



Clinical guideline :

Symptom control and end of life care in adults with advanced renal disease.

BACKGROUND

These guidelines bring together information and recommendations from the Palliative Care Formulary (PCF8). Prescribing guidance is presented for:

1. Palliative patients in the last weeks/months of life
2. Patients in the last days of life.

Common symptoms of renal failure are:

- Breathlessness (which may relate to fluid overload or acidosis),
- Myoclonic jerks (related to both increased drug toxicity and uraemia),
- Delirium
- Restless legs.
- Nausea (eGFR less than 10 mL/min)
- Itch (eGFR less than 10 mL/min)

Measuring renal function:

eGFR is reported in routine laboratory results using the modification of diet in renal disease (MDRD) formula, it is less accurate at values of $> 60\text{ mL/min}$. (90% of estimates $< 60\text{ mL/min}/1.73\text{ m}^2$ will be within 30% of the true value). Changes in MDRD eGFR are more reliable than single estimates, with a decrease of $\geq 15\%$ likely to represent a true change in renal function. Hospital pathology labs give eGFR based on MDRD and the British National Formulary gives its drug dose adjustments based on this but other dose adjustment calculations (e.g. manufacturers and renal handbook and PCF) are based on Cockcroft-Gault calculation.

For most patients, the difference in renal function estimated using either equation will not lead to a difference in drug dosages. However, consider using the Cockcroft-Gault in the following circumstances:

- At extremes of muscle mass ($\text{BMI} < 18\text{ kg/m}^2$ or $> 30\text{ kg/m}^2$).
- Elderly patients (aged 75 years or older).
- Patients taking nephrotoxic drugs / drugs with narrow therapeutic index if predominantly renally excreted.
- Other comorbidities or clinical concern.

In palliative care patients who are elderly, malnourished, cachectic, and/or oedematous renal impairment may exist even when the serum creatinine or the lab eGFR are within normal limits. It may be prudent to assume that there is at least mild renal impairment in such patients. Even when abnormal, the serum creatinine or the lab eGFR may both underestimate the actual degree of renal impairment.



A baseline serum creatinine and lab eGFR can help to indicate the need for dose modification and serial measurements can be used to monitor the effect of the drug on renal function.

STAGES OF RENAL DISEASE

Table 1: Five stages of chronic kidney disease (CKD) are categorized according to eGFR

CKD stage 1	Normal renal function	
CKD stage 2	Mild impairment (eGFR 60-89 ml/min)	Asymptomatic
CKD stage 3a CKD stage 3b	Moderate impairment (eGFR 45-59 ml/min) Moderate impairment (eGFR 30-44 ml/min)	Asymptomatic Anaemia, fatigue, muscle cramps
CKD stage 4	Severe impairment (eGFR 15-29 ml/min)	In addition: anorexia, nausea, insomnia, neuropathy, gout
CKD stage 5	End stage renal disease (eGFR < 15 ml/min)	In addition: itch, headache, cognitive impairment; death

MANAGEMENT OF COMPLICATION IN CKD

Hypertension:

Where appropriate aim to control hypertension and optimise BP but avoid ACE inhibitors and Angiotensin 2 receptor blockers in advanced nephropathy.

Fluid retention:

The trial of small doses of diuretics is possible but beware risk of rise in creatinine and potential electrolyte imbalance. If severe fluid retention / generalised swelling then may need to consider admission for intravenous or subcutaneous diuretics.

Exposure to renal insults:

Advise patients to keep a record of previous events including what happened, when and how to avoid. To advise patients to avoid dehydration, treat infections promptly and relieve urinary retention.

Increased Phosphate levels:

To ensure full bone profile is checked. Consider phosphate binders and referral to dietician services. Of note: high phosphate, low/normal calcium and high parathyroid hormone levels are expected in patients with stages 3 to 5 CKD.

Anaemia:

Ensure full haematonic screen is sent including ferritin levels. Try to correct iron levels first by administering either oral or intravenous iron and / or Erythropoietin (EPO). Please consult with your local / regional renal team to clarify doses and frequency. Please note oral iron likely to be ineffective in chronic disease due to a chronic inflammatory state.

Glycaemic Control:

Optimise glycaemic control but to be aware of potential hypoglycaemia risk which is common in chronic kidney disease. Reducing doses of diabetic medication may need to be considered.

Table 2: Hypoglycaemic Drugs in CKD

Drug	Excretion	Risk	Recommendation	Caution
Metformin	Renally	Lactic acidosis	NICE guidelines Reduce dose if eGFR between 30-60mls/min Avoid if eGFR <30mls/min	Co-treatment with NSAIDs, Diuretics, Contrast, ACEi's, fluctuating UCE's
Sulphonylureas	Active metabolite excreted through kidney	Severe Hypos	Gliclazide can be used (intermediate acting sulphonylurea) Avoid if <45mls/min	Not eliminated in Dialysis patients. Some drugs (including B-Blockers and warfarin) can increase their free levels
Glinides	Liver	Less hypos	Can be used for CKD/Dialysis pts	
Glitazones	Liver	No dose adjustment	Caution if eGFR <60mls/min Avoid if eGFR <30mls/min	CCF present alongside CKD (as can cause fluid retention)
Gliptins	Linagliptin excreted by liver. All other Gliptins renally excreted	Low risk of hypo	Dose adjustment/reduction advised (With exception of Linagliptin)	Experience is still limited for CKD and Dialysis patients
Insulin	Decrease in renal insulin catabolism		Therapeutic education Adjust if eGFR falls below 60 by 25% Below 20 by 50%	Haemodialysis and Peritoneal Dialysis patients

Metabolic acidosis:



If bicarbonate levels <21 mmol/l consider adding oral sodium bicarbonate 500mg – 1g b.d. / t.d.s. (for cautious introduction and titration if calcium is low and fluid retention present). There is also the option to consider IV Sodium Bicarbonate – please discuss with renal team for further advice.

Hyperkalaemia:

Review medications and if need to stop or reduce doses. Aim to correct any metabolic acidosis present and optimise hyperglycaemia. Consider referral to dietetic services and avoid calcium resins long term. In oncology patients, consider the possibility of tumour lysis syndrome.

Veltassa (Patiomer) can also be considered. This is a non-absorbed cation exchange polymer which contains a calcium – sorbitol complex. Veltassa increases faecal potassium excretion through binding of potassium in the gastro-intestinal tract. Binding of potassium reduced the concentration of free potassium in the gastrointestinal tract, resulting in a reduction of potassium levels.

In cases of acute severe hyperkalaemia where escalation appropriate, transfer to hospital must be considered. If giving calcium salts, the adult renal association advise to achieve the recommended calcium dose of 6.8 mmol: **30ml** of calcium gluconate 10% or **10ml** calcium chloride 10% must be used by slow intravenous injection.

If any further advice is required, please contact the Renal team at Bradford Teaching Hospitals Foundation Trust (via main switchboard 01274 542200) for further discussion.

Alternatively, your local Specialist Palliative Care Services can also be contacted for further advice/ support.

PRESCRIBING GUIDELINES

- Many drugs need dose alteration in renal impairment especially if severe. This includes most analgesics, some antibiotics and antiemetics among others.
- If you are starting a new drug in someone with renal impairment you should check if it needs dose alteration by either using a reliable reference source such as the BNF, PCF8 or the Renal Drug Handbook, or by speaking to a pharmacist.
- When a drug dose modification has been necessary, or for drugs known to cause renal impairment, a clinical review and evaluation of renal function should be carried out within 2 weeks, or at any time if drug-induced nephrotoxicity is suspected, e.g. symptoms such as rash, arthralgia, oedema.
- Table 3 gives some guidance on common analgesics and antiemetics used in palliative care and these are based on recommendations in the palliative care formulary.

PAIN

Paracetamol is safe to use.

Caution with NSAIDs – be aware of increased bleeding tendency. Note there is an increased risk of nephrotoxic effects of drugs, which may be a particular consideration for patients with mild to moderate renal impairment. Decision to prescribe depends on the balance of risks and benefits.



Neuropathic agents.

- Amitriptyline start with low dose and titrate cautiously.
- Gabapentin/pregabalin. Requires dose reduction.

OPIOIDS AND RENAL IMPAIRMENT

In renal impairment and end-stage renal failure, regardless of the opioid used, and whether the patient is on dialysis or not, extra caution is always required. This is particularly necessary in patients with rapidly deteriorating renal function or the acutely unwell, e.g. because of sepsis. Clear written instructions regarding analgesic drug regimens should routinely be provided together with close monitoring. Patients and their carers should be educated about the early symptoms of opioid toxicity and the actions required should they occur.

Opioids differ in their potential to cause toxicity when renal function is impaired. However, the evidence base from clinical studies is limited, and stratification of risk is based on the presence of active metabolites, risk of accumulation, and expert opinion. The pharmacokinetics and pharmacodynamics of opioids are altered by renal impairment. Accumulation of an opioid or active metabolite will lead to a prolonged duration of action and increased toxicity. Changes in plasma protein concentrations or alterations in the blood-brain barrier also increase the potential for toxicity with any opioid. If an opioid is necessary, it is important to:

- start at lower than usual doses
- consider increasing the intervals between doses
- monitor closely for toxicity, both immediate and delayed.

If eGFR is less than 50 ml/min and/or rapidly deteriorating, there should be a review of the opioid prescribed and consideration of conversion from morphine to oxycodone preparations (if applicable). **At the end of life**, UK guidelines suggest it may be appropriate to consider either fentanyl or alfentanil as the strong opioid of choice for patients with severe renal impairment or failure. Experience with this approach is increasing. However, in some settings, the cautious use of a familiar opioid may still be preferred over switching to an unfamiliar (albeit 'renally safer') one. Please seek specialist palliative care advice if needing further guidance in prescribing fentanyl or alfentanil

For patients able to take oral medication, avoid codeine and morphine. Use oxycodone oral solution 5mg/5mL, initially 1.25 to 2.5mg PO as needed (minimum dosage interval 2 hours). Request a medical review if more than TWO as needed doses are required in 24 hours and patient remains symptomatic.

The preferred opioids for background analgesia when pain is mild or stable are Buprenorphine/ fentanyl transdermal patches e.g., Buprenorphine 5 micrograms/hr (approximately equal to 10 mg of oral morphine over 24 hrs, See opioid conversion guide). Use as needed Oxycodone for breakthrough pain.

For subcutaneous route:

If GFR 10 to 30 mL/min

Use oxycodone instead of morphine (unless patient also has synthetic liver dysfunction then refer to liver failure guidelines).



If GFR below 10 or rapidly falling

- Oxycodone as needed can still be used.
- If a regular opioid is required start a continuous SC infusion of alfentanil. Continue with oxycodone SC as needed for breakthrough pain.
- Monitor patient as decreased dose and increased dosing intervals may be required.



Table 3: Prescribing advice for palliative care patients with chronic kidney disease/renal impairment

For further information see: Palliative Care Formulary

Drug	Renal Impairment			Dialysis Clearance		Comments
	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR <30 ml/min	HD*	PD*	
ANALGESICS						
Paracetamol (oral)	Normal starting dose	6 hourly dosing	Start 500mg q6-8h Max 3g/24h	Yes	No	Safe non-opioid Dose reduction when weight <50kg
NSAIDs	CAUTION Consider 50-75% dose reduction	AVOID	AVOID	No	No	Nephrotoxic, □ risk of GI bleed (platelet dysfunction).
Codeine/ dihydrocodeine	Normal starting dose (monitor closely)	AVOID or use small dose and titrate slowly Max 30mg q6h	AVOID codeine: Dihydrocodeine:	No	No	Metabolites accumulate. Reports of severe toxicity in CKD stage 4/5.
Tramadol	Normal starting dose	50mg oral immediate release preparation, 12 hourly (Max 200 mg / 24 hrs)	CAUTION	Yes	Unknown	Use 50mg oral immediate release preparation, 12 hourly for dialysis patients. Risk of confusion/delirium. Drug interactions. Check BNF.
Morphine/diamorphine	75% normal dose	50% normal dose, 6 hourly or consider safer alternative	AVOID or use very small doses – seek advice	Yes Occasionally - post dialysis dosing.	No	CNS depot clears slowly in HD. Metabolites accumulate in PD. Single dose post HD can be used. Monitor closely.
Oxycodone	Normal starting dose	Normal starting dose usually safe, but monitor carefully for toxicity, may require dose reduction	AVOID or use very low dose & monitor closely	Unknown	Unknown	□ half life, and □ excretion of metabolites. Once pain controlled consider switch to transdermal buprenorphine or fentanyl.



Fentanyl	Normal starting dose	Normal starting dose usually safe, but monitor carefully for toxicity, may require dose reduction	May require 50% normal dose	No	No	Can accumulate after longer term use; monitor and adjust dose. Only use when pain stable
Buprenorphine	Normal starting dose	May require 75% normal dose	May require 50% normal dose	No	No	Has an active metabolite which may accumulate, clinical relevance uncertain. Use when pain stable
Drug	Renal Impairment			Dialysis Clearance		Comments
	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR <30 ml/min	HD*	PD*	
Alfentanil (see: guideline)	Normal starting dose	Normal starting dose	Normal starting dose	No	No	Short acting
Hydromorphone	75% normal dose	50% normal dose, 6 hourly or consider safer alternative	AVOID or use very small doses – seek advice	Possible	Possible	Active metabolites all renally excreted therefore risk accumulation.
Methadone	Normal starting dose	Normal starting dose	50% normal dose	No	No	Seek specialist advice re dose and titration
ANTI-EMETICS						
Metoclopramide	Normal starting dose (10mg, 8 hourly)	50% dose, 8 hourly	50% dose, 8 hourly	No	No	Reduced clearance; more risk of arrhythmias and extrapyramidal side effects.
Domperidone	Normal starting dose (10mg, 6-8 hourly)	Normal starting dose (10mg, 6-8 hourly)	Reduce dose frequency to 12hrly	No	No	
Cyclizine	Normal starting dose (50mg, 8 hourly)	Normal starting dose (50mg, 8 - 12 hourly)	Normal starting dose (50mg, 8 - 12 hourly)	No	No	Dry mouth. More CNS side effects. Hypotension, tachyarrhythmias reported.
Haloperidol	Normal starting dose (1.5mg, nocte)	Normal starting dose (1.5mg, nocte)	50% normal dose	No	No	Lowers seizure threshold, ↑ risk cardiac arrhythmias, may accumulate.
Levomepromazine	Normal starting dose (2.5mg-6.25mg, nocte)	Start low & titrate	Start low & titrate	No	No	Sedation at higher doses. Causes hypotension. Lowers seizure threshold.
Ondansetron/ Granisetron	Normal starting dose	Normal starting dose	Normal starting dose	No	No	May help itch, constipating.



BENZODIAZEPINES						
Diazepam	Normal starting dose	Start lower	Avoid if possible, start at 50% dose and slow titrate	No	No	Used for insomnia, anxiety and muscle spasm/ myoclonus. Start lower and titrate dose for all benzodiazepines. Metabolites excreted renally and protein binding is reduced.
Lorazepam	0.5mg, oral, 6 hourly	0.5mg, cautious titration. May need to increase dosing interval	0.5mg, cautious titration. May need to increase dosing interval	No	No	
Midazolam SC	2.5mg 1-2 hourly	Start lower	Start lower & titrate	No	Unlikely	
Temazepam	Normal starting dose	Max dose 20mg, oral	Max dose 10mg, oral	No	Unknown	
Clonazepam	0.5mg, oral, nocte	Start low dose & titrate	Lower dose & titrate	No	Unknown	

Drug	Renal Impairment			Dialysis Clearance		Comments
	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR <30 ml/min	HD*	PD*	
ANTI-EPILEPTICS						
Gabapentin	Starting dose 200mg tds Max dose 600mg tds	Starting dose 100mg tds Max dose 300mg tds	eGFR 15-29: Starting dose 100mg nocte, titrate slowly Max dose 300mg bd eGFR <15(nondialysis/peritoneal dialysis only): Starting dose 100mg on alternate nights, max dose 300mg nocte	Yes	Probable	Parent drug accumulates. Withdraw gradually, over several weeks. HD patients with urine output >100ml/24h: start with 100mg nocte. Consider either supplementary dose after each HD session or time daily dose postHD. For anuric HD patients: start with 100mg stat dose and 100mg after each HD session



Pregabalin	Starting dose 25-50mg bd Max dose 300mg bd	Starting dose 25mg bd Max dose 150mg bd	eGFR 15-29: Starting dose 25-50mg od, max dose 150mg od eGFR <15: Starting dose 25mg od, max dose 75mg od	Yes will need a post dialysis dose	Probable	Withdraw gradually , over several weeks HD patients: dose adjust according to creatinine clearance and to give a supplementary single dose after each dialysis session (see PCF 7 for more details)
Sodium valproate	Oral starting dose 150-200mg, 12 hourly	Normal starting dose	Normal starting dose	No	Unknown	Well tolerated, avoid if liver disease. Titrate slowly.
Carbamazepine	Oral starting dose 50100mg, 12 hourly	Normal starting dose	Normal starting dose	No	No	Drug interactions. Check BNF.
Amitriptyline	Oral starting dose 10mg, nocte	Normal starting dose	Normal starting dose	No	No	Drug interactions, side effects, and contraindications can limit use. Titrate slowly.
Levetiracetam	Starting dose 250mg to 500mg BD, if necessary increase by 250mg500mg every 2 weeks Max 1000mg BD	Start 250mg BD Max 750mg BD	Start 250mg BD Max 500mg BD	Yes	Yes	For PD/HD patients: PO/IV start with 750mg stat then maintenance dose as once daily dose plus supplementary dose 250mg to 500mg after each HD session, or timing the daily dose after HD session.
ANTI-DEPRESSANTS						
Citalopram	Normal starting dose	Normal starting dose	Use with caution	No	No	Check BNF for drug interactions (e.g. with Tramadol). Start at lowest dose and titrate carefully in CKD stages 4/5. Sertraline anti-depressant of choice in end stage renal failure. Citalopram can be used cautiously due to risk of QT prolongation
Sertraline	Normal starting dose	Normal starting dose	Normal starting dose			
Mirtazapine	Normal starting dose	Normal starting dose	Start at low dose and monitor closely. Max dose 30mg po nocte			
Drug	Renal Impairment			Dialysis Clearance		Comments
	Mild: GFR 60-89 ml/min	Moderate: GFR 30-59 ml/min	Severe: GFR <30 ml/min	HD*	PD*	
OTHERS						



Baclofen	Max 5mg, oral, 8 hourly	Max 5mg, oral, 12 hourly	AVOID	Unknown	Unknown	See PCF for further details Withdraw gradually.
Ketamine oral or SC	Oral starting dose 5-10mg, 6 hourly	Normal starting dose	May be tolerated in standard doses but start at low dose and monitor closely	No	Unknown	Little information available. Less than 2-3% of ketamine is excreted unchanged. Can accumulate. Seek specialist advice.
Ranitidine	Normal starting dose	Normal starting dose	50-100% normal dose	Yes	Unknown	Accumulates.
PPIs	Normal starting dose	Normal starting dose	Normal starting dose	Unknown	Unknown	Also use reduced dose in hepatic failure
Fluconazole	Normal starting dose	50% dose	50% normal dose	Yes	Yes	Drug interactions. Check PCF or BNF.
Hyoscine butylbromide (Buscopan) SC	20mg SC, oral, 1-2 hourly	Normal starting dose	Normal starting dose	Unknown	Unknown	Peripheral antimuscarinic side effects Use for respiratory secretions, bowel colic, bladder spasms.

*Dialysis clearance sufficient to require a change in dosing regimen

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References:

Palliative Care Formulary 8th Edition (2022)

The Renal Drug Handbook 5th Edition (2019)

Renal Drug Database: <http://renaldrugdatabase.com/>

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Symptom management for patients in the last days of life

In the context of patients entering the last days of life, review all oral medicines and consider SC route

Pain

- Usually leave buprenorphine and fentanyl patches in place (to avoid reduction in background analgesia) and continue to administer/change as usual.
 - Continue to use as needed analgesia, usually SC oxycodone
 - If an increase in background analgesia is needed a CSCI of oxycodone may be added. Please seek specialist advice if unsure
- If opioid naïve:
 - oxycodone (10mg/mL) 1 to 2mg SC as needed (minimum dosage interval 1 hour). Request medical review if TWO as needed doses have been given in the last 24 hours. Request an urgent medical review if FOUR as needed doses have been given and patient remains symptomatic.
 - Consider starting a continuous SC infusion (CSCI) if 2 or more as needed doses are given in 24 hours.
 - If GFR 10 to 30 mL/min suggest CSCI of oxycodone
 - If GFR less than 10 or rapidly falling suggest CSCI of Alfentanil. Seek specialist palliative advice.
 - Continue SC as needed Oxycodone and dose may not need to be increased.
- If converting from oral oxycodone to 24 hour continuous SC infusion (CSCI) of oxycodone divide the 24 hour PO dose of oxycodone by 2. Prescribe as needed SC oxycodone at a maximum of 1/6th of the background daily dose, low doses may be needed if signs of accumulation and/or toxicity.

Breathlessness

Consider opiate prescriptions in line with pain advice above. If associated with anxiety or agitation, consider anxiolytic prescriptions in line with agitation advice below.

Agitation

- Consider reversible causes.
 - Non drug management is the most important strategy
 - Prescribing advice:
 - Midazolam (10mg/2mL) 2.5 mg to 5mg SC as needed (minimum dosage interval 30 minutes). It is suggested that as needed dose range is prescribed.
 - OR ○ Haloperidol (5mg/mL) 500 micrograms to 1 mg SC as needed (minimum dosage interval 1 hour). It is suggested that as needed dose range is prescribed.
- Max 5 mg/24 hrs

- For both midazolam and haloperidol request medical review if TWO as needed doses have been given in the last 24 hours. Request an urgent medical review if FOUR as needed doses have been given and patient remains symptomatic.

Nausea and vomiting



If on effective antiemetic this can be continued. If unable to take oral medication convert to SC route. The conversion from oral to SC is 1:1 for most antiemetics. Seek advice if unsure

For those with new or anticipated symptoms:

- Haloperidol (5mg/mL), start with a low dose e.g. 500micrograms SC as needed (minimum dosage interval 1 hour). Request medical review if TWO as needed doses have been given in the last 24 hours.
- Levomepromazine (25mg/mL), start with 2.5mg to 6.25mg SC as needed (minimum dosage interval 1 hour). Request medical review if 6.25mg or more has been given in the last 24 hours.
- For persistent symptoms both drugs have relatively long half-lives so may be given as intermittent injections (daily or twice daily) or given by continuous SC infusion.

Respiratory secretions in the last days of life

Non-pharmacological management such as positioning is the most important component of treatment.

- Avoid hyoscine hydrobromide because of its central effects.
- Hyoscine butylbromide is the favoured drug treatment as it is non-sedating,
 - Hyoscine butylbromide (20mg/mL) 20mg SC as needed (minimum dosage interval of 1 hour). Request medical review if TWO or more as needed doses have been given in the last 24 hours.
 - *Note* it is short-acting therefore if effective consider a continuous subcutaneous infusion (typical starting dose 60mg SC over 24 hours).
 - Ensure good mouth care as dry mouth is a side effect

Pruritis

- Treat dry skin with emollients such as Diprobase or zeroderm
- Midazolam for sedation if causing distress and sedation acceptable

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