GUIDELINES FOR PRESCRIBING IN RENAL FAILURE

37.1 GENERAL PRINCIPLES

- Renal impairment constitutes a major source of morbidity and mortality in patients with malignancy. [1, 2]
- Acute renal failure is defined as a sudden decrease in the glomerular filtration rate (GFR) associated with a rise in serum urea and/or creatinine. There is usually, but not always, a reduction in urine output. [3, 4]
- Acute renal failure is often reversible if diagnosed and treated promptly. [3]
- The causes of acute renal failure in cancer patients may be multifactorial (see Table 37.1).

Table 37.1 Causes of acute renal failure in cancer patients [1, 2]

Causes	Comments
Drugs	NSAIDs, mitomycin-C, platinum compounds, methotrexate, ifosfamide, ACE inhibitors, diuretics
Extracellular fluid depletion	Poor oral intake, vomiting or diarrhoea
Hypercalcaemia	
Hyperuricaemia	
Sepsis	Following chemotherapy
Tumour infiltration	
Tumour lysis syndrome	Renal vein or ureter
Urinary tract obstruction	Following chemotherapy

- Chronic renal failure is a long-term condition in which there is reduction in glomerular function. It is often progressive and irreversible. [5]
- Drugs or drug metabolites may accumulate in renal failure, leading to toxicity. Prescribing in renal failure should be approached with caution and should be in accordance with the estimated GFR. [6]
- Evidence suggests that some opioids are safer to use than others. However all patients with renal impairment are at risk of drug toxicity and therefore should be monitored on a regular basis. Signs of opioid toxicity may include visual hallucinations, myoclonus, drowsiness or confusion.[7]
- Long acting opioid preparations should be avoided (e.g. MST®/MXL®) as the metabolites accumulate in renal failure. An exception to this rule is transdermal fentanyl as renal failure does not affect the pharmacokinetics of the drug. [6, 7, 8]

37.2 GUIDELINES

37.2.1 Assessment of acute renal failure

- If acute renal failure is diagnosed, an assessment of the cause should be carried out where appropriate (see Table 37.2).

Table 37.2 Assessment of acute renal failure [3] [Level 2]
Assessment of fluid status
Review of medication. Discontinue nephrotoxic drugs
Baseline bloods e.g. FBC, urea and electrolytes, urate, Ca^{2+}(corr)
Septic screen: including MSSU and blood cultures
Dipstick urine/ measure urine output
Urinary catheterisation
Renal ultrasound

37.2.2 Calculating the degree of renal impairment [5, 9, 10] [Level 1]

- When diagnosing renal failure the serum creatinine may be misleading as it is significantly influenced by muscle mass, age and sex. [5]
- The estimated Glomerular Filtration Rate (eGFR) should be calculated using one of the formulae in Table 37.3. The result may then be used to estimate the degree of renal impairment and the stage of chronic kidney disease (see Table 37.4). Alternatively, on line calculations may be done at www.renal.org/eGFRcalc/GFR.pl
- Clinical biochemistry laboratories can report the eGFR if requested. An estimated GFR should not be used for acute renal failure or in patients on dialysis.

Table 37.3 Formulae for calculations of eGFR [5, 9, 10] [Level 1]	
Modification of Diet in Renal Disease-abbreviated (MDRD) [11]	eGFR (ml/min) = 186 x $(Creat/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if black)
Cockcroft and Gault Equation [12] (males)	eGFR(ml/min) = (140 - age) x weight (kg) x 1.23 divided by Serum creatinine (micromols/l)
Cockcroft and Gault Equation [12] (females)	eGFR(ml/min) = (140 - age) x weight (kg) x 1.04 divided by Serum creatinine (micromols/l)

Table 37.4 Stages of chronic kidney disease (CKD) [5, 13]			
Stage	**GFR (mls/min)**	**Description**	**Complications**
1	>90	Normal renal function	
2	60-89	Mildly reduced renal function	Early hyperparathyroidism
3a 3b	45-60 30-45	Moderately reduced renal function	Renal anaemia, altered bone metabolism
4	15-29	Severely reduced renal function	Acidosis, hyperkalaemia, accumulation of drug metabolites
5	<15	Very severe or end stage renal failure	Anorexia, vomiting, pruritus, sodium retention

37.2.3 Analgesic prescribing in renal failure

- If the GFR is below 30mls/min (Stage 4 or 5 CKD), there is an increased risk of toxic side-effects with all opioids due to drug and metabolite accumulation. Opioids should therefore be used with caution. [7] [Level 2+]
- NSAIDs should be avoided if possible, unless a patient is already on dialysis. If a NSAID must be prescribed, the lowest effective dose should be used and the renal function should be rechecked within five to seven days of starting the drug. [5] [Level 4]
- Table 37.5 suggests guidelines for analgesic use according to the World Health Organisation (WHO) analgesic ladder in patients with severe renal failure (stage 4 and 5) who are able to swallow medication. [14] [Level 2-]
- When prescribing oral strong opioids, the immediate release forms are preferred. [7, 14] [Level 4]
- Once a patient is established on a regular dose of strong opioid, conversion to transdermal fentanyl may be better tolerated as the metabolites are inactive. [7, 14] [Level 4]
- If a patient requires more than three stat subcutaneous doses of a strong opioid, consider starting a continuous subcutaneous infusion. [7, 14] [Level 4]
- Alfentanil is pharmacokinetically the safest analgesic to use in renal failure. The metabolites are non toxic and only 1% is excreted unchanged by the kidneys. The limitations are that it can only be given parenterally and it has a very short half life. Fentanyl is an alternative strong opioid.[15, 16, 17, 18] [Level 3]

Table 37.5 Guidelines for the use of analgesia in patients with renal failure (CKD Stages 4 and 5) [7,14, 15, 16, 17, 18, 26] [Level 3 / 4]

WHO ladder	Name of drug	Dose	Notes
Step 1	Paracetamol	Maximum daily dose 4g orally	Reduce to maximum of 3g if additional liver impairment. Avoid effervescent tablets because of high sodium content.
Adjuvants	NSAIDs	Lowest effective dose	Use is not recommended due to lack of safety data from controlled clinical studies. If prescribed need to monitor renal function closely.
Step 2	Cocodamol 8/500 or 30/500	4 tablets in 24 hours	Use with caution. Accumulation of metabolites may cause profound narcosis and respiratory depression.
	Codeine Phosphate 30mg	120mg in 24hrs (orally)	Use with caution.
	Dihydrocodeine 30mg	120mg in 24hrs (orally)	Use with caution.
	Tramadol	50mg-100mg 6-8 hourly (orally)	Only use immediate release preparation. Start at 50mg and titrate upwards. If creatinine clearance is ≤ 30ml/min give 12 hourly. May be poorly tolerated in Stage 5 CKD.
Step 3	Morphine	Oral Titrate with low starting dose e.g. 2.5mg-5mg 6-8hrly Parenteral Titrate with low starting dose e.g. 2.5mg as required	Use with caution. Accumulation of parent drug and metabolites reported to cause profound respiratory depression and narcosis.
	Hydromorphone	Oral Titrate with low dose e.g. 1.3mg 6-8hrly	Use with caution as limited data. Evidence suggests pharmacokinetic properties safer than morphine. Parenteral preparation available as unlicensed special order
	Oxycodone Hydrochloride	Oral Titrate with low starting dose e.g. 2.5mg-5mg 6-8hrly Parenteral Titrate with low starting dose e.g. 2.5mg subcutaneously as required	Use with caution as limited data. Evidence suggests pharmacokinetic properties safer than morphine, however 10% of parent drug excreted renally therefore toxicity may occur.
	Methadone	Reduce by 50-75% of normal starting dose	Use with caution as limited data. Evidence suggests pharmacokinetic properties safer than morphine.
	Diamorphine	Titrate with low starting dose e.g. 2.5mg-5mg subcutaneously as required	Use with caution. Accumulation of parent drug and metabolites reported to cause profound respiratory depression and narcosis.
	Fentanyl	Transdermal patch for stable pain only	Recommended. Liver metabolism mainly. No toxic metabolites. 10% parent drug excreted renally so may get some accumulation in renal failure. Use may be limited by size of patches and difficulties in titration. Can be given subcutaneously.
	Alfentanil	$1/10^{th}$ dose of diamorphine Use in CSCI only	Recommended. Not excreted renally. Liver metabolism. No toxic metabolites.Do not use rescue doses of alfentanil to titrate the background dose because of its short half life.
	Buprenorphine	Normal dose and interval	Not excreted renally, however very limited evidence for safe use in humans.

37.2.4 Dialysis and opioids [7] [Level 3]

- The role of dialysis and how it affects the clearance of a drug is very complex and depends on many factors including the properties of the parent drug and its metabolites. The technical aspects of the dialysis procedure are also important. [7]
- If a drug is cleared by dialysis, it should be administered after the dialysis procedure. [7]
- Table 37.6 illustrates the effect of dialysis on different strong opioids.

Table 37.6 Effect of dialysis on opioids [7] [Level 3]

Drug	Effect of Dialysis
Codeine	Little evidence. Metabolites not cleared well.
Tramadol	Little evidence. Only slowly removed by dialysis.
Morphine/Diamorphine	45% cleared by haemodialysis. Metabolites cleared less well.
Oxycodone	Little evidence. Properties suggest cleared significantly by dialysis.
Hydromorphone	Little evidence. Properties suggest cleared significantly by dialysis.
Fentanyl	Not cleared by dialysis.
Alfentanil	Little evidence. Properties suggest not cleared by dialysis.
Methadone	Not cleared by dialysis. Wide inter-patient variation.

37.2.5 Other drugs used in palliative care

Gabapentin / pregabalin [6, 27, 28] [Level 3]

- Dosage adjustment is recommended in patients with compromised renal function (see Table 37.7) and/or those undergoing haemodialysis. Gabapentin 100mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 37.7 Dosage of gabapentin in adults based on renal function [27] [Level 3]

Creatinine Clearance(ml/min)	Total Daily Dose [a] (mg/day)
≥ 80	900-3600
50-79	600-1800
30-49	300-900
15-29	150-600 [b]
<15 [c]	150-300 [b]

a *Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).*

b *To be administered as 300 mg every other day.*

c *For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).*

- Pregabalin is eliminated from the systemic circulation primarily by renal excretion as an unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance, dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance as indicated in Table 37.8.

Table 37. 8 Pregabalin dosage adjustment based on renal function [28] [Level 3]			
Creatinine Clearance (ml/min)	**Total daily dose of pregabalin**		**Dose regimen**
	Starting dose(mg/day)	**Maximum dose (mg/day)**	
≥ 60	150	600	bd or tds
≥30 < 60	75	300	bd or tds
≥15 < 30	25-50	150	once daily or bd
< 15	25	75	once daily

Metoclopramide [30] [Level 3]

- Clearance reduced by 50% in renal failure. Increased risk of extra-pyramidal side effects. May want to consider lower initial doses. Titrate as necessary. Patient should be monitored closely.

Haloperidol [29] [Level 4]

- Haloperidol is the drug of choice for uraemia induced nausea.

Bisphosphonates

(See Guidelines on the User of Bisphosphonates in the Management of Malignant Bone Disease for further details)

- To avoid renal toxicity with bisphosphonates, serum creatinine should be checked and hydration status clinically assessed prior to each treatment. The serum calcium should also be checked prior to every infusion. [20, 21] [Level 4]
- The risk of renal failure is directly related to drug infusion time and dosage. High dose zoledronic acid with a short infusion time is especially nephrotoxic. [22, 26] [Level 4]
- Treatment with zoledronic acid and disodium pamidronate should not be initiated in patients with severe renal impairment (Cr Cl < 30mls/min) unless in cases of life threatening hypercalcaemia where the benefits are judged to outweigh the risks. If there is a marked deterioration in renal function following initiation of therapy then treatment should be stopped. It should only be restarted when the serum creatinine has returned to within 10% of the baseline. [23, 24, 25] [Level 4]
- If using bisphosphonates for bone pain it may be clinically appropriate to consider dose reduction or use of a longer infusion time rather than stopping treatment. [20] [Level 4]
- There is a growing body of evidence showing that ibandronic acid is better tolerated in renal failure compared to other bisphosphonates. [24] [Level 2+] However monitoring, dose reduction and longer infusion times are still required if there is severe renal impairment.[20] [Level 4]

Midazolam [29] [Level 4]

- Midazolam metabolites accumulate in renal failure. Patients may be more sensitive to midazolam. The lowest effective dose should be used.

Glycopyrronium [31][Level 4]

- Glycopyrronium accumulates in renal failure and a dosage reduction will be necessary

37.2.6 Management of other symptoms in the dying phase [26] [Level 4]

- Uraemia may cause or contribute to agitation in the dying phase.
- Consider the use of haloperidol if the patient is suffering from delirium rather than agitation/anxiety.
- The renal LCP guidelines give useful information on managing symptoms during the dying phase for patients with renal failure.

37.3 STANDARDS

1. Estimated GFR (e GFR) should be used to determine renal function. [12, 14] [Grade B]
2. In severe renal impairment, drug doses should be reduced and/or dosing intervals increased as appropriate. [15] [Grade C]
3. All patients should be closely monitored for evidence of drug toxicity or drug induced renal impairment. [9, 15] [Grade C]
4. If a non-dialysis patient is started on an NSAID, the renal function should be rechecked within 5-7 days. [6] [Grade D)]
5. In patients with severe renal impairment, alfentanil or fentanyl are the strong opioids of choice for use in a CSCI. [4, 5] [Grade D]

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