunleavy - Senior Renal Pharmacist, Crosshouse Hospital, Kilmarnock

Pooja M Gudka - Senior Specialist Pharmacist - Renal Services, Royal Free London NHS Foundation Trust

Charlotte Mallindine – Senior Renal Pharmacist, East and North Hertfordshire NHS Trust

Maria Martinez - Consultant Renal and Transplant Pharmacist, University Hospitals of Leicester NHS Trust

Clare Morlidge - Lead Renal Pharmacist, East and North Hertfordshire NHS Trust

Cathy Pogson - Renal Specialist Pharmacist, Portsmouth Hospitals NHS Trust

Christine Sluman - Principal Pharmacist Renal and Emergency Medicine, North Bristol NHS Trust

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