Prescribing in Renal Failure: Re-audit
Happy World Kidney Day!
March 14th 2013
Audit Group

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Audit Presentation

- Overview of current Standards & Guidelines and areas reviewed
- Literature review
- ICN Survey - Survey of Practice - Patient Survey
- Renal Specialists Survey
- Updated Standards & Guidelines
- Questions & Comments
Current Standards & Guidelines
Current Standards & Guidelines

- Focus on prescribing in Renal Failure, particularly:
  - Analgesics including opiates, neuropathic agents
  - Bisphosphonates
  - Anti-emetics and end of life drugs
- Emphasis on renal failure in patients with malignancy
S&G: Areas to be reviewed

• Review of prescribing advice in current guidelines, with additional literature review of antidepressants and adjuvant analgesics
• Review of symptom control needs of patients with End Stage Renal Failure and those supported by Renal Replacement Therapy
• Greater emphasis on Renal Failure in those with malignant and non-malignant disease
Renal Failure Audit
Literature Review
Renal Failure: An update
Renal Failure: Classification\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Normal renal function</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced renal function</td>
</tr>
<tr>
<td>3A</td>
<td>45-59</td>
<td>Moderately reduced renal function</td>
</tr>
<tr>
<td>3B</td>
<td>30-44</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced renal function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Very severe, or end stage renal failure</td>
</tr>
</tbody>
</table>

- Prevalence of Stage 3–5 CKD in an age standardised population is 8.5% (10.6% in females and 5.8% in males), there is a dramatic increase in prevalence with age\textsuperscript{1}.

2. Renal Association: CKD Stages
http://www.renal.org/whatwedo/InformationResources/CKDeGUIDE/CKDstages.aspx
eGFR = estimated Glomerular Filtration Rate

- eGFR is the most accurate measure of renal function, as accounts for age and therefore changes in muscle mass
- Renal function declines with age, and many elderly pts have a reduced GFR. This may not be reflected by an elevated creatinine due to reduced muscle mass – therefore using creatinine alone can underestimate the degree of renal impairment
- Calculated using the abbreviated MDRD equation:

\[\text{eGFR} = \frac{186 \times (\text{Creat} / 88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})}{\text{}}\]

- Online calculator - http://www.renal.org/eGFRcalc/GFR.pl

3. Renal Association: About GFR
http://www.renal.org/whatwedo/InformationResources/CKDeGUIDE/AbouteGFR.aspx
Prescribing in Renal Failure

Problems in use of drugs in patients with impaired renal function:

- Altered pharmacokinetics – changes in absorption, tissue distribution, plasma protein binding, metabolism and excretion – often these changes are interrelated/complex.
- Further complicated in pt undergoing Renal Replacement Therapy
- For some drugs – some of these parameters are unknown
- Sensitivity to some drugs is increased, even if elimination is not impaired
- Many side effects are particularly poorly tolerated by renally impaired patients
- Some drugs are ineffective when renal function is reduced

End of Life Care for End Stage Renal Failure Patients/Dialysis Patients
Chronic Kidney Disease (CKD) and ESRF

- No of pts with CKD rising, as are numbers supported by RRT (2004 – 103 per million population).
- Increase in incidence of CKD is most marked in older pts
- 20% of pts with advanced CKD - managed conservatively
- Pts >65 starting dialysis have a 14.5% 5 year survival
- Studies suggest that for older patients with high co-morbidity dialysis may offer no survival advantage
- Sx burden at and of life is similar to cancer patients, with high levels of psychological distress.

Symptom Burden – ESRF patients/RRT patients

- One study found haemodialysis patients reported an average of 10.5 symptoms\textsuperscript{7}.
- Most common symptoms reported in the study – lack of energy, drowsiness, numbness of hands/feet, dry mouth, pain, itch, cough, SOB\textsuperscript{7}.
- Another study looking at potential under treatment of symptoms in haemodialysis patients found only 45% of patients reporting pain received analgesia\textsuperscript{8}.
- Several studies have found QOL is significantly impaired in those with ESRF\textsuperscript{7}.

Symptom Management at EOL for patients with Advanced CKD

- **Pain/dyspnoea** – see opiates Literature Review
- **Nausea** – Haloperidol recommended 1st line, 50% of normal dose. Levomepromazine – 2nd line.
- Suggests avoid Metoclopramide – increased risk of extrapyramidal reactions. Avoid Cyclizine – increased risk of hypotension/tachyarrhythmia.
- **Agitation** – Midazolam at reduced dose.
- **Secretions** – Glycopyrronium 1st line (50% dose reduction), Hyoscine Hydrobromide – increased risk of drowsiness and paradoxical agitation.

Opiates in Renal Failure
Summary of evidence

• Low quality and limited evidence
• No RCTs
• 4 Systematic Reviews
• Observational studies – prospective and retrospective
• Case reports
• Guidelines based on evidence/expert opinion
Morphine

- Most studied and therefore greatest evidence for use in CKD
- 90% of Morphine converted to metabolites – M3G, M6G
- M6G most likely to cause problems
  - multiple studies have shown increased accumulation in patients with CKD\(^5,9,10,11\)
    - Accumulation of M6G linked with toxicity including respiratory depression and CNS effects which can be prolonged\(^5,9,10\)
- Also some small studies showing a lack of correlation between renal dysfunction and toxicity/side effects, but numbers small and patients with more severe renal failure excluded, (e.g. Cr >1.5 x normal)
- Codeine/Diamorphine – assumed to have similar profile as similar metabolic pathways
Tramadol

- Metabolised by liver to O-demethyl-tramadol, 90% of oral dose is excreted by the kidneys.
- Also inhibits noradrenaline and serotonin uptake, so risk of serotonin-type side effects.
- In severe renal impairment there is a 2x increase in elimination half-life, therefore recommended dose interval is increased, and MR preparation avoided\(^9,11\).
- There is mixed evidence for use with case reports of toxicity in renal failure patients -1 case report of a 67 year old man who received 180mg Tramadol post-operatively in 2 hours IV/PCA , renal function not documented\(^12\).
- Also documented clinical experience of safe use in patients with renal impairment at modified doses\(^11\).
Hydromorphone

• Metabolised in the liver to H3G, and other metabolites, which are renally excreted, therefore reduced clearance in CKD.
• H3G thought to have neuroexcitatory actions, leading to agitation, confusion and hallucinations.
• A retrospective case notes review by Lee et al, 2001\textsuperscript{13}, compared 26 pts with normal renal function with 29 pts with impaired renal function (Mean Ur 10.9, Mean Cr 127.5) switched to hydromorphone from morphine
• Found no significant differences in side effects, dose or response to change
• Paramanandam et al, 2011\textsuperscript{14}, reviewed the notes of 54 patients with EGFR <60 taking Hydromorphone. 20% tremor, 20% myoclonus, 48% agitation, 39% cognitive dysfunction – seemed to be a threshold effect.
• Again there are also documented reports of experience of safe use in renal failure again at reduced doses\textsuperscript{3}, as well as case reports of toxicity.
Oxycodone

- Main metabolites – noroxycodone and oxymorphone, their role in analgesic and toxic effects is unclear\(^9\).
- There is prolongation of elimination half-life in renal failure
- Case reports of toxicity in association with oxycodone use in renal impairment with increased sedation and accumulation of oxycodone and its metabolites\(^10\).
- Although limited evidence, thought to be safer than Morphine, due to better side-effect profile, particularly for CNS symptoms\(^15\).
- Some reports of successful use at 75% of dose when GFR 10-50 and 50% of dose when GFR<10, not evidence based\(^16\).
- Overall limited poor quality studies
Fentanyl

- Inactive metabolites, therefore thought to be safe in renal failure. Wide inter-patient variability.
- Most studies relate to IV Fentanyl.
- A retrospective study, Mazzacato, et al, 2006 of 53 pts in a palliative care unit all treated with SC Fentanyl, found pain control partial/complete in 85%\(^5\).
- Improvement seen in those with opioid related neurotoxicity pre-switch to Fentanyl in 57%\(^5\).
- Reports of successful use in cancer patients intolerant of morphine\(^9\), but also of toxicity when fentanyl given as an infusion to critically ill patients with increased half-life\(^11\).
- Some recommendations to reduce dose if GFR <50\(^11\).
- Short duration of action, but may be prolonged at higher doses.
Alfentanil

- Again thought to have inactive metabolites, and no change in elimination/volume of distribution in CKD, so recommended as safer in renal impairment – evidence limited.

- One study of 41 patients with renal impairment on Alfentanil CSCI, showed 50% of patients developed toxicity within 48 hrs of being switched back to oral opioids\(^9\).

- Also case reports of adequate analgesia and improved symptoms in pts with renal impairment switched from other opioids due to poor tolerability\(^9\).

- Limitation for PRN use - short duration of action.
Methadone

- Methadone is thought to be relatively safe in renal failure, it has no active metabolites and limited plasma accumulation due to enhanced elimination in faeces. Not removed by dialysis\(^{21,22}\).

*Renal Handbook*\(^4\).

- GFR >10 – dose as in normal renal function
- GFR <10 – 50% of normal dose, and titrate according to response
- HD/CAPD – not dialysed, dose as in GFR<10
- Methadone probably not suitable for patients with severe renal impairment

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Guidelines for use of opiates in Renal Failure
Metabolite activity and risk stratification

<table>
<thead>
<tr>
<th>Group 1 (No clinically active metabolites)</th>
<th>Group 2 (Active/probably active metabolites)</th>
<th>Group 3 (Insufficient evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td><em>a) Possible reduced risk of toxicity</em></td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Tramadol</td>
<td>Sulfentanil</td>
</tr>
<tr>
<td>Methadone</td>
<td>Hydromorphone</td>
<td>Reminfentanil</td>
</tr>
<tr>
<td></td>
<td>*b) Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Codeine/Dihydrocodeine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>c) High Toxicity Risk</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pethidine</td>
<td></td>
</tr>
</tbody>
</table>


**Mild – Moderate Renal Failure (eGFR 30-89)**

- All opioids can be used but consider reduced dose/frequency
- Monitor Renal function and consider opiate switch if rapidly deteriorating renal function
- Assess for any reversible factors

**Severe and ESRF (eGFR <30)**

- 1\textsuperscript{st} line – Fentanyl 12.5 – 25mcg sc PRN
- 2\textsuperscript{nd} line – Alfentanil 100mcg sc PRN

*Use with care*

- Tramadol 50mg bd/Hydromorphone 0.5 – 1.3 mg qds/PRN

<table>
<thead>
<tr>
<th>Drug</th>
<th>ESRD &lt;15ml/min</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Recommended</td>
<td>Max 3g/24 hrs if GFR &lt;10</td>
</tr>
<tr>
<td>Codeine/Dihydrocodiene</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Use with caution</td>
<td>50mg bd</td>
</tr>
<tr>
<td>Morphine</td>
<td>Not recommended</td>
<td>Start 2.5mg sc 4-12 hrly</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>Not recommended</td>
<td>Start 2.5mg sc 4-12 hrly</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Limited evidence</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Recommended</td>
<td>Consider reducing starting dose by 25-50%, Start PRN 25mcg sc 4 hourly</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Recommended (not PRN)</td>
<td>CSCI only</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Limited evidence</td>
<td>Use with caution. Start 1.3mg tds</td>
</tr>
<tr>
<td>Methadone</td>
<td>Recommended</td>
<td>Reduce dose 50-75%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Limited evidence</td>
<td>Use with caution, 2.5mg po tds/bd</td>
</tr>
</tbody>
</table>

Patients GFR <30mmol/min

- Fentanyl sc is recommended for pain and dyspnoea
- Alfentanil is recommended by continuous infusion if the patient develops signs of toxicity with Fentanyl
- Oxycodone, hydromorphone, morphine and diamorphine should only be used short term if alternative opioids are not available
- Morphine/Diamorphine should not be given regularly/CSCI.
**Recommendations: Dialysis Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dialysable</th>
<th>Safe and effective use in dialysis patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>No/partially dialysable with certain membranes</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>No</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Methadone</td>
<td>No</td>
<td>Yes (with caution, only by clinicians experienced in its use for pain relief</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Yes</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Yes (metabolite but not parent drug)</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Morphine</td>
<td>Yes</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Codeine</td>
<td>Yes</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Conflicting evidence</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No</td>
<td>Yes (with caution)</td>
</tr>
</tbody>
</table>
Summary: Opioids in Renal Failure

• There is no clear prospective evidence for the safe use of any opioid in renal impairment so all should be used with a degree of caution.
• There are no studies giving a clear relative risk for different opiates.
• There is evidence for the activity and accumulation of Morphine metabolites in renal failure, leading to toxicity.
• There is assumed similar potential for toxicity with Diamorphine, Codeine and Dihydrocodeine because the same metabolic pathways are involved.
• There is evidence that Oxycodone, Tramadol & Hydromorphone all have active metabolites, but there is inconsistency on the significance of any accumulation.
Summary: Opioids in Renal Failure

- Opioids thought to have no active metabolites should be used first line.
- There are thought to be no clinically significant metabolites in Alfentanil or Fentanyl, and therefore they are thought to be safer in renal impairment. However their use is limited by a short duration of action.
- It is recommended all opiates used in renal failure are titrated from low dose, with consideration of reduced frequency.
- Medication should be used regularly if indicated, not just as required
- Inform patient and family to be observant for signs of toxicity
Adjuvants in Renal Failure
Gabapentin

- **Pharmacodynamics** – precise mechanism of action unknown, although gabapentin has a similar structure to GABA and binds at the α2 subunit of voltage gated sodium channels.
- Eliminated unchanged solely by renal excretion, therefore clearance is reduced in pts with renal impairment and dose adjustment is needed. Clearance is directly proportional to eGFR.

<table>
<thead>
<tr>
<th>eGFR (ml/min)</th>
<th>Total Daily Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>900-3600</td>
</tr>
<tr>
<td>50-79</td>
<td>600-1800</td>
</tr>
<tr>
<td>30-49</td>
<td>300-900</td>
</tr>
<tr>
<td>15-29</td>
<td>150-600</td>
</tr>
<tr>
<td>&lt;15</td>
<td>150-300</td>
</tr>
</tbody>
</table>


- Gabapentin toxicity in renal failure pts is under-recognised
- Toxicity more common and more severe in those undergoing dialysis
- Predisposing factors to Gabapentin toxicity in CKD –advanced age and co-morbidities
Gabapentin – Dialysis Patients

- Gabapentin is removed by haemodialysis, therefore dose adjustment is needed.
- For *anuric* pts undergoing HD who have never received gabapentin, a loading dose of 300-400mg of gabapentin following each 4 hr dialysis is recommended. On dialysis-free days, there should be no treatment with gabapentin.
- For *renally impaired* pts undergoing dialysis, the maintenance dose of gabapentin should be based on the dosing recommendations in table. In addition to the maintenance dose, an additional 200-300mg dose following each 4 hour dialysis is recommended\(^{17}\).
- Can also be used for dialysis induced itch\(^4\).

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Pregabalin

- Pregabalin binds to voltage gated calcium channels
- Peak plasma levels occur after 1 hour
- Pregabalin is eliminated from the system primarily by renal excretion as an unchanged drug.
- Pregabalin clearance is directly proportional to eGFR

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150 – 600 (bd/tds)</td>
</tr>
<tr>
<td>≥30 - &lt;60</td>
<td>75 – 300 (bd/tds)</td>
</tr>
<tr>
<td>≥15 - &lt;30</td>
<td>25 – 150 (bd/od)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25 – 75 (od)</td>
</tr>
</tbody>
</table>


2 cases:

1. 1st Pt – 67 year old man, having HD, started on PG 300mg/day and increased to 450mg/day.
   - Unwell with drowsiness, myoclonic jerks, aphasia and dysarthria.
   - Recovered after Pregabalin withdrawal and 3 HD sessions

2. 2nd Pt – 43 year old man with DM, CKD4, started on PG 75mg/day.
   - Unwell after 2 days – drowsiness, myoclonus, recovered after PG withdrawal.
Pregabalin – Dialysis Patients

Use in pts undergoing haemodialysis

- Pregabalin is removed effectively by haemodialysis (50% of drug in 4 hours)
- For patients receiving haemodialysis, daily dose should be adjusted as per table.
- In addition to the daily dose a supplementary dose should be given immediately following each 4 hour haemodialysis treatment\(^{19}\).

Ketamine

Renal Handbook\textsuperscript{4}.

- Safe in renal failure, no active metabolites – therefore no dose adjustment suggested.
- Not dialysed, therefore no adjustment suggested for haemodialysis or CAPD patients.
- However caution advised as contra-indicated in those with severe hypertension, and renal failure patients may be more susceptible to side effects, consider low starting dose.

Antidepressants
Antidepressants


- Prevalence of depression high in those with CKD 5 (14-30%)
- Unclear whether AD’s effective in CKD 3-5 – limited evidence
- Drug pharmacokinetics of AD’s are altered in renal impairment
- Fluoxetine/Citalopram – no adjustment
- Mirtazapine – start at 15mg, increase carefully


- Depression is common, under-recognised, and under-treated in CKD patients and is associated with increased morbidity and mortality
- Some evidence from small trials showing SSRIs safe in advanced CKD/ESRF.
Antidepressants

Renal Handbook⁴.

- Amitriptylline – dose as normal, not dialysed, significant interactions, SEs – dizziness/hypotension may be more problematic
- Citalopram – dose as normal, GFR <10 (use with caution), not dialysed, significant drug interactions. Escitalopram – similar guidance (isomer of citalopram)
- Fluoxetine – GFR<10 – use low dose or on alternate days and titrate, not dialysed, accumulation can occur in chronic treatment.
- Mirtazapine – dose as normal, GFR<10 – start at low dose and monitor closely, unlikely to be dialysed.


2. Renal Association: CKD Stages
   http://www.renal.org/whatwedo/InformationResources/CKDeGUIDE/CKDstages.aspx

3. Renal Association: About GFR
   http://www.renal.org/whatwedo/InformationResources/CKDeGUIDE/AbouteGFR.aspx


1. Which ICN do you work in?
2. Which setting do you work in?

- Hospital: 44
- Hospice Inpatient: 37
- Outpatient: 30
- Community: 17
3. Which professional group do you belong to?

Consultant
SpR
SAS
Pharmacist
CNS
Other

Other – GP, GP trainee, FY2, Medical Officer, Nurse Prescriber, Clinical Director
4. Which blood parameter do you use to determine renal function? (Tick all that apply)
5. When assessing patients with renal impairment, in the absence of signs of toxicity, what level of renal impairment would prompt you to change the type and dose of opioids prescribed?

- Mild Renal Failure (60-89)
- Moderate Renal Failure (30-59)
- Severe Renal Failure (<30)
- I wouldn't review opioids in the absence of signs of toxicity
6. In opiate naive patients with Renal Failure, which drug and dose would you suggest 1st line for PRN opiate analgesia in these circumstances?
**Average PRN oral opiate doses in opiate naive patients**

<table>
<thead>
<tr>
<th>Renal Failure Level</th>
<th>Average PO PRN Morphine Dose</th>
<th>Average PO PRN Oxycodone Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Renal Failure</td>
<td>4.8mg</td>
<td>2.6mg</td>
</tr>
<tr>
<td>Moderate Renal Failure</td>
<td>4.1mg</td>
<td>2.3mg</td>
</tr>
<tr>
<td>Severe Renal Failure</td>
<td>3.1mg</td>
<td>1.9mg</td>
</tr>
</tbody>
</table>
7. Would you avoid using or suggesting the prescription of background opiates for patients with Renal Failure in any of these circumstances?

- Mild Renal Failure
- Moderate Renal Failure
- Severe Renal Failure
- Dialysis Patient

- Don't Know
- No
- Yes
7b) If you would use background opiates, what drug would you suggest 1st line for background opiate analgesia?

- Depends on the severity of the renal failure. For Moderate Renal Failure I would suggest Oxycodone, for severe or patients on dialysis I would suggest Oxycodone or Alfentanil depending on eGFR and clinical situation.
- Mild – Morphine, Moderate – Oxycodone/Fentanyl, Severe – Fentanyl
- Alfentanil for severe renal failure otherwise Morphine or Oxycodone
- Oxycodone if Mild/Moderate Renal failure, otherwise Alfentanil
8. Would you routinely convert patients with renal failure who are on stable doses of long acting opiates to Transdermal Fentanyl?

Comments
Depends on clinical situation. Only if clinically indicated. If pain controlled and no toxicity, then no, leave alone. Dependent on level of severity and signs of toxicity.
9. Would you consider prescribing or recommending an NSAID for a patient with renal failure in any of these circumstances?
10. If you would prescribe or recommend an NSAID for patients with renal failure, which drug/dose would you choose?
11. If you would prescribe or recommend an NSAID for patients with renal failure – how frequently after commencing an NSAID would you monitor renal function?
12. Consider your prescribing or advisory practice regarding the following drugs in patients with Moderate to Severe Renal Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Use but monitor more regularly</th>
<th>Use at reduced dose</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>6%</td>
<td>17%</td>
<td>66%</td>
<td>11%</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>6%</td>
<td>18%</td>
<td>70%</td>
<td>6%</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>57%</td>
<td>31%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>60%</td>
<td>25%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>60%</td>
<td>26%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>43%</td>
<td>22%</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Midazolam</td>
<td>32%</td>
<td>27%</td>
<td>41%</td>
<td>0%</td>
</tr>
<tr>
<td>H. Hydrobromide</td>
<td>55%</td>
<td>26%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Glycopyrronium</td>
<td>58%</td>
<td>18%</td>
<td>23%</td>
<td>1%</td>
</tr>
</tbody>
</table>
13. Would you prescribe or recommend a Bisphosphonate in Moderate to Severe Renal Failure?

**Comments**

14. If you would prescribe or recommend a Bisphosphonate in Moderate to Severe Renal Failure, which Bisphophonate would you choose?
15. If a patient’s renal function deteriorated (absence of obstructive uropathy), in which situation/s would you consider referral for a Renal Specialist opinion?

- Mild Renal Failure
- Moderate Renal Failure
- Severe Renal Failure
- Good PS
- If symptomatic
- Aetiology unclear
- I wouldn't generally refer
16. How confident would you feel to recommend adjustments to medications for dialysis patients?
ICN Survey: Patient Survey
1. Which ICN do you work in?
2. Which setting do you work in?

- Hospital: 17
- Hospice Inpatient: 23
- Outpatient: 20
- Community: 11

Legend:
- Hospital
- Hospice Inpatient
- Outpatient
- Community
3. What is the patient’s gender?

- Male: 26
- Female: 19
4. What is the patient’s age?
5. What type of renal impairment does the patient have?

- Acute Renal Failure: 5
- Chronic Renal Failure: 25
- Acute on Chronic Renal Failure: 3
- Don't Know: 7
6. What is the most recent Urea/Creatinine/eGFR of this patient?

Mean Urea – 17
(4.2-63.2 mmol/l)

Mean Creatinine – 239
(51-2041 µmol/l)
7. Was a PRN opiate prescribed?

- Yes: 35
- No: 5
- Don't Know: 10

**Pie Chart:**
- Oxycodone: 26
- Morphine: 8
- Diamorphine: 1
- Fentanyl: 0
- Alfentanil: 1
8. Was the patient on a background opiate (long-acting opiate or opiate delivered via syringe driver)?

- Yes - 26
- No - 16
9. Is there any evidence that the type or dose of opiates has been changed in the last 4 weeks?
9b) If yes describe the change and rationale for the decision.

- Morphine → Oxycodone – 3 patients
- Oxycodone → Alfentanil – 2 patients
- When acute renal failure became apparent, changed from Diamorphine to Alfentanil
- Dose reduction in Alfentanil
- Changed to Fentanyl patch and Oxynorm prn to avoid accumulation of Morphine metabolites causing side effects
- Switch from Fentanyl patch due to unstable pain
10. Was the patient under the care of a Renal Physician?

- Yes: 23
- No: 13
- Don't Know: 6
Renal Specialists Survey
Renal Specialists Survey

• Short survey of Renal Consultants, Trainees and CNS’s at 2 centres
• To find out about prescribing practice for patients with Renal Failure amongst Renal Specialists
• To learn more about training and knowledge of Palliative Care and End of Life Care
1. Which hospital trust do you work in?

- Royal Liverpool & Broadgreen University Hospitals NHS Trust: 3
- Aintree University Hospitals NHS Foundation Trust: 8
2. Which professional group do you belong to?

Other: Accredited Nephrologist, Renal Nurse Specialist (therapies education), Community Nurse
3. In opiate naive patients with Renal Failure, which opiate would you prescribe or recommend first line for PRN analgesia?

- Mild Renal Failure
- Moderate Renal Failure
- Severe Renal Failure

- Alfentanil
- Fentanyl
- Hydromorphone
- Oxycodone
- Morphine
4. Would you consider suggesting the prescription of background opiates for patients with Renal Failure in any of these circumstances?
5. Would you consider prescribing an NSAID for a patient with renal failure in any of these circumstances?
6. Consider your prescribing or advisory practice regarding the following analgesics in patients with Moderate to Severe Renal Failure?
7. How confident would you feel to recommend or prescribe PRN medications to control symptoms (Pain/SOB/Secretions/Nausea) in dying patients with Moderate to Severe Renal Failure?

- Very Confident
- Confident
- Neither Confident/Unconfident
- Unconfident
- Very Unconfident
8. Have you had any training in Advance Care Planning?

- Yes: 5
- No: 3
- Don't Know: 2
9. When initiating patients on dialysis, how frequently would you discuss the possibility of withdrawal of treatment in the future?

- Always
- Frequently
- Sometimes
- Never
- Not Applicable

Comments – challenges to withdrawal of dialysis
Ensuring patients understand what will happen. Clashes with other professionals over whether patients should be withdrawn or not, or indeed even start dialysis. Misconceptions. Expectations of patient and family. Conflict – pt vs family wishes.
10. When would you consider referral to the palliative care team for a patient with renal failure?
Revised Standards & Guidelines
General Principles

- Renal impairment constitutes a major source of morbidity and mortality in patients with malignancy.

- The presence of renal failure in itself can cause a high burden of symptoms, in particular pain, itch, nausea and fatigue.

- Acute Kidney Injury (AKI) is defined as a sudden decrease in the glomerular filtration rate (GFR) associated with a rise in serum urea and/or creatinine.

- AKI is often treatable if diagnosed and treated promptly.

- The causes of AKI (in cancer patients) may be multi-factorial. (changes to table)
Chronic Kidney Disease (CKD) is a long term condition in which there is reduction in glomerular function. It is often progressive and irreversible.

Prescribing for patients with renal impairment may be complex due to altered pharmacokinetic properties of many medications. This may be further complicated in patients undergoing renal replacement therapy.

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.

The Renal Handbook provides useful prescribing advice on dosing regimens for patients with renal failure.
Assessment of AKI:

- If AKI is diagnosed, an assessment of the cause should be carried out where appropriate
  - Assessment of fluid status
  - Review of medication
  - Baseline bloods eg FBC, U&E, urate, corrected calcium
  - Septic screen, including MSSU and blood cultures
  - Dipstick urine/measure urine output
  - Urinary catheterisation
  - Renal ultrasound

- If the patient has a good performance status, a referral for a specialist Renal opinion should be considered for patients if the aetiology of renal failure is unclear, or in the case of progressive impairment.
• Calculating the degree of renal impairment

  – When diagnosing renal failure, the serum creatinine may be misleading as it is significantly influenced by muscle mass, age and sex.

  – The estimated Glomerular Filtration Rate (eGFR) should be calculated using the MDRD/ Cockcroft and Gault equation to estimate the degree of renal impairment and the stage of CKD.

  – Clinical biochemistry can report the eGFR if requested. Alternatively, online calculations may be accessed via www.renal.org/eGFRcalc/GFR.pl

  – An eGFR should not be used to assess acute kidney injury or in patients on dialysis.

• Stages of CKD table – unchanged
Guidelines (iii)

Analgesic Prescribing in Renal Failure:

- NSAIDS should be avoided if possible, unless a patient is already on dialysis and anuric. If an 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. (Level 4)

- If the eGFR is below 30mls/min (CKD 4/5), 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 and should be monitored on a regular basis. Signs of opioid toxicity may include visual hallucinations, myoclonus, drowsiness or confusion. (Level 2+)

- When prescribing oral (strong) opioids, the immediate release forms are preferred. Long acting opioid preparations should be avoided (eg MST/MXL) as the metabolites accumulate in renal failure.
Guidelines (iv)

- Parenteral alfentanil or fentanyl are pharmacokinetically the safest analgesics to use in renal failure as the metabolites are non-toxic. The limitations are that they have a very short half life. (Level 3)

- If a patient requires more than three stat subcutaneous doses of a strong opioid, consider starting a continuous subcutaneous infusion. (Level 4)

- Once a patient is established on a regular stable dose of strong opioid, conversion to transdermal fentanyl may be better tolerated. (Level 4)

- Table 37.5 suggests guidelines for analgesic use in patients with severe renal failure (CKD 4/5) who are able to swallow medication. (level 2-)

## Metabolite activity and risk stratification

<table>
<thead>
<tr>
<th>Group 1 (No clinically active metabolites)</th>
<th>Group 2 (Active/probably active metabolites)</th>
<th>Group 3 (Insufficient evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>*a)*Possible reduced risk of toxicity</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Tramadol</td>
<td>Sulfentanil</td>
</tr>
<tr>
<td>Methadone</td>
<td>Hydromorphone</td>
<td>Reminifentanil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>b)</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Codeine/Dihydrocodeine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*c)*High Toxicity Risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pethidine</td>
<td></td>
</tr>
</tbody>
</table>
## Guidelines (vi)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ESRD &lt;15ml/min</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Recommended</td>
<td>Max 3g/24 hrs if GFR &lt;10</td>
</tr>
<tr>
<td>Codeine/Dihydrocodiene</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Use with caution</td>
<td>50mg bd</td>
</tr>
<tr>
<td>Morphine</td>
<td>Not recommended</td>
<td>Start 2.5mg sc 4-12 hrly</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>Not recommended</td>
<td>Start 2.5mg sc 4-12 hrly</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Limited evidence</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Recommended</td>
<td>Consider reducing starting dose by 25-50%, Start PRN 25mcg sc 4 hourly</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Recommended (not PRN)</td>
<td>CSCI only</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Limited evidence</td>
<td>Use with caution. Start 1.3mg tds</td>
</tr>
<tr>
<td>Methadone</td>
<td>Recommended</td>
<td>Reduce dose 50-75%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Limited evidence</td>
<td>Use with caution, 2.5mg po tds/bd</td>
</tr>
</tbody>
</table>
Guidelines (vii)

• Dialysis and Opioids: (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.
  
  – If a drug is cleared by dialysis, it should be administered after the dialysis procedure
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dialysable</th>
<th>Safe and effective use in dialysis patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>No/partially dialysable with certain membranes</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>No</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Methadone</td>
<td>No</td>
<td>Yes (with caution, only by clinicians experienced in its use for pain relief</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Yes</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Yes (metabolite but not parent drug)</td>
<td>Yes (with caution)</td>
</tr>
<tr>
<td>Morphine</td>
<td>Yes</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Codeine</td>
<td>Yes</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Conflicting evidence</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No</td>
<td>Yes (with caution)</td>
</tr>
</tbody>
</table>
• Adjuvant Analgesics:
  – Gabapentin: (Level 3)
    • dosing table: unchanged
    • Gabapentin is removed by haemodialysis, therefore dose adjustment is needed
    • For *anuric* pts undergoing HD who have never received gabapentin, a loading dose of 300-400mg of gabapentin following each 4 hr dialysis is recommended. On dialysis-free days, there should be no treatment with gabapentin.
    • For *renally impaired* pts undergoing dialysis, the maintenance dose of gabapentin should be based on the dosing recommendations in table. In addition to the maintenance dose, an additional 200-300mg dose following each 4 hour dialysis is recommended\(^\text{17}\).
    • Can also be used for dialysis induced itch\(^4\)
Guidelines (x)

Adjuvant Analgesics:

- Pregabalin: (level 3)
  - Dosing table: unchanged
  - Pregabalin is removed effectively by haemodialysis (50% of drug in 4 hours)
  - For patients receiving haemodialysis, daily dose should be adjusted as per table.
  - In addition to the daily dose a supplementary dose should be given immediately following each 4 hour haemodialysis treatment\(^\text{19}\).

- Ketamine: (level 3)
  - Safe in renal failure, no active metabolites – therefore no dose adjustment suggested
  - Not dialysed, therefore no adjustment suggested for haemodialysis or CAPD patients.
  - However caution advised as contra-indicated in those with severe hypertension, and renal failure patients may be more susceptible to side effects, consider low starting dose.
Guidelines (xi)

- **Anti-emetics:**
  - Haloperidol is the drug of choice for nausea in patients with renal failure, but should be used at a dose reduction of 50%. (Level 4)
  - Levomepromazine is a useful alternative anti-emetic (Level 4)
  - Cyclizine should be avoided due to the risk of hypotension/tachyarrhythmias (Level 3)
  - Metoclopramide should be avoided due to the increased risk of extrapyramidal reactions (level 3)

- **Sedatives:**
  - Midazolam metabolites accumulate in renal failure. Patients may be more sensitive to the effects of midazolam. The lowest effective dose should be used. (level 4)
  - Uraemia may cause or contribute to agitation in the dying phase. (level 4)
  - Consider the use of haloperidol if the patient is suffering from delirium rather than agitation/anxiety. (level 4)

- **Anti-secretory:**
  - Glycopyrronum is the drug of choice for managing secretions. It accumulates in renal failure and a dose reduction of 50% is recommended (level 4)
  - Hyoscine hydrobromide has an increased risk of drowsiness and paradoxical agitation. (level 4)
• Anti-depressants: (Level 3)

  – Citalopram – dose as normal, GFR <10 (use with caution), not dialysed, significant drug interactions. Escitalopram – similar guidance (isomer of citalopram)
  – Fluoxetine – GFR<10 – use low dose or on alternate days and titrate, not dialysed, accumulation can occur in chronic treatment.
  – Mirtazapine – dose as normal, GFR<10 – start at low dose and monitor closely, unlikely to be dialysed.
  – Amitriptylline – dose as normal, not dialysed, significant interactions, dizziness/hypotension may be more problematic

• Bisphosphonates: (Level 4)

  – The risk of renal failure is directly related to drug infusion time and dosage.
  – There is no evidence that any particular bisphosphonate is better tolerated in patients with renal failure.
  – See Guidelines on the Use of Bisphosphonates for further details.
Revised Standards
Standards

1. Estimated GFR (eGFR) should be used to determine renal function. (Grade B)

2. In severe renal impairment, drug doses should be reduced and/or dosing intervals increased as appropriate.

3. All patients should be closely monitored for evidence of drug toxicity or drug induced renal impairment, and medications altered accordingly. (Grade C)

4. If a non-dialysis patient is started on an NSAID, the renal function should be re-checked within 5-7 days. (Grade D)

5. In patients with severe renal impairment, alfentanil or fentanyl are the strong opioids of choice for use in a csci. (Grade D)

6. ? Recommendation for first line prn opioid
Questions & Comments?