The Hearing Aid Podcasts

Episode 9.10

The Ageing Kidney

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Learning Outcomes

Knowledge

- Understand the normal ageing process of the kidneys and the clinical relevance of this
- Understand the classification/staging of CKD
- Recall the common causes of chronic kidney disease (CKD) in older adults

Skills

- To be familiar with aids like the BNF to guide prescribing and medication reviews in older adults with renal impairment.
- Recognise signs and symptoms of advanced CKD

Attitudes

- To be aware of conditions causing/contributing to CKD and factors we can control to prevent progression to worse renal function
- To be alert to nephrotoxic medications and those to be cautious with when prescribing in CKD

Definitions

Chronic Kidney Disease (CKD) definition

"Abnormalities of kidney function or structure present for more than 3 months" (The Renal Association)

This includes everyone with markers of kidney damage or an eGFR (estimated glomerular filtration rate) of less than 60 ml/min, on at least 2 occasions, 90 days apart.

CKD classification (NICE guidelines)

CKD is divided into 5 stages based on eGFR, with 3 categories for proteinuria based on albumin:creatinine ratio.

Classification of chronic kidney disease using GFR and ACR categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73 m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk

Increasing risk

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

The NICE guidelines for staging CKD are taken from the *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)*

https://renal.org/information-resources/the-uk-eckd-guide/ckd-stages/

https://www.nice.org.uk/guidance/cg182/chapter/Introduction

Main Discussion

The normal ageing process in the kidneys:

In 1999, eGFR replaced creatinine as a measurement of kidney function. Since then, many more older adults have been labelled with CKD: over half of people over 70 have eGFR <60.

eGFR is an abbreviation for 'estimated glomerular filtration rate'.

- This is a value that we get from a blood test to assess renal function.
- Creatinine, a breakdown product of muscle, is the substance which is physically measured by the test, and this result then used to calculate the eGFR.
- We will go into more detail later re the accuracy and pitfalls of these tests

There is some debate about the usefulness of labelling all of these older adults with chronic kidney disease, based on their eGFR (>50% of over 70s have CKD stage 3a or worse, based on criteria of eGFR<60).

- **AGAINST:** Some would argue that the decline in GFR reflects the normal ageing process of the kidney and these people shouldn't be labelled as "diseased"
- .**FOR:** increased recognition of CKD is good because it means better recognition and patient care in the circumstances where it is a disease and not normal ageing

This is an interesting scenario to reflect on after talking about pragmatic investigation in the first episode of this series, where we talked about balancing risks and benefits of investigating and diagnosing older patients. Even though the 'investigation' in question here is a simple blood test and carries little to no risk in itself, it could be worth assessing the consequences of the test having been done, using some of the strategies we covered such as the 'BRAN' mnemonic.

- **B**enefits: recognition of disease that can be optimised and prevent morbidity
- **R**isks: overdiagnosis of something which may not be clinically relevant
- **A**lternatives: none / period of monitoring

- **N**othing: may miss clinically significant disease

Whether you agree or disagree with labelling patients with renal disease based on their eGFR, it is important still to be aware that the kidney undergoes senescence as we age. This is because this changing physiology does have a clinical significance worth being aware of, which might affect your practice:

- Older adults may develop more advanced kidney disease if a new nephropathy develops
- Older adults have Increased susceptibility to developing an AKI (acute kidney injury)
- Older adults are at higher risk of toxic accumulation of renally cleared drugs.

Pathophysiology of the ageing kidney

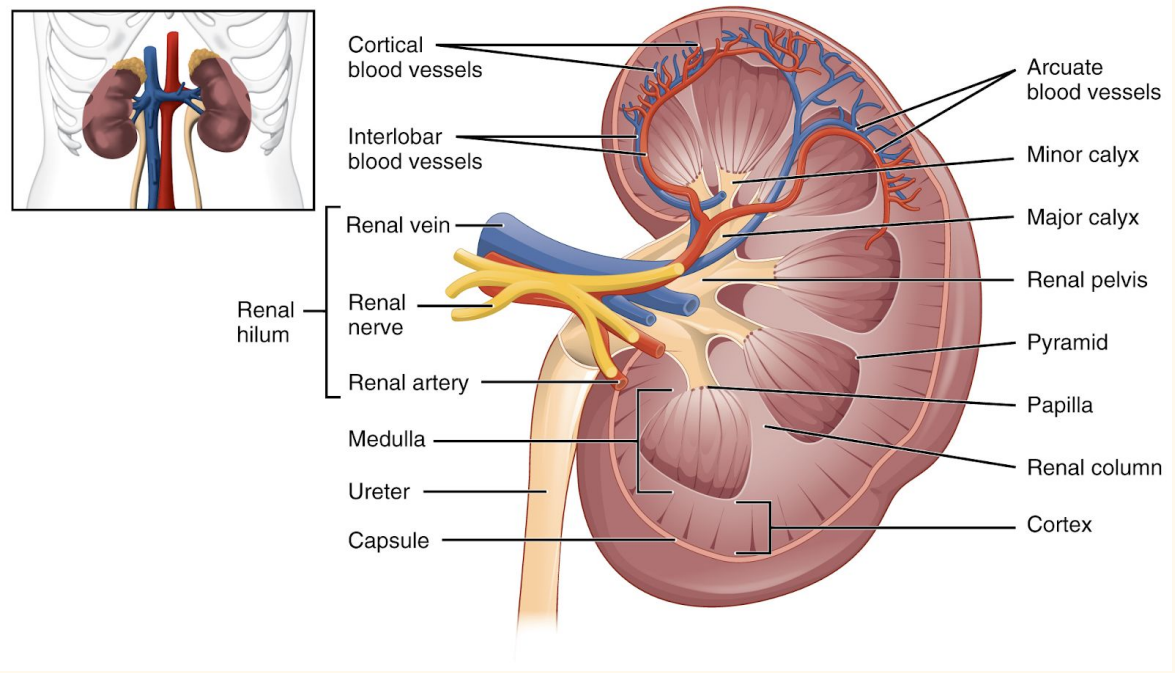
Assessing the physiological and pathological changes in the ageing kidney can be done in several different ways

1. **Structurally**

Macroscopic changes:

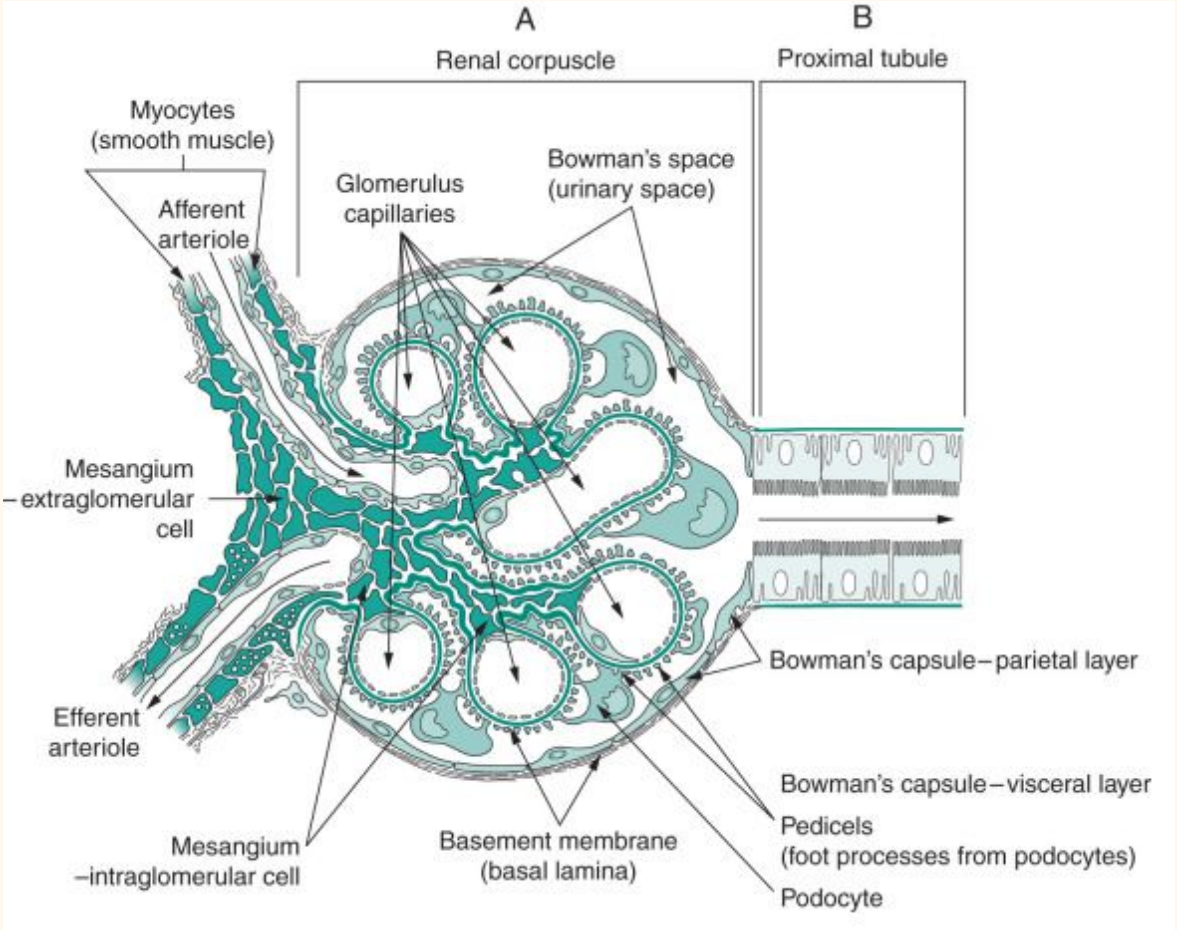
- Renal *cortical* volume (cortex = outside part) *decreases* with age, whilst *medullary* volume (medulla = inside part) *increases* with age.
- Renal cysts become more common with increasing age, and these grow over time.
- People also develop more fat around their kidneys as they get older.
- All in all, these changes mean that assessing the total kidney volume is a *poor* marker of age-related nephron loss.

Structural changes can only be seen on imaging or renal biopsy, which is not an appropriate or justifiable investigation for most people.



Microscopic changes

- We are born with between 700,000 and 1.8 million functional nephrons per kidney and we lose approximately 50 nephrons per kidney per day.
- Glomerulosclerosis develops as we age: The glomerular tuft is the ball of capillaries where waste products are filtered out of the blood into the Bowman's space and on into the nephron. These glomerular tufts wrinkle and eventually collapse, due to a combination of *reduced podocyte density* (the cells wrapped around the capillaries) and *ischaemic damage*. Collagen then fills the Bowman's capsule instead and the glomerulus becomes sclerosed.
- The ischaemic damage is thought to result from degenerative change in the small arteries, affecting the whole nephron and causing *nephrosclerosis.*
- As nephrons are lost, the remaining functional nephrons undergo hypertrophy (they get bigger).



Dean DF, Molitoris BA. Critical Care Nephrology. 3rd ed. Elsevier, 2019. Chapter 7: The physiology of the glomerulus.

https://opentextbc.ca/anatomyandphysiology/chapter/25-3-gross-anatomy-of-the-kidney/

2. **Functionally.**

A more practical way to assess the ageing process of the kidneys is to look at functional changes and we do this using laboratory blood tests:

Glomerular filtration rate (**GFR**) - how well the kidneys filter the blood to excrete waste into the urine over a period of time - declines with normal ageing, by about 8 ml/min per decade of life.
NOTE - although similar, this is NOT **eGFR** but a TRUE measurement.

Measurement of this *true* GFR is cumbersome and time-consuming: it requires an exogenous filtration marker (given IV), repeated blood sampling and 24h urine collection….so it's only used in research and isn't practical day-to-day.

In clinical practice we use the value that we mentioned earlier (from the NICE guidelines for diagnosing CKD) - *estimated* GFR (or eGFR) which is a function of the creatinine level in the blood, plugged into a mathematical equation and routinely reported on blood test reports.

Creatinine is a breakdown product of muscle, cleared largely by the kidneys, and therefore the amount still circulating in the blood gives us an idea of how effective the kidneys have been at clearing it.

eGFR is the tool we use on a daily basis on the wards, in clinics and in the community to get an idea of how well a person's kidneys are functioning. It is good for chronic measurement of kidney function, whereas the creatinine measurement itself gives us a good indicator of acute changes in function.

Management of CKD complications:

While these changes happen within the kidney and are visible on blood tests and biopsy, *symptoms* of renal impairment only tend to develop from *stage 4 onwards* and are mostly related to the complications of renal failure.

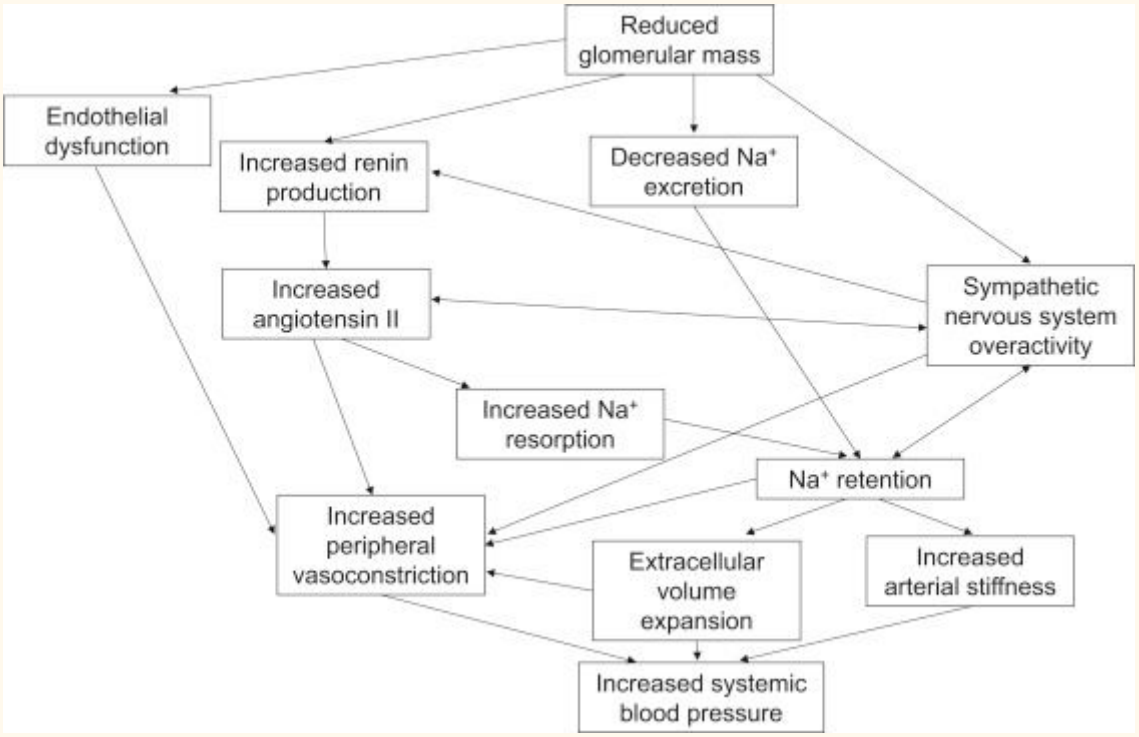
- **Fluid overload** is mainly due to problems with sodium homeostasis. Symptoms include shortness of breath and oedema
- **Hyperkalaemia** usually develops in patients who are oliguric (peeing less), taking an ACEi/ARB, who have increased tissue breakdown (eg in rhabdomyolysis, more cancers), or a high potassium intake.
- **Metabolic acidosis (increased pH/acidity of the blood)** is due to increased loss of base (bicarbonate), and decreased acid (H^+) excretion
- **Renal bone disease**: secondary hyperparathyroidism develops due to phosphate retention, hypocalcaemia and problems with vitamin D metabolism.
- **Anaemia** due to reduced production of erythropoietin by the kidney and causing symptoms of breathlessness, fatigue, lightheadedness.

Common causes of CKD in older adults:

Hypertension:

- 60-90% of people with CKD are hypertensive (depending on the stage and cause of CKD). Both hypertension and CKD contribute to the development and progression of the other, via mechanisms such as pathological activation of the renin angiotensin aldosterone system (hormone system which regulates blood pressure) and damage to the kidneys causing glomerulosclerosis due to higher pressure in the vessels.

Pathophysiologic mechanisms of hypertension in CKD



More information about CKD and Hypertension:
https://www.ajkd.org/article/S0272-6386(19)30094-0/fulltext

Interestingly a decline in GFR with age is also seen in isolated populations who don't follow a modern "western" lifestyle (with all its associated risk factors such as high blood pressure), which further supports the idea that a decline in GFR with age is not necessarily related to hypertension, and that other factors are at play.

Age, renal perfusion and function in island-dwelling indigenous Kuna Amerinds of Panama, Hollenberg et al, 1999
https://pubmed.ncbi.nlm.nih.gov/10364705/

Diabetes:

- Diabetes is the leading cause of CKD and end-stage renal disease (ESRD) worldwide.
- There are several different mechanisms of kidney damage in diabetes
    - One of these is "hyperfiltration" where the GFR is abnormally elevated due to high intraglomerular pressure. Over time, hyperfiltration leads to glomerulosclerosis (thickening and stiffening of the glomeruli). Limiting hyperfiltration is one of the reasons we aim for good blood pressure control in diabetic patients, using an ACE inhibitor or ARB.

https://www.uptodate.com/contents/treatment-of-diabetic-kidney-disease?search=diabetes%20kidney%20disease&topicRef=3103&source=see_link#H2546483452

More information about the pathophysiology of diabetic kidney disease:

https://www.uptodate.com/contents/diabetic-kidney-disease-pathogenesis-and-epidemiology?search=diabetes%20kidney%20disease&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

Obstructive (post-renal) nephropathy:

- An obstruction in the system can occur anywhere from the kidneys all the way down to the urethra and can be acute (eg a stone or an infection) or chronic (eg BPH, tumour),
- This can cause irreversible renal injury if prolonged and it is important to consider 'post renal' causes when a patient's renal function declines - whilst bearing in mind that a reduced eGFR is a late sign, as this does not usually change until the function of an entire kidney has been lost. Creatinine is more useful in detecting abnormalities in this situation.

http://edren.org/ren/education/textbook/conditions-that-affect-the-kidney/obstruction/
https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-urinary-tract-obstruction-and-hydronephrosis?search=obstructive%20nephropathy&topicRef=102837&source=see_link#H1323380487

There are numerous other rarer causes of chronic kidney disease, often related to systemic disease. These include atherosclerotic renal artery stenosis, ANCA-positive small vessel vasculitis and amyloidosis.

Prescribing in older people with CKD

Perhaps one of the most important reasons to be aware of the renal function of your patients is the need to amend, reduce, monitor and sometimes increase the doses of medication we give to patients with CKD.

Knowing what the correct prescription for your patient is starts with knowing what their renal function is, as accurately as possible.

The estimated GFR is just that - estimated. Results sometimes overestimate the true GFR in older people, especially if your patient has very low muscle mass, as the formulae do not take the patient's weight into account. Weight is relevant because the eGFR result relies on creatinine - if you have less muscle mass ie you are lighter, you will have lower levels of circulating creatinine, and this will be interpreted as the kidney having been more efficient at filtering this product out (rather than there being a lower level in the first place).

https://www.uptodate.com/contents/the-aging-kidney?search=elderly%20kidney&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H9530922

For these reasons, it is usually most accurate to calculate an older person's *creatinine clearance rather than the eGFR,* and this uses another mathematical equation - the Cockroft-Gault formula (available in apps such as MedCalc or QxMD). This takes a person's weight into account and is safer to use if you are working out drug doses.

Case Study with Emily Knox, Rotational Pharmacist

As a general rule, I (Emily) would calculate the creatinine clearance for anyone over the age of 75 regardless of their visible appearance of muscle mass.

Mrs Renaldi is 90 years old, of British and West African heritage, and has a serum creatinine of 70.

Using the MDRD calculation: (we used MDcalc to do this)

https://www.mdcalc.com/mdrd-gfr-equation

1) Her **eGFR** is 88ml/min if we class Mrs Renaldi as 'black', and 73ml/min if we say sh is 'non black'

Let's say she weighs 45kg: - weight is not taken into account in the eGFR calculation above.

2) We can then work out her **creatinine clearance.** This is 34ml/min. Definitely a significant difference!

'The Colour of kidneys' - an interesting article (link below) explores the following;

As well as weight, having to state the ethnicity of your patient may be a source of error in the eGFR measurement. The equations used to calculate eGFR from creatinine require you to state the person's ethnicity as a binary choice of "African-American or not". This is because, on average, people of black heritage have slightly higher creatinine levels at baseline than the rest of the population. In practice, however, an individual's ethnicity is often not so binary, and there is no room in the calculation for a spectrum of backgrounds.

"The Color of Kidneys", Toni Martin MD, American Journal of Kidney Diseases, 2011
https://www.ajkd.org/article/S0272-6386(11)01273-X/fulltext#%20

To add further, extra complication - there is some debate over which weight to use to calculate creatinine clearance in obese patients as this can change the results drastically. When we say 'which weight', we are talking about actual body weight, ideal body weight or adjusted body weight.

For obese patients it is recommended to use **ideal body weight** or on occasion **adjusted body weight** as creatinine is a broken down from muscle tissue but not fat.

From the example, if Mrs Renaldi weighed 80kg and was 160cm tall, her ideal body weight is 52kg and her adjusted body is 63kg.:

Using these different weights, her calculated creatinine clearances are very different;

Actual body weight, CrCl = 59ml/min

Adjusted body weight, CrCl = 47ml/min

Ideal body weight, CrCl = 39ml/min

To put all of this into a more clinical context, we can look at what dose of antibiotic we would give Mrs Renaldi if she needed IV treatment for a UTI. If gentamicin dosing was based on an eGFR of 88ml/min, she would receive around 225mg of gentamicin. With a CrCl of 34ml/min, she would receive 135mg. The concern here is that if eGFR is used rather than creatinine clearance it might lead to large overdoses resulting in further damage to the kidneys and ototoxicity.

Safe prescribing

Medications can cause renal impairment, contribute to it or be affected by its presence.

Medications should be reviewed in light of any newly identified renal impairment, and regularly in the context of CKD to ensure they are still safe and effective.

Q&A with Emily Knox, Rotational Pharmacist

Consider 3 key aspects (information below correct at the time of recording 12/2020)

1. **Nephrotoxic drugs** which damage the kidneys themselves - People with CKD and impaired kidneys are more susceptible to these nephrotoxic effects, which can in turn cause progression of CKD
    - There are many nephrotoxic drugs that can damage the kidneys in different ways.
        - A classic example is the non-steroidal anti-inflammatories (NSAIDs) family of medications, which should always be used with caution in older people and those with any degree of renal impairment.
            - These are prescribed commonly for musculoskeletal conditions, including osteoarthritis and are often on medication lists.

        - NSAID use is associated with a variety of renal syndromes, including AKI, acute tubular necrosis and acute interstitial nephritis. These acute syndromes can result in permanent loss of function.
        - NSAIDs include ibuprofen, high dose aspirin, diclofenac
    - Antibiotics (commonly penicillins), all diuretics and allopurinol, among other drugs can also cause acute renal dysfunction.

2. The effect of **reduced renal excretion of a drug** or its metabolites may cause toxicity; examples including
    - Opioids (eg morphine) which can cause drowsiness and respiratory depression.
    - DOACs (e.g. rivaroxaban, edoxaban, apixaban) –
        - Clinical trials for this group of anticoagulants when being tested and developed used creatinine clearance for their dosing calculations. This is therefore important to replicate in practice to ensure correct dosing based on the evidence that we have. Consequences of incorrect dosing and accumulation could be catastrophic (bleeding).
    - Metformin (there is an increased risk of lactic acidosis when given to patients with impaired renal function)
    - Enoxaparin (prescribed for almost all patients!) may need dose adjustment in renal failure.

3. Some drugs are **not effective** when renal function is reduced
    - e.g. nitrofurantoin, an antibiotic used commonly to treat urinary tract infections. This should be used with caution in patients with an eGFR of <45, and is absolutely contraindicated in patients with an eGFR <30.
    - SGLT-2 inhibitors, used in diabetes (eg dapagliflozin). These are contraindicated in patients <60ml/min as cause glucose to be excreted via the kidneys/urine)

Where can we go for more information?

- The BNF gives clear instructions for drugs that require dose adjustment in renal impairment, based on creatinine clearance.
    - Whilst the BNF is a good resource for renal dosing, it provides dosing based on trial data and these are the licensed doses in renal impairment. The renal drug database is a good resource to use for renal dosing as its doses are based on experience in practice rather than

licensing and tends to be a bit more lenient than the BNF dosing. It does however require a subscription; most hospital pharmacy departments should be able to access this site. Another useful source can be microguide which is set up by individual trusts, and many have a renal dosing section particularly for antibiotics.

https://bnf.nice.org.uk/guidance/prescribing-in-renal-impairment.html

Patient resources:

- Kidney Patient Guide forum - public forum where anyone affected by kidney disease can exchange information and find support.
- Kidney Care UK - patient support charity providing advice, support and financial assistance.
- National Kidney Foundation - American voluntary health organisation that provides information and support. It also publishes several journals including the American Journal of Kidney Diseases
- EdRen.org - From the Edinburgh renal unit. Education for patients and health professionals. It provides free case-based questions to try as an educational resource.

Curriculum Mapping

NHS Knowledge Skills Framework

- Core 2 Level 1
- HWB6 Level 1
- HWB8 Level 3

Foundation Programme

- Sec 1:4 Self directed learning
- Sec 3:10 Frail pt
- Sec 3:13 Discussion of medication, Review of prescriptions

GPVTS

- 3.05 Maintaining performance, learning and teaching
- 3.05 Practising holistically and promoting health

Internal Medicine Stage 1

- Category 1: Professional behaviour and trust: learning & teaching
- Renal medicine: Chronic kidney disease, Renal replacement therapy

Geriatric Medicine Specialty Training

- Managing long term conditions and promoting patient self-care: Natural history of disease
- Health promotion and public health: Lifestyle
- Diagnosis and Management of Chronic Disease and Disability