Medication Considerations for Patients with Renal Disease

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Disclosure of Relevant Financial Relationships

I have the following financial relationships to disclose:
None

Disclosure of Off-Label and/or investigative Uses

I will not discuss off label use and/or investigational use in my presentation.

Objectives:

1.

To review how to detect and ***evaluate the degree of renal impairment*** *present in frail seniors*

2.

To be familiar with ***renal dose adjustments*** *for commonly used medications*

3.

To have an improved understanding of ***drugs commonly used by nephrologists*** *in chronic kidney disease*

Chronic kidney disease

- Structural or functional abnormality
- Present for longer than 3 months
- Stages 1 to 5
  - Defines prognosis and priorities rather than necessarily sequential stages of progression
  - Includes those on dialysis (stage 5D)
  - Includes those with a kidney transplant

Assessment of Kidney Function

- Serum creatinine
- Serum cystatin C
- Timed urine collections
  - Creatinine clearance
  - Exogenous markers
    - Inulin clearance
    - Iothalamate Clearance
    - Iohexol
    - Radiolabeled markers

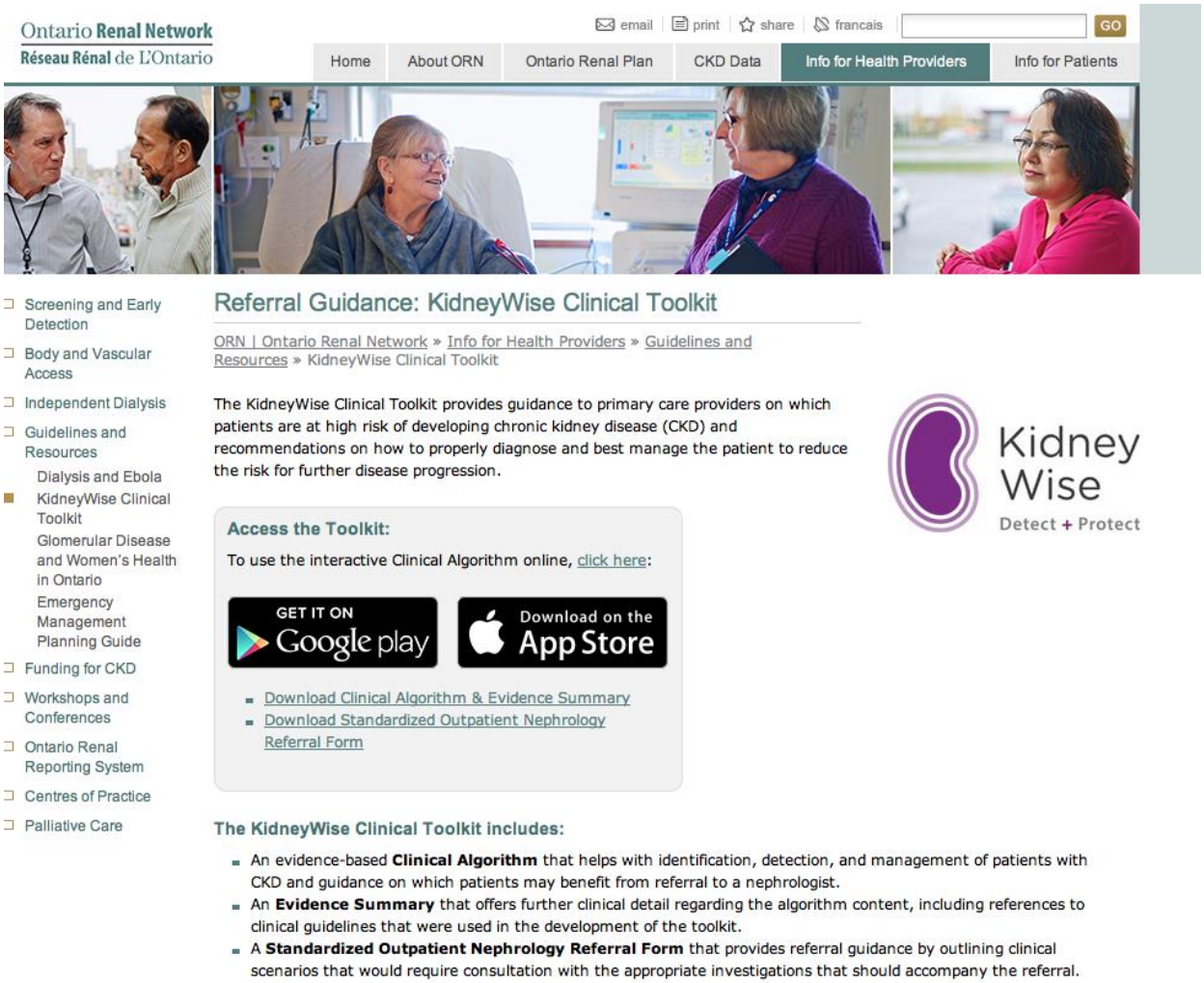
Question 1

What is the optimal method to estimate renal function when determining the dose and frequency of oseltamivir (*Tamiflu*) during a flu outbreak?

1. eGFR using the MDRD equation
2. eGFR using the CKD_{epi} equation
3. eGFR using either MDRD or CKD_{epi} eqn
4. Cockcroft-Gault eqn (CrCl)
5. 24 hour urine collection for CrCl

WHAT IS THE PURPOSE?

ORN Toolkit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Independent Dialysis
Guidelines and Resources
Dialysis and Ebola
KidneyWise Clinical Toolkit
Glomerular Disease and Women's Health in Ontario
Emergency Management Planning Guide
Funding for CKD
Workshops and Conferences
Ontario Renal Reporting System
Centres of Practice
Palliative Care
Referral Guidance: KidneyWise Clinical Toolkit
ORN | Ontario Renal Network » Info for Health Providers » Guidelines and Resources » KidneyWise Clinical Toolkit
The KidneyWise Clinical Toolkit provides guidance to primary care providers on which patients are at high risk of developing chronic kidney disease (CKD) and recommendations on how to properly diagnose and best manage the patient to reduce the risk for further disease progression.
Kidney Wise
Detect + Protect
Access the Toolkit:
To use the interactive Clinical Algorithm online, click here:
GET IT ON Google play
Download on the App Store
Download Clinical Algorithm & Evidence Summary
Download Standardized Outpatient Nephrology Referral Form
The KidneyWise Clinical Toolkit includes:
An evidence-based Clinical Algorithm that helps with identification, detection, and management of patients with CKD and guidance on which patients may benefit from referral to a nephrologist.
An Evidence Summary that offers further clinical detail regarding the algorithm content, including references to clinical guidelines that were used in the development of the toolkit.
A Standardized Outpatient Nephrology Referral Form that provides referral guidance by outlining clinical scenarios that would require consultation with the appropriate investigations that should accompany the referral.

CKD – disease progression

- Best predicted using eGFR & albuminuria

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

"Stage 5D" = dialysis

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Drug dosing is different

Most pharmacological doses are based on ***Creatinine Clearance****, measured using Cockcroft-Gault equations, as a measure of renal function*

One consideration

- Most studies have used CrCl for adjustment

- CrCl is not corrected for body surface area
- eGFR is corrected for body surface area
- Drug filtered is proportional to the ‘raw’ GFR

Graham RD Jones, Clin Biochem Rev 2011

Altered PCK in Renal Disease

- **Absorption**
  - Both rate and extent of absorption may be altered
  - Not well studied in CKD pts
  - May also be affected by Vd and plasma clearance of the drug
  - Patients on many drugs so potential drug interactions

Verbeeck et al. Eur J Clin Pharm 2009;65:757-773

Altered PCK in Renal Disease

- **Distribution**
  - Generally increased
    - Thus decreased in serum concentrations
    - Reasons for increased Vd
      - Fluid overload- problematic for hydrophilic drugs like cephalosporins
      - Decreased protein binding-phenytoin

Verbeeck et al. Eur J Clin Pharm 2009;65:757-773

Altered PCK in Renal Disease

- **Metabolism**
  - Chronic renal failure can decrease hepatic enzyme activity
  - CYP 3A4, CYP2C11 and CYP 3A2 have decreased (35%) activity
  - Mechanisms unknown ?Relate to accumulation of uremic toxins +/- chronic inflammation
- **Metabolite Elimination**
  - Metabolites may have similar pharmacologic activity (oxypurinol) or
  - dissimilar activity (normeperidine / meperidine).

Verbeeck et al. Eur J Clin Pharm 2009;65:757-773

Altered PCK in Renal Disease

Renal Excretion

Glomerular Filtration

– Affects if MW < 30KD & <80% protein bound

– diuretics

Renal Proximal Tubule secretion

– digoxin, antidiabetics, B lactam antibiotics, anticancer drugs, NSAIDs, HIV drugs, drug metabolites (glucuronide conjugates), cimetidine

Tubular Reabsorption

– Passive diffusion

Verbeeck et al. Eur J Clin Pharm 2009;65:757-773

Clinical Caveats

- Body structure – frail, amputations etc
- Dialysis dependency
- Volume status – transient changes with dehydration
- Diet – vegetarian, “tea‘n-toaster”

Calculations based on *ideal* body weight

1.

Thin, frail elderly lady (40kg) in a nursing home

2.

Thin, well nourished petite elderly lady (50kg) with good appetite

3.

Robust elderly lady (75kg) with good appetite

Clinical Caveats

- Body structure – frail, amputations etc
- Dialysis dependency
- Volume status – transient changes with dehydration
- Diet – vegetarian, “tea‘n-toaster”

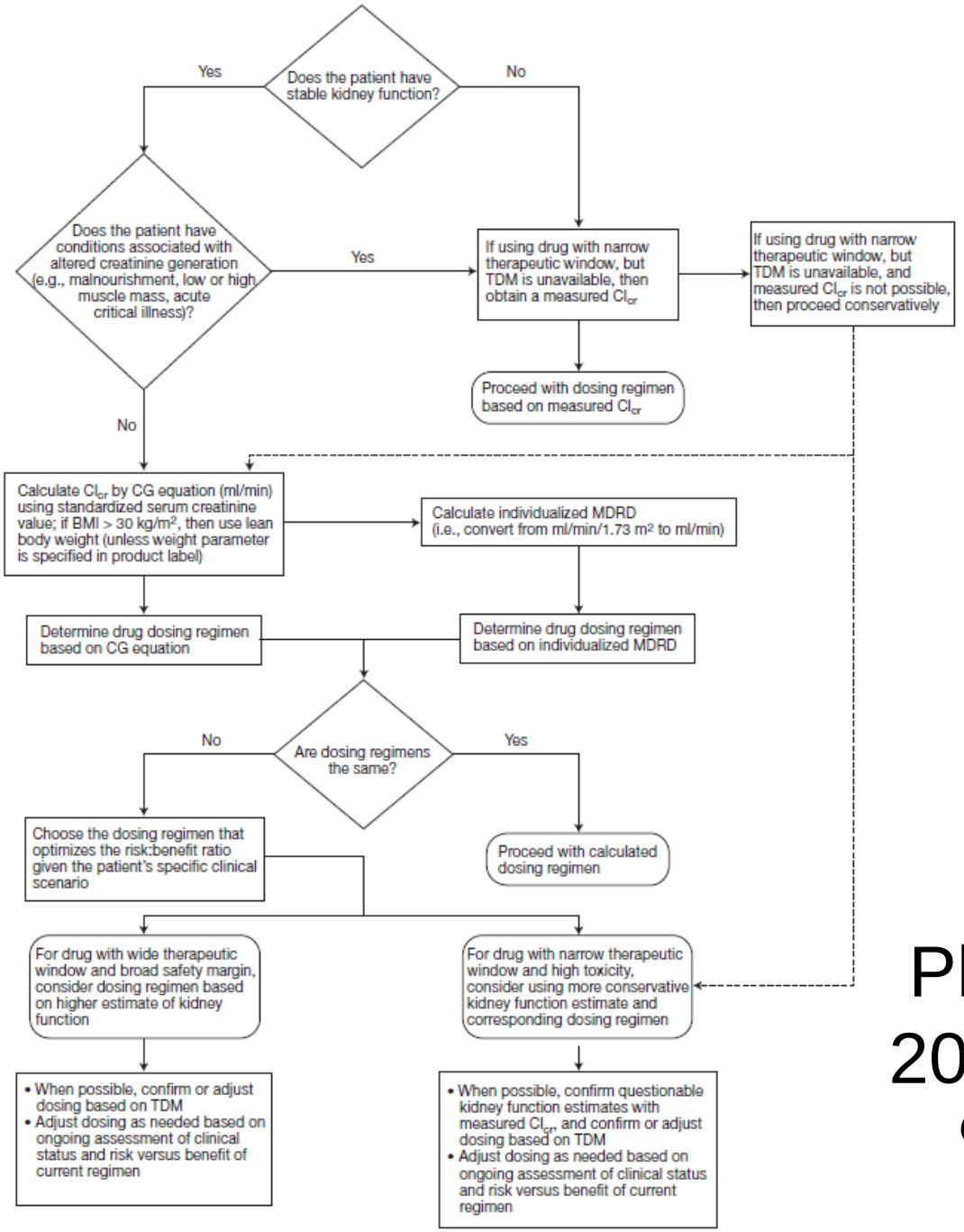
Cases

SCr	Gender	Age	IW	CG (ml/min)	MDRD (ml/min 1.73m²)	CKD EPI (ml/min/ 1.73m²)
130	M	40	70	**66.1**	**56**	**59**
130	M	80	60	**34**	**49**	**44**
130	F	80	50	**24.1**	**37**	**33**

Question 2

80 year old female, independent at home.
She weighs 38kg, IBW 50kg and SCr 130µmol/L (CrCl 24, eGFR 37) .
The product monograph identifies 3 different dose thresholds. Which threshold do you use?

1. No dose adjustment
2. Dose according to 30-50mls/min
3. Dose according to 15-30mls/min



A Pragmatic Approach

Adapted from Pharmacotherapy 2011;31:1130-1144

Courtesy of M Battistella

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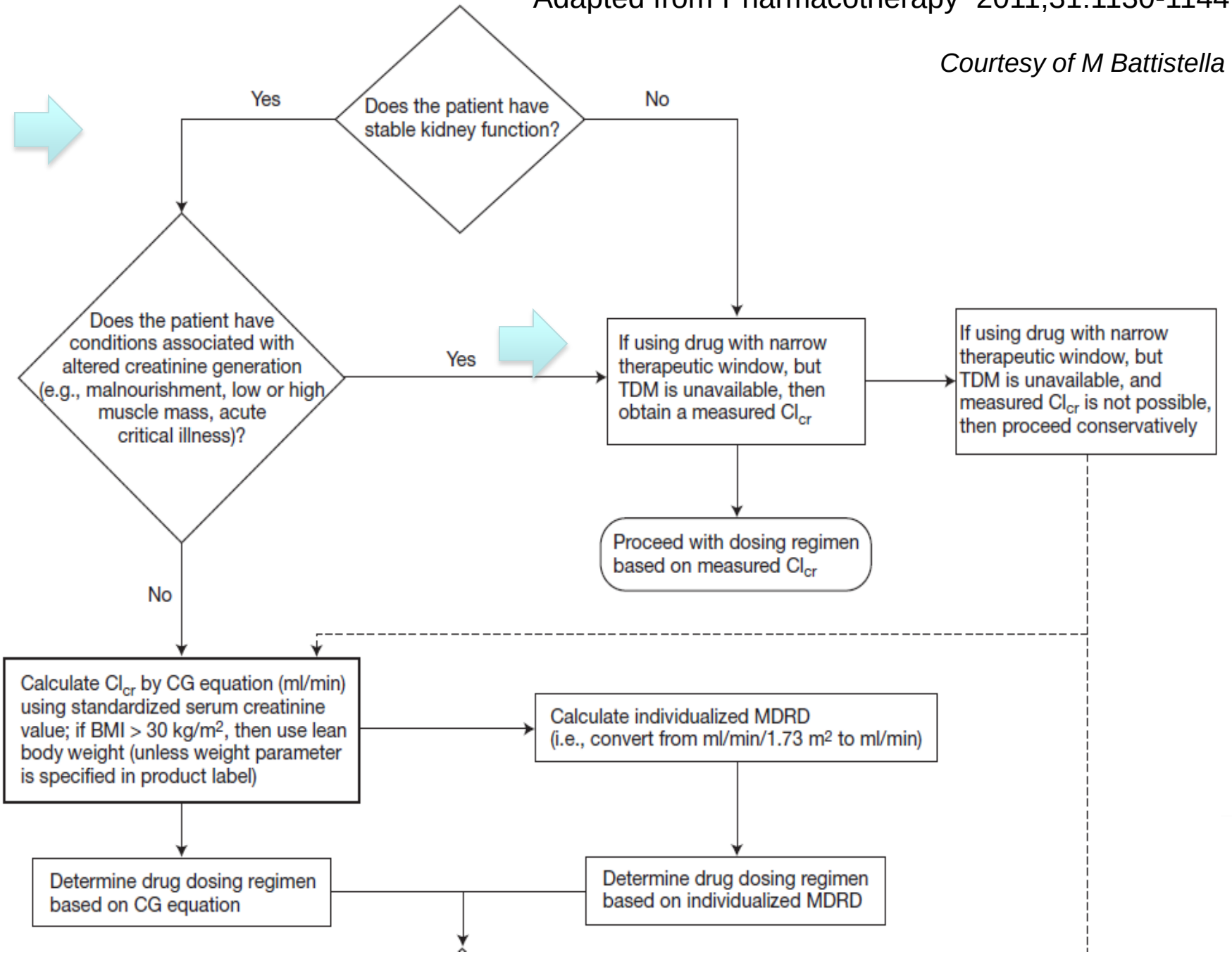
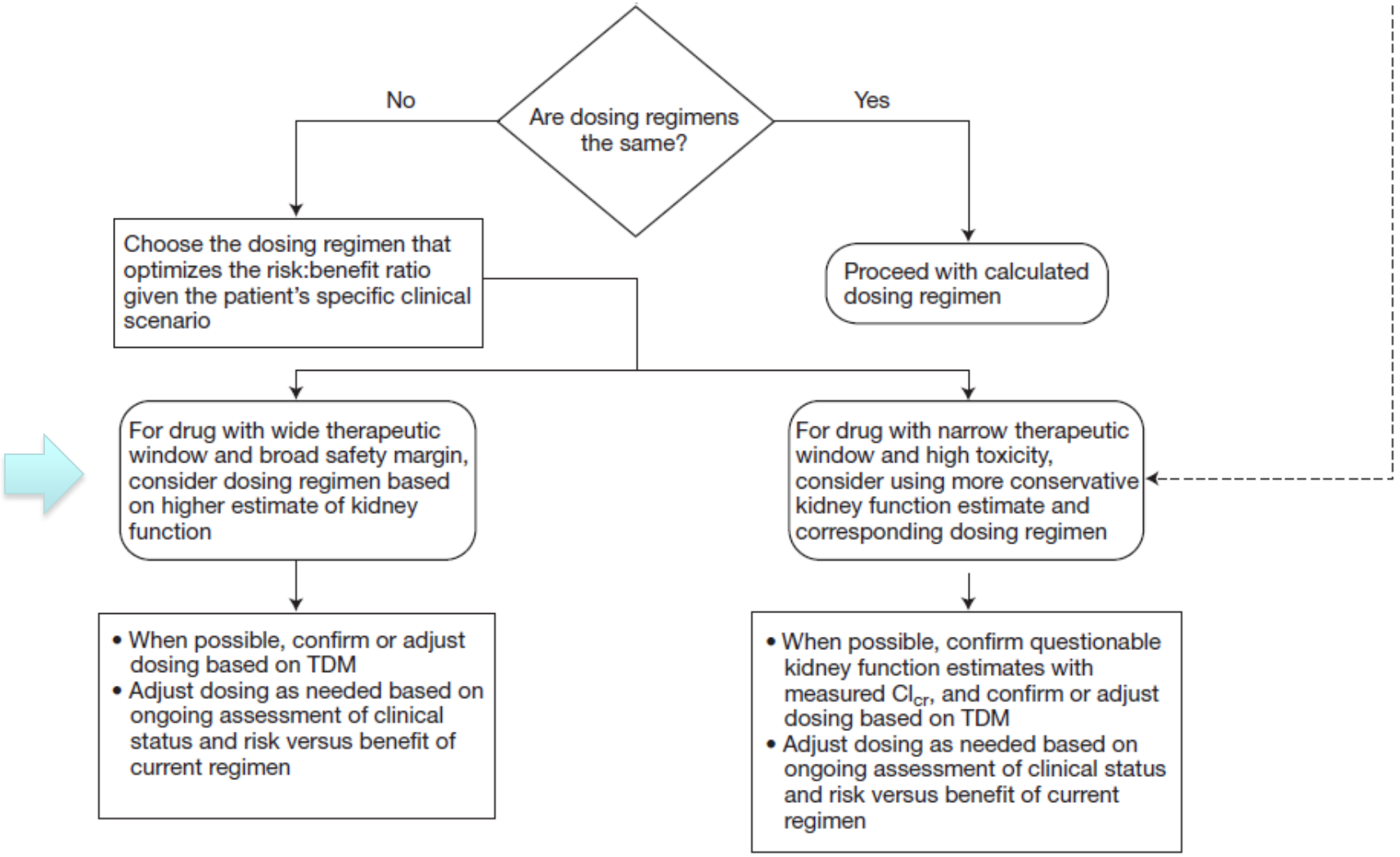




Courtesy of M Battistella

Adapted from Pharmacotherapy 2011;31:1130-1144

COMMON PRESCRIBING DILEMMAS

“Do not use”

- Absolute contraindication
  - NSAIDs
- Relative contraindications
  - Bone health (Bisphosphonates, Teriparatide (*Forteo*); Denosumab (*Prolia*) and Vit D)
  - Antibiotics and antiinfectives
  - Statins
  - Anticoagulants and antithrombotics
  - Metformin & sulphonylureas
  - Gadolinium

Bone Health – vit D

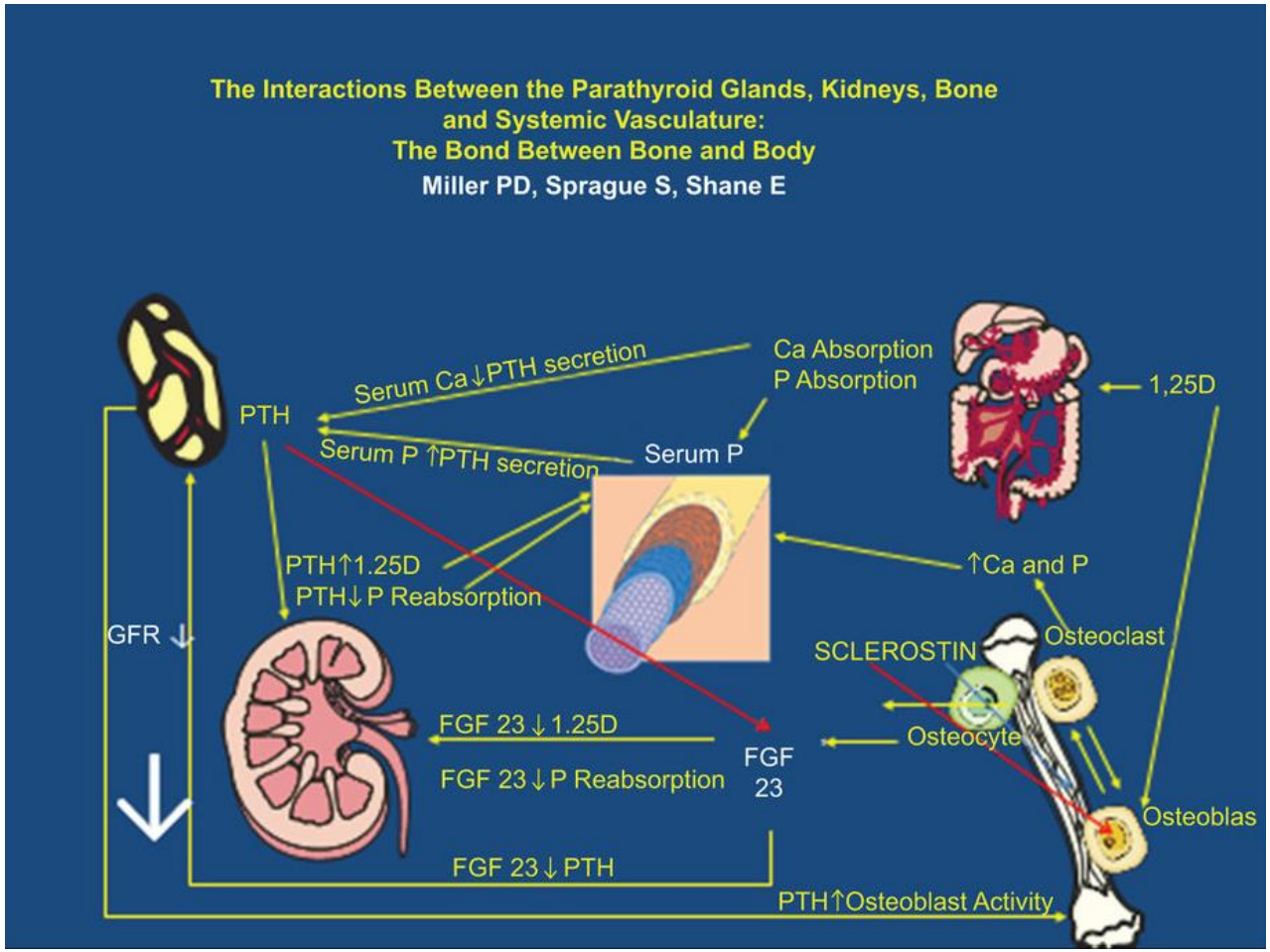
- Vit D / activated vit D (calcitriol/paracalcitriol)
  - *Controversy persists*
  - 161 studies registered at clinicaltrials.gov
  - Many completed
  - Many terminated
  - Few published

Bone Health - bisphosphonates

- Inhibit the resorption of bone by osteoclasts
- Transient ↑SCr reported with IV zoledronic acid & ibandronate

  => slow infusion

Renal bone disease @ ~30mls/min



Bone Health - bisphosphonates

- Inhibit the resorption of bone by osteoclasts
- Transient ↑SCr reported with IV zoledronic acid & ibandronate
- Renally cleared
- Renal disease dominated by fibrosis and a severely retarded *anabolic* process
- In certain circumstances, bisphosphonates will worsen bone disease

Antibiotics & antiinfectives

- Cirpofloxacin
- Aminoglycosides and Vancomycin
  - Toxic but monitoring reduces concern
- Cephalosporins
- High dose penicillins
- Acyclovir and valacyclovir
- Oseltamivir (Tamiflu)

Dose: interval vs quantity

Aminogycosides	Mild CKD (30-60) 60-80mg BID IV	Reduce frequency; closely monitor levels
Vancomycin	Mild CKD (30-60) 15-20mg/kg every 24h	Reduce frequency; closely monitor levels
Cephalosporins	Mild CKD (30-60) 1-1.5g every 8h	Reduce frequency
Penicillens	Mild CKD (30-60)	Reduce dose and frequency
Acylovir	Mild CKD (30-60)	Reduce frequency
Oseltamivir	Mild CKD (30-60) 30mg BIDx5d (Rx); 30mg ODx10-14d (Prx)	Reduce dose and frequency

… GFR, estimates and tubular function

1.	2.	3.
CrCl *22.5* *mls/min*	***MDRD*** *36* *mls/min/1.73m²*	***CKD(Epi)*** *32* *mls/min/1.73m²*

Case 3

- 84 y.o. lady, with known hypertension presents with confusion, BP 110/62 and fever due to urosepsis

- Serum creatinine 149µmol/L
- Current weight 39kg, ideal weight 50kg

- Culture: E.Coli sensitive to Cipro

What treatment do you prescribe?

1. Ciprofloxacin 500mg po twice daily
2. Ciprofloxacin 250mg po twice daily
3. Ciprofloxacin 500mg po once daily
4. Ciprofloxacin 250mg once daily

What is her Renal Function?

1.	2.	3.
CrCl *22.5* *mls/min*	***MDRD*** *36* *mls/min/1.73m²*	***CKD(Epi)*** *32* *mls/min/1.73m²*

Ciprofloxacin (Prod. Monograph)

My answer?

- 500mg ciprofloxacin over 24hr (divided dose)

Pragmatic approach needed

- Urosepsis and clinically well:
  - goal is to treat without side effects
- Endocarditis and clinical risk:
  - goal is to achieve stable MICs with high vigilance for early signs of SAEs
- HSV encephalitis:
  - Goal is therapy, but high morbidity with overdose, so more cautious

Statins

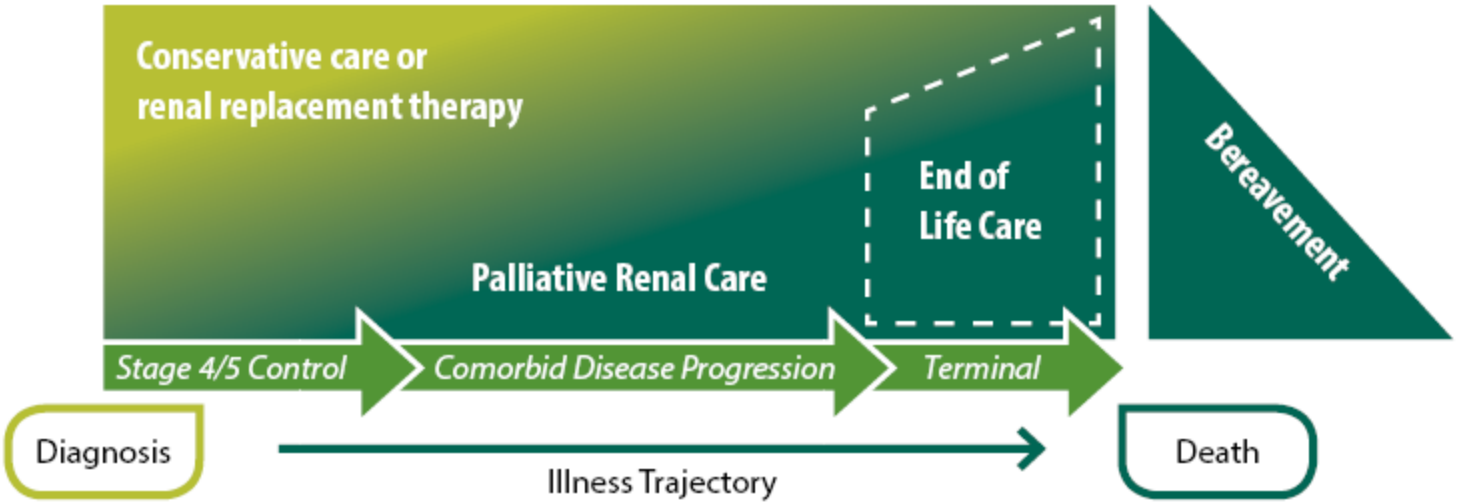
- Rosuvastatin
  - 3 fold incr in blood levels at eGFR<30
  - Higher risk of myopathy
  - At high dose new onset proteinuria in 3% of those given high dose (transient)
- Atorvastatin
  - Efficacy in CKD; lower doses (20mg)
  - Data in dialysis not/less compelling

Antithrombotic & anticoagulants

- Controversy in patients on maintenance dialysis
- Good evidence of higher bleeding risk
- +/- evidence of benefit esp in atrial fibrillation

DRUGS NEPHROLOGISTS USE

Palliative Renal Care Framework



Adapted with permission from "Advancing High Quality, High Value Palliative Care in Ontario: Declaration of Partnership and Commitment to Action," HPCO, 2011.

Recommendations - Definitions

Comprehensive Conservative Renal Care is planned holistic patient-centred care for patients with Stage 5 CKD that includes:

- Interventions to delay progression of kidney disease and minimize risk of adverse events or complications
- Shared decision-making;
- Active symptom management;
- Detailed communication including advance care planning;
- Emotional support;
- Social and family support; and
- Cultural and spiritual domains of care.

Comprehensive conservative renal care is full renal care that does not include dialysis.

Recommendations - Definitions

Palliative Dialysis is an approach to dialysis care that prioritizes the relief of suffering over the attainment of treatment targets and includes holistic patient-centred care that includes:

- Interventions to minimize immediate symptoms and distress, and promote well-being;
- Shared decision-making;
- Active symptom management;
- Detailed communication including goals of care and advance care planning;
- Emotional support;
- Social and family support; and
- Cultural and spiritual domains of care.

RAS inhibitors

- ACEi and ARB are used in early stages to reduce rate of progression
  - Profibrotic stimuli
  - Reduces stretch induced cytokines
- Also cultprit for AKI: “Sick Day” med

- Discontinued when “time to start” dialysis
- May prolong time to dialysis

“Binders” & activated vit D

- Calcium based drugs
- Sevelamer
- Lanthanum/ Aluminum
- One alpha/ calcitriol / paracalcitriol

- CKD Target “normal range”
- Dialysis Target <1.8 or “towards normal”

  (In elderly individuals on HD low PO4 not infrequent)

Bicarbonate

- Serum Bicarb >20-24 associated with less progression
- Intervention effective (and cheap)
- Low adverse events

Erythrocyte Stimulating Agents (ESAs)

- Erythropoietin (Epoetin) vs Darbepoeitin (Aranesp) vs CERA
- SC or IV administration
- Frequency x3/week to qmonthly
- Hb ≈ GFR; not Epo levels
- Started when Hb ~90-95
- Target 100-110, tho 95-115 accepted

Iron supplements

- Oral iron common
- IV iron used, but concern re oxidative effects
- Heavy emphasis onlow transferrin saturation (<0.2-0.3) particularly if ferritin <500

Palliative Care Drugs

- Evolving experience

- Caution and collaboration wrt drug dosing
  - Diuretic dosing
  - Gabapentin, pregabalin
  - Opiods
  - NSAIDs
  - Antidepressant drugs

Conclusion

- Complex and challenging
- Collaboration is key
- Experienced renal pharmacists are golden