

常見 門診 腎毒性藥品評估

馬偕醫院 呂宛真藥師

2021/5/9

66 y/o male Dx:

- ▶ 1. Unstable angina with IHD, CHF, CAD
- ▶ 2. HTN & HCVD
- ▶ 3. Hyperlipidemia
- ▶ 4. CKD, proteinuria
- ▶ 5. BPH
- ▶ 6. Anxiety disorder
- ▶ 7. Gout Hx & hyperuricemia
- ▶ 8. GU Hx

2021/04 Creatinine 1.3 (eGFR 55.2),
Potassium 5.6

用藥

- ▶ Clopidogrel 、 Propranolol
- ▶ Crestor, Ezetrol
- ▶ Duodart (Dutasteride & Tamsulosin) ,
Fronil (Imipramine)
- ▶ Famotidine
- ▶ Erispan-S (Fludiazepam)
- ▶ Benzbromarone
- ▶ 腎內 FORFLOW* 400mg(pentoxifylline)
- ▶ Canaglu (Canagliflozin) 100mg 1# QD
- ▶ Aprovel (Irbesartan)150mg 1# BID

案例

發生甚麼事？

- ▶ 1. 病人已嚴格進行飲食控制，但血鉀一直偏高

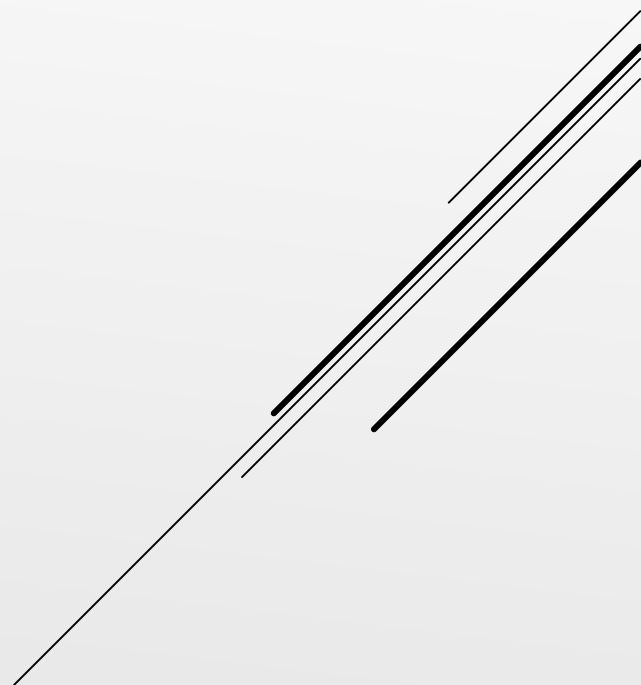
疑似Aprovel related hyperkalemia，請病人先停用此藥，密切監測血壓，與醫師討論換藥或減量事宜

- ▶ 2. Hba1c 5.3，glucose ac 103，處方Canaglu Tablets 100mg (SGLT2 inhibitor for renal protection)，用藥後體重降2kg，Scr 上升至1.6 (eGFR<45)，停用後回復至1.3

建議先停用canagliflosin，與醫師討論使用之必要，衛教SGLT2常見副作用與注意事項

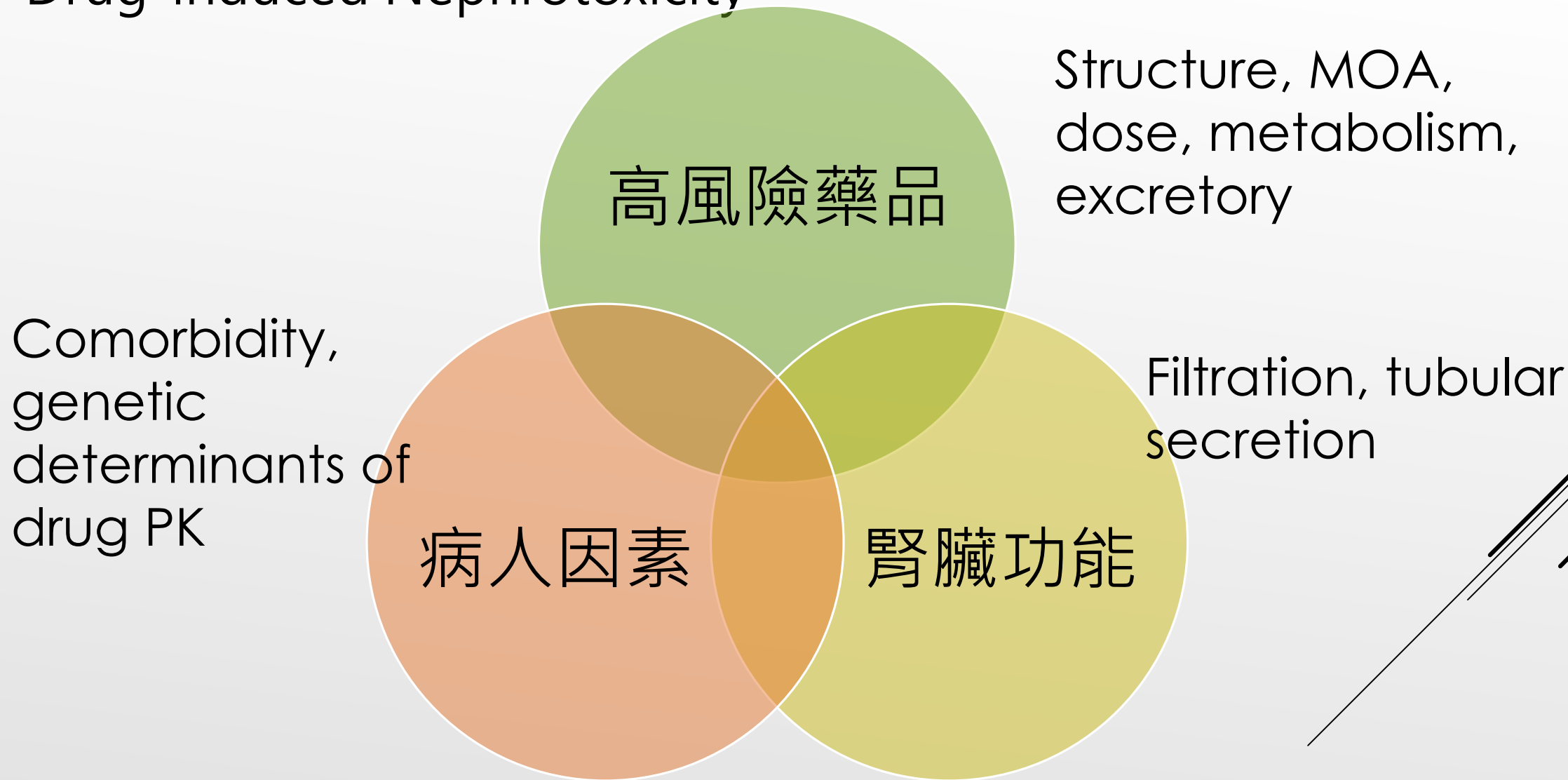
門診病人常見用藥

- ▶ 慢性疾病用藥
- ▶ 中草藥、健康食品
- ▶ 檢查用藥: 清腸藥品、顯影劑



藥物造成的腎毒性

Drug-induced Nephrotoxicity



造成腎衰竭的可逆性(可校正)原因:

- ▶ Decreased renal perfusion (減少腎臟血流)
- ▶ Administration of nephrotoxic drugs (腎毒性藥物)
- ▶ Urinary tract obstruction (尿道阻塞)

Identified & Corrected

預防 勝於 治療

(就像打COVID-19疫苗)



Analgesics

NSAIDs

Selective COX-2 inhibitors

Phenacetin

Analgesic combinations

Immunosuppressives

Calcineurin inhibitors

Sirolimus, everolimus

Other

ACE inhibitors/ARBs/renin inhibitors

SGLT-2 inhibitors (canagliflozin, dapagliflozin)

Methoxyflurane

Sucrose (IVIg excipient), hydroxyethyl starch, mannitol, dextran

Pamidronate, Zolendronate

Topiramate, Zonisamide

Orlistat

Statins

Mesalamine

Table 1. Nephrotoxic drugs and intoxicants

Therapeutic medications

Antimicrobial

Aminoglycosides

Antiviral agents

Amphotericin B

Colistin

Polymixin B

Sulfadiazine

Quinolones

Vancomycin

Chemotherapy

Platins

Ifosfamide

Mitomycin

Gemcitabine

Methotrexate

Pentostatin

Interleukin-2 (high dose)

Antiangiogenesis agents

Alternative/health products

Herbal remedies

<i>Aristolochic acid</i>	馬兜鈴酸
<i>Ephedra sp.</i>	麻黃
<i>Glycyrrhiza sp.</i>	甘草
<i>Datura sp.</i>	曼陀羅
<i>Taxus celebica</i>	南方紅豆杉
<i>Uno degatta</i>	(秘魯草藥)
<i>Cape aloes</i>	好望角蘆薈

Adulterants

Mefenamic acid
Dichromate
Cadmium
Phenylbutazone
Melamine

Diagnostic agents

Radiocontrast

High osmolar
Low osmolar
Iso-osmolar

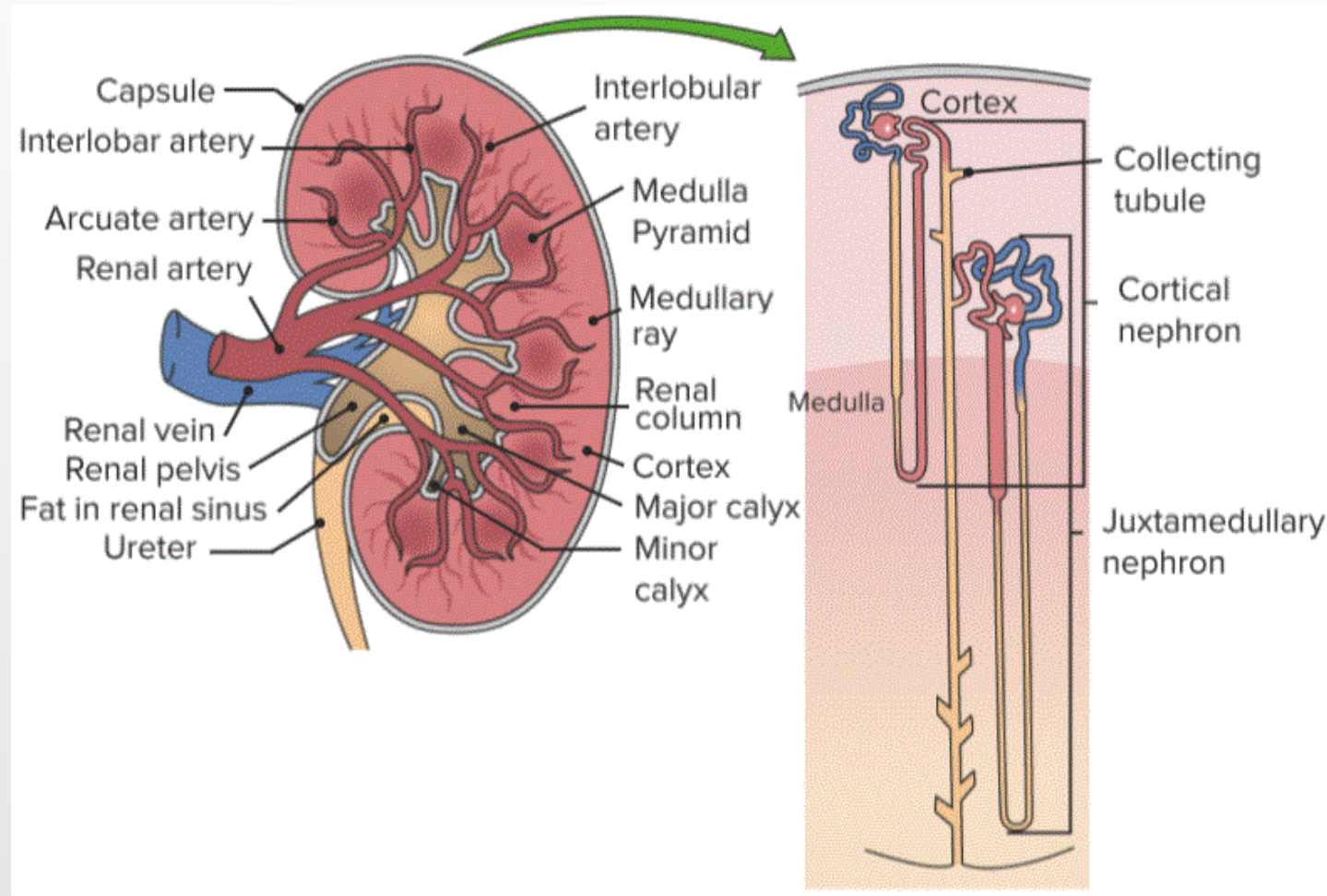
Other agents

Gadolinium (in high dose)
Oral NaP solution (colonoscopy prep)

Clin J Am Soc Nephrol 13:
1897-1908, 2018

急性腎損傷(Acute Renal Injury)

- ▶ Prerenal azotemia
- ▶ Intrarenal toxicity
 - ▶ Vascular injury
 - ▶ Interstitial injury
 - ▶ Glomerular injury
- ▶ Postrenal injury



Cortex. Image by Lecturio.

PRERENAL AZOTEMIA (腎前氮血症)

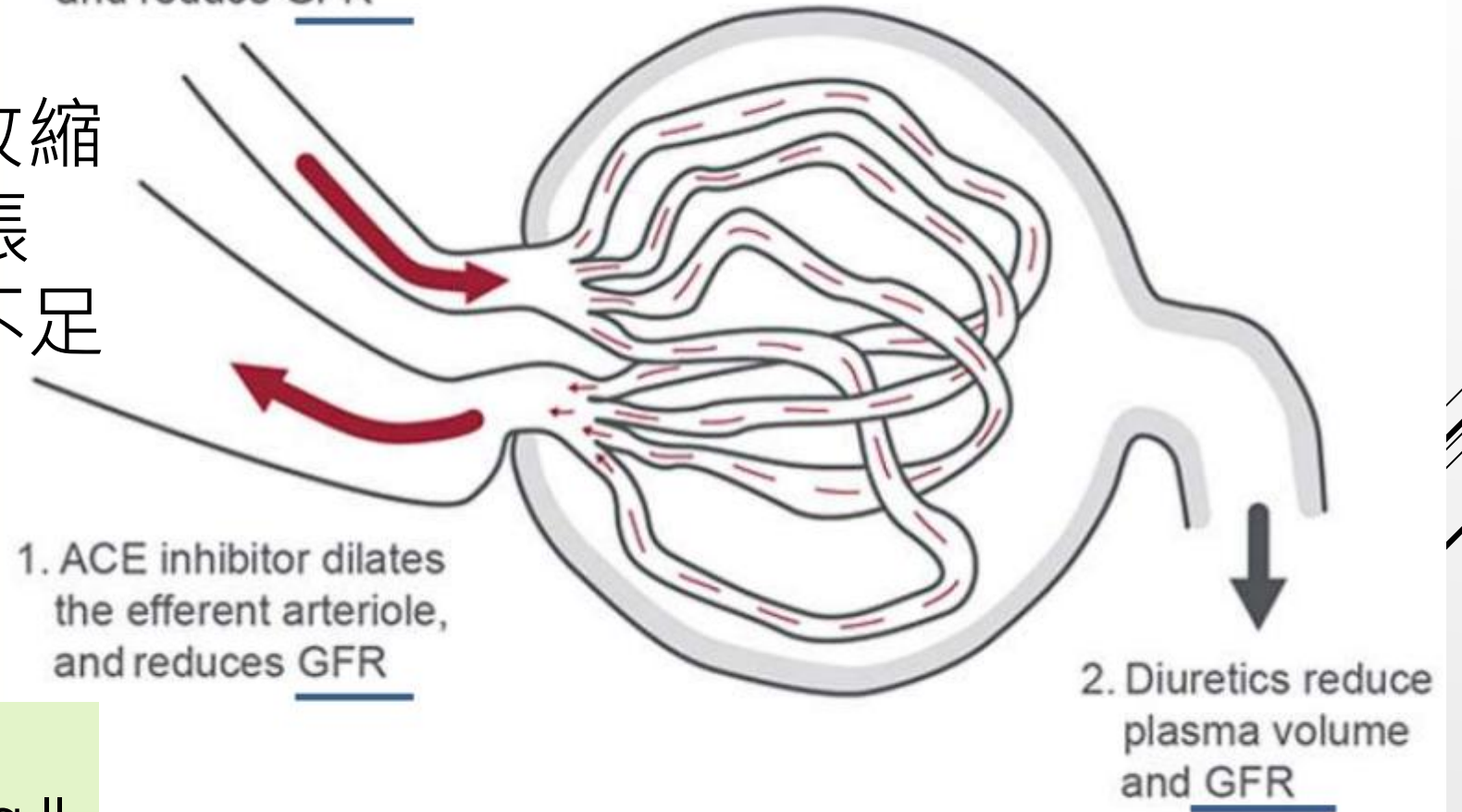
Decreased Renal Perfusion

- ▶ Diuretics
- ▶ Vasodilators: ACEI/ARB
- ▶ NSAID/COX inhibitor
- ▶ cyclosporine
- ✓ 合併藥物使用
- ✓ 老年、衰弱
- ✓ 大量體液流失: 嘔吐, 腹瀉
- ✓ 血管內容積不足: 心輸出下降、
肝硬化、腎病症候群

NSAID: 入球小動脈收縮
ACEI: 出球小動脈擴張
Diuretics: 體液容積不足

3. NSAIDs constrict blood flow into the glomerulus via the afferent arteriole and reduce GFR

Afferent arteriole
Vasodilatory PG

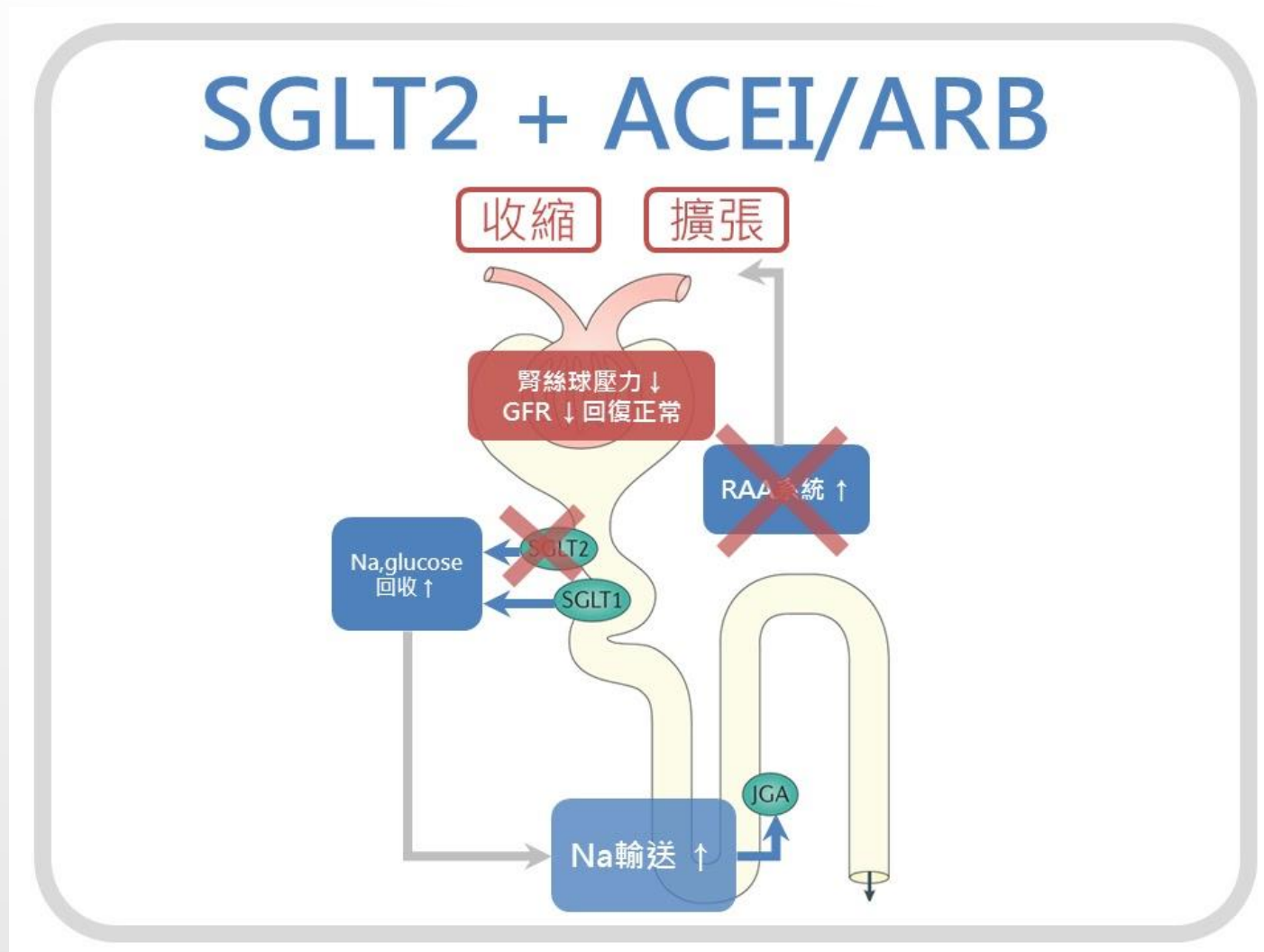


Efferent arteriole
Vasoconstrictor Ang II

The 'triple whammy' effect to reduce glomerular filtration rate.

SGLT2 Inh 前三個月可觀察到 腎絲球過濾率 短暫而明顯的下降

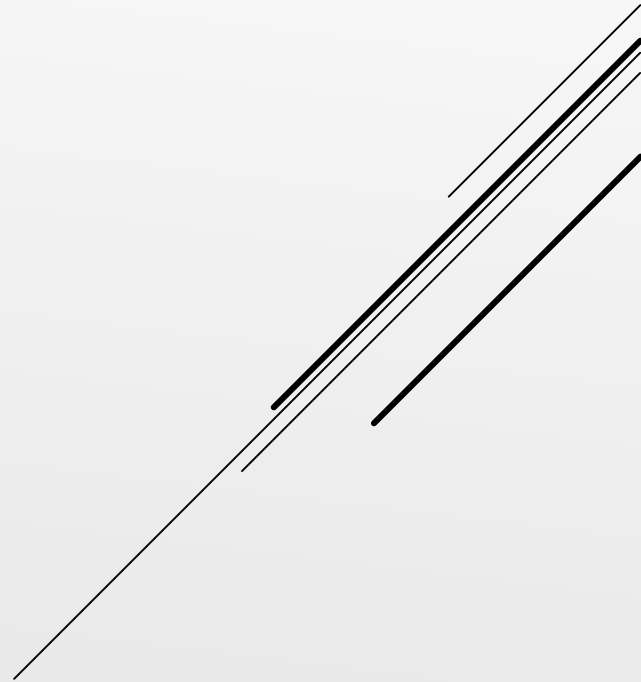
使用 SGLT2 抑制劑時，抑制了 Na 和水的回收，使 Na 至後段輸送增加，腎小球旁受器 (JGA ， juxtaglomerular apparatus) 感應了，判斷過濾量太多，會縮緊腎絲球的入口 (入球小動脈)，使腎絲球過濾率降低



From 腎臟科醫師看降血糖藥 SGLT2 抑制劑 - 葉時孟醫師

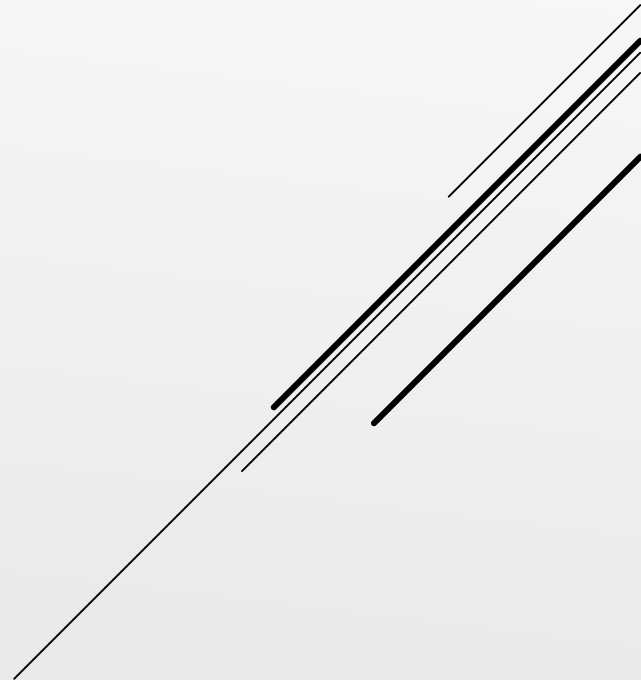
INTRARENAL TOXICITY (腎内毒性)

- ▶ Vascular injury (血管性傷害)
- ▶ Tubular injury (腎小管傷害)
- ▶ Interstitial injury (腎間質傷害)
- ▶ Glomerular injury (腎絲球傷害)



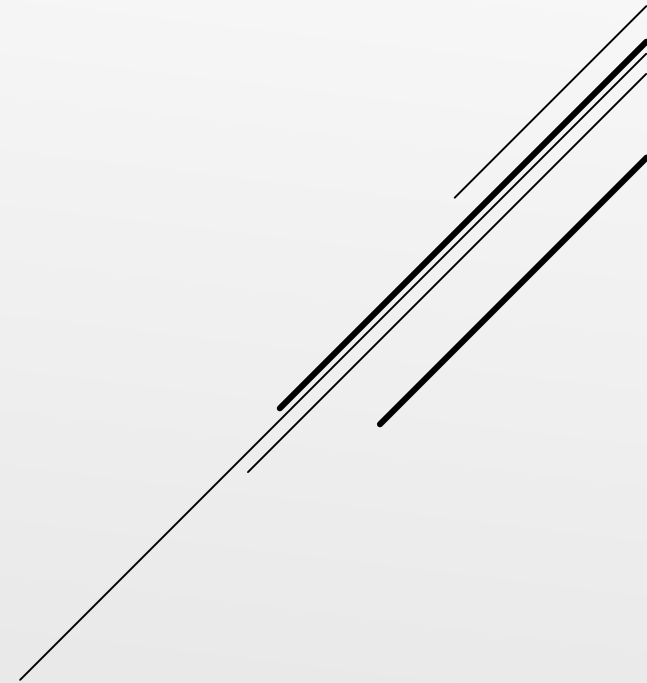
TUBULAR INJURY

- ▶ Aminoglycosides, **quinolones**, amphotericin B
- ▶ cisplatin, foscarnet, zoledronate
- ▶ **radiocontrast media**
- ▶ cidofovir, **adefovir, tenofovir**,
- ▶ mannitol, dextran, hydroxyethylstarch



Intrinsic renal injury (Immune-mediated interstitial inflammation)

- ▶ penicillin, cephalosporins
- ▶ rifampin, ciprofloxacin, clarithromycin
- ▶ sulfonamides
- ▶ phenytoin, allopurinol
- ▶ pantoprazole, omeprazole
- ▶ atazanavir



Intrinsic renal injury (vascular effects: thrombotic microangiopathy)	Ciclosporin, tacrolimus, mitomycin C, conjugated estrogens, quinine, 5-fluorouracil, ticlopidine, clopidogrel, interferon, valaciclovir, gemcitabine, bleomycin	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, supportive care, plasmapheresis if indicated
Intrinsic renal injury (vascular effects: cholesterol emboli)	Heparin, warfarin, streptokinase	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, supportive care, plasmapheresis if indicated
Intrinsic renal injury (tubular toxicity)	Aminoglycosides, radiocontrast media, cisplatin, nedaplatin, methoxyflurane, outdated tetracycline, amphotericin B, cephaloridine, streptozocin, tacrolimus, carbamazepine, mithramycin, quinolones, foscarnet, pentamidine, intravenous gammaglobulin, fosfamide, zoledronate, cidofovir, adefovir, tenofovir, mannitol, dextran, hydroxyethylstarch	FENa >2%, UOsm <350, urinary sediment with granular casts, tubular epithelial cells	Drug discontinuation, supportive care
Intrinsic renal injury (rhabdomyolysis)	Lovastatin, ethanol, codeine, barbiturates, diazepam	Elevated CPK, ATN urine sediment	Drug discontinuation, supportive care
Intrinsic renal injury (severe hemolysis)	Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephénytoin	High LDH, decreased hemoglobin	Drug discontinuation, supportive care
Intrinsic renal injury (immune-mediated interstitial inflammation)	Penicillin, methicillin ampicillin, rifampin, sulfonamides, thiazides, cimetidine, phenytoin, allopurinol, cephalosporins, cytosine arabinoside, furosemide, interferon, NSAIDs, ciprofloxacin, clarithromycin, telithromycin, rofecoxib, pantoprazole, omeprazole, atazanavir	Fever, rash, eosinophilia, urine sediment showing pyuria, white cell casts, eosinophiluria	Discontinue medication, supportive care
Intrinsic renal injury (glomerulopathy)	Gold, penicillamine, captopril, NSAIDs, lithium, mefenamate, fenoprofen, mercury, interferon-α, pamidronate, fenclofenac, tolmetin, foscarnet	Edema, moderate to severe proteinuria, red blood cells, red blood cell casts possible	Discontinue medication, supportive care

Vascular injury	Cyclosporine, tacrolimus	Discontinue medication, supportive care
Tubular injury	Aminoglycosides, radiocontrast media zoledronate adefovir, tenofovir	
Interstitial injury	Penicillin, cephalosporines, sulfonamides, thiazide, cimetidine, phenytoin, allopurinol, NSAID, ciprofloxacin, PPI	
Glomerular injury	Captopril, NSAID, lithium, pamidronate	

POSTRENAL INJURY (腎後阻塞性傷害)

- ▶ Intratubular obstruction: renal colic with flank pain

Acyclovir, ganciclovir, methotrexate, sulfanilamide, indinavir, foscarnet

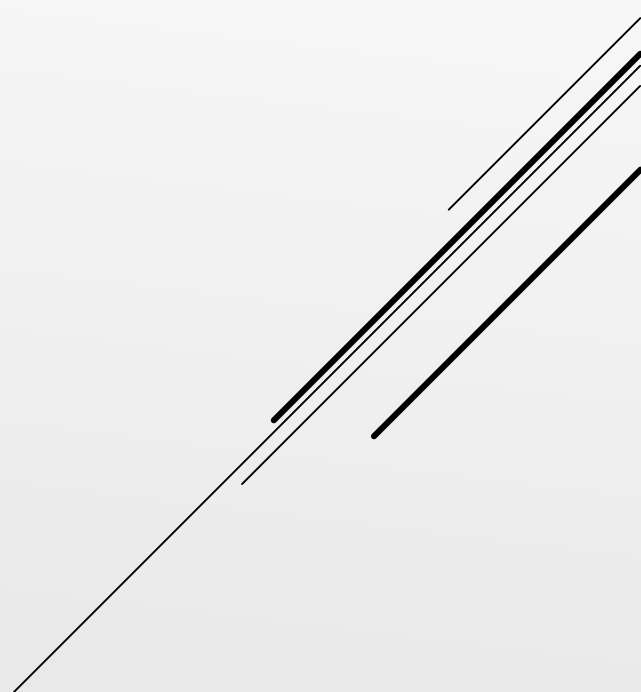
- ▶ Ureteral obstruction: hydronephrosis

Methysergide, ergotamine, dihydroergotamine, methyldopa, hydralazine, atenolol



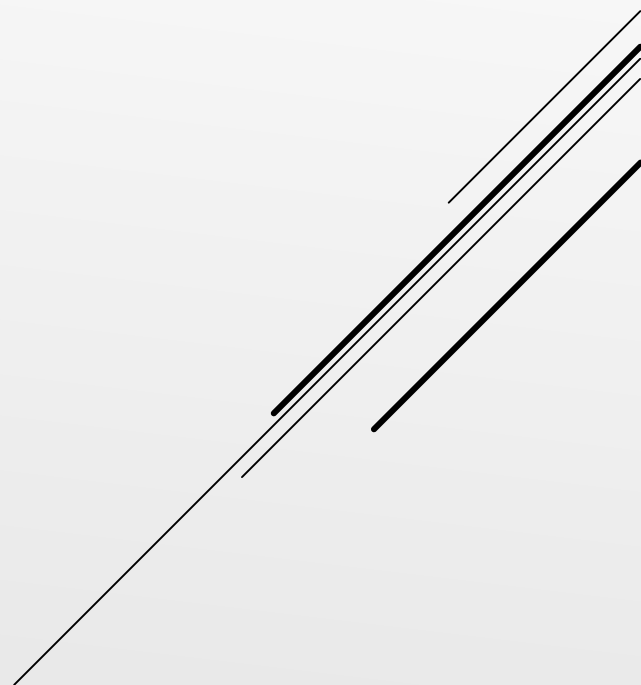
長期使用造成的腎毒性(Chronic use)

- ▶ Analgesics: NSAID, acetaminophen
- ▶ Calcineurin inhibitors
- ▶ Lithium: nephrogenic diabetes insipidus



門診病人

- ▶ 止痛
- ▶ 抗生素
- ▶ 三高: 高血壓、糖尿病、高血脂、心衰竭
- ▶ 免疫調節



具潛在影響腎功能風險藥品 (2020台灣急性腎損傷處置共識)

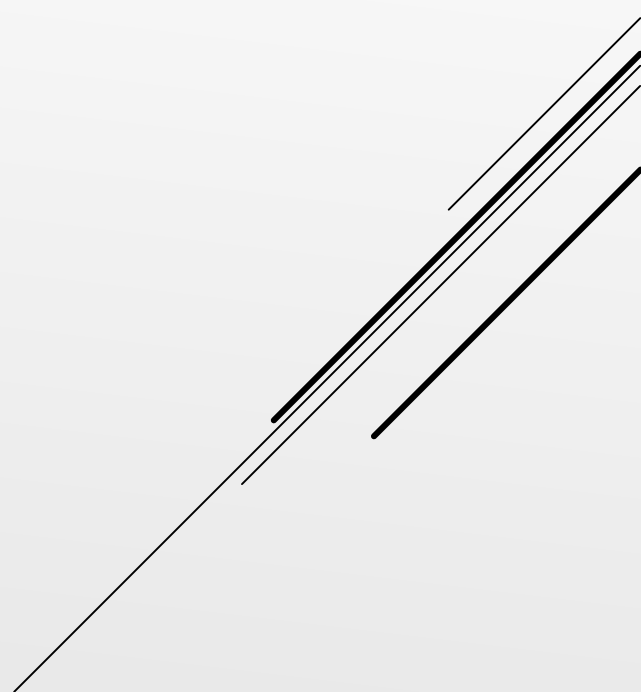
Drug	Incidence	LOE
5-Aminosalicylic acid	-	C
ACEi and ARB	6-38%	B
Allopurinol	-	B
Cyclosporine	25-38%	A
Furosemide	14%	B
H2-receptor antagonist	-	C
Hydralazine	-	C
Lithium	11.6-15%	B
Loop diuretic	-	C
Methotrexate (>500 mg/m ²)	12%	A

Drug	Incidence	LOE
NSAID	1-7%	A
Phenytoin	-	C
PPI	-	C
Propylthiouracil	-	C
Radiocontrast media	0-81%	A
Tacrolimus	-	A
Thiazide diuretic	-	C
Topiramate	1-3%	A
Valproic acid	-	C
Zonisamide	1.9-4%	B

Drug	Incidence	LOE
Ampicillin	-	C
Beta-lactam antibiotic	-	C
Ciprofloxacin	-	C
Erythromycin	-	C
Rifampin	-	B
Sulfamethoxazole + Trimethoprim	11-22%	B
Sulfadiazine	29%	B
Acyclovir	-	C
Valacyclovir	-	C
Valganciclovir	-	C
Tenofovir	12%	A
Atazanavir	-	A
Indinavir	12-21%	A

判斷可疑藥物

1. 時序關係: 新增藥品、增加劑量
2. 劑量、頻次、血中濃度 (劑量相關: type A)
3. 合併危險因子: 脫水、感染、疾病惡化
4. 藥物交互作用(合併多種腎毒性藥物)
5. 停藥後反應(可逆與不可逆腎毒性)



預防方式

- ▶ 辨認高風險藥物，避免使用，或選用替代藥物
 - ▶ 必需使用/無替代藥物，則應
 1. 依腎功能調整劑量
 2. 使用最低有效劑量，最短療程
 3. 給與相對應的預防措施(促進藥物排除、給與保護劑)
 4. 密集監測腎功能(初期須頻繁監測)
 5. 衛教病人腎功能惡化之徵兆，及早發現處理
- 

HERPES ZOSTER/VARICELLA

Acyclovir (po)

CrCL	Dose
> 25	800 mg q4h (5 times daily)
10 to 25	800 mg q8h
0 to 10	800 mg q12h

Valacyclovir

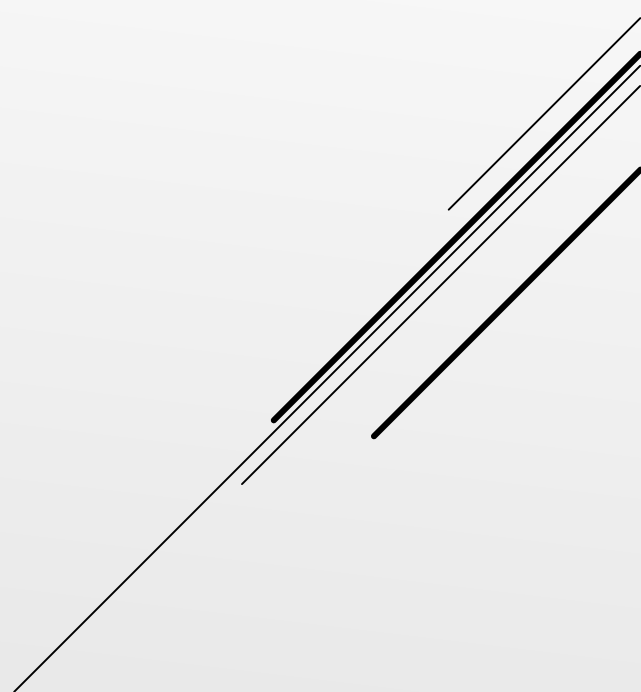
CrCl	Dose
≥50	1 g q8h
30 to 49	1 g q12h
10 to 29	1 g q24h
< 10	500 mg q24h

Famciclovir

CrCL	Dose
>60	500 mg q8h
40 to 59	500 mg q12h
20 to 39	500 mg q24h
<20	250 mg q24h
HD	250 mg following each dialysis

已發生腎毒性之處理方式

1. 停藥或換藥
2. 給與解毒劑
3. 促進藥物之排除(eg 透析、鹼化尿液)
4. 校正危險因子、避免其他腎毒性藥物



假性腎毒性

Pseudo- nephrotoxicity

- ▶ Competition with creatinine for tubular secretion
 - ✓ trimethoprim
 - ✓ cimetidine

Drug-associated renal dysfunction and injury
Nature Clinical Practice Nephrology volume 2, pages80–91(2006)

Box 1 Drugs that cause pseudo-elevation of blood urea nitrogen and creatinine.

Competitive tubular secretion of creatinine

- Trimethoprim
- Cimetidine
- Probenecid
- Triamterene
- Amiloride
- Spironolactone

Interference with laboratory determination of creatinine

- Ascorbic acid
- Cephalosporins (cefoxitin and cephalothin)
- Flucytosine
- Levodopa
- Methyldopa

Hypercatabolic effect

- Steroids
- Tetracycline

附表 6-1：急慢性腎臟疾病照護與衛教計畫-藥事照護評估紀錄

病人基本資料 (身份證字號: _____)

收案編號(系統代入): _____-_____

姓名:	病歷號:	評估藥師:
年齡: ☐ 男 ☐ 女	身高/體重:	主治醫師:
過敏藥物:	Scr/eGFR:	CKD Stage:

☐新收案評估(P*****)

☐定期追蹤(P#####)

☐年度評估(P!!!!)

(日期: YY/MM/DD)

(日期: YY/MM/DD)

(日期: YY/MM/DD)

收案條件: ☐ postAKI ☐ 具 CKD 外 2 項以上(含)共病; ☐ 用藥品項≥10 項; ☐ 近期使用 NSAID ☐ 其它				
Post AKI	AKI 日期: YY/MM/DD	基礎 Scr 值:	最高 Scr 值	AKI 最高分期: ☐ 1 ☐ 2 ☐ 3 ☐ RRT

風險藥品	☐ RAS inhibitor ☐ 保鉀利尿劑 ☐ 其它: _____
影響腎功能藥品 (參閱台灣 AKI 共識 ²⁾)	☐ 顯影劑(14 天內) ☐ NSAID ☐ Acyclovir ☐ Cyclosporin ☐ Lithium ☐ Protease inhibitor (Atazanavir、Indinavir) ☐ Sulfamethoxazole-trimethoprim ☐ Tacrolimus ☐ Tenofovir ☐ Valaciclovir ☐ Valganciclovir ☐ 針劑及其他: _____

病人現有伴隨系統性疾病(參閱附表 2-1): ☐B01 (糖尿病), ☐B02 (高血壓), ☐B03 (痛風), ☐B04 (鬱血性心衰竭),
☐B05 (缺血性心臟病), ☐B06 (腦血管病變), ☐B07 (慢性肝疾病/肝硬化), ☐B08 (惡性腫瘤), ☐B09 (結核), ☐B10 (高
 血脂), ☐B11 (視網膜病變), ☐B12 (神經病變), ☐B13 (貧血), ☐B14 (自體免疫疾病), ☐B15 (其他):

附表 6-3 藥師藥事指導/衛教項目 (6-1-3 參照使用)

面向	項目內容
疾病自我照顧之指導及建議	☐ A1 三高共病控制的必要性 ☐ A2 影響腎功能惡化的因子(原衛教 3-3) ☐ A0 其他：_____
用藥知識及藥物使用指導	☐ B1 整體目前用藥說明/注意事項 ☐ B2 吃藥的好處/不吃藥的壞處 ☐ B3 正確使用止痛藥 ☐ B4 正確用藥 5 大核心能力(對明白/用正確) ☐ B5 貧血治療:使用 EPO 與鐵劑治療(原衛教 4-2) ☐ B0 其他：_____
指導用藥技巧	☐ C1 提供服藥完整性評估及指導，如：_____ ☐ C2 提供藥盒輔具 ☐ C3 提供_____衛教單

避免藥物腎傷害

- ☐ D1 腎毒藥品用藥衛教 (參閱台灣 AKI 共識)
- ☐ D2 即將進行顯影劑檢查前後之用藥衛教

其他可能造成
急性腎衰竭
之藥物

Afatinib, Dasatinib, Erlotinib

Amiodarone, Dronedarone

Deferasirox, Deferoxamine

Dexlansoprazole

Exenatide, Liraglutide

Fenofibrate

Isoniazid/Rifampin

Memantine

Paroxetine

Pravastatin, Rosuvastatin

Rivastigmine

Sitagliptin, Saxagliptin

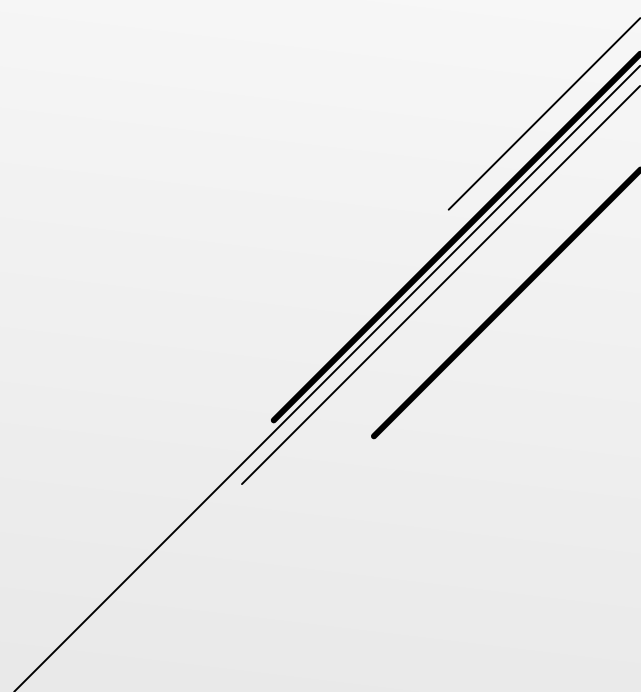
Sirolimus

Tretinoin

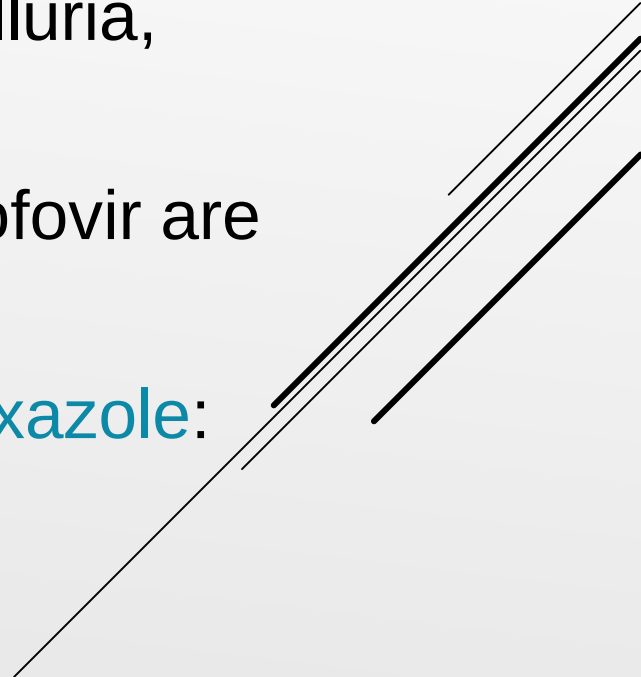
Diltiazem, Verapamil

其他特殊用藥

- ▶ HIV相關治療藥物
- ▶ 檢查用藥: 清腸劑與顯影劑



HIV病人常見之腎毒性藥物

- **Tenofovir disoproxil fumarate (TDF)** –A newer prodrug, tenofovir alafenamide (TAF)
 - Protease inhibitors – **Indinavir** and **atazanavir**: crystalluria, nephrolithiasis, and AKI. (alternative: darunavir)
 - Other antiviral agents – **Acyclovir**, foscarnet, and cidofovir are drugs used to treat HSV or CMV infection.
 - Anti-Pneumocystis drugs – **Trimethoprim-sulfamethoxazole**: interstitial nephritis
- 

清腸用瀉劑 ★

大分子等滲透性緩瀉劑，幾乎不會被腸道吸收

- ✓ 刻見清(Klean-Prep powder, Polyethylene glycol 3350)
- ✓ 耐福力散(NIFLEC, PEG 4000)
- ▶ 護舒達 (Fleet Phospho-Soda)：高滲透壓型**磷酸**鈉瀉劑
- ▶ 保可淨 (Bowklean)：picosulfate sodium (刺激性瀉劑) 和**magnesium** citrate (滲透性瀉劑)
- ▶ 鎂福內服液(Magvac Oral Solution): **magnesium** citrate



顯影劑引起的腎病變

- ▶ Contrast-associated AKI (CA-AKI)
- ▶ Contrast-induced AKI (CI-AKI)=contrast-induced nephropathy (CIN)
- ▶ Scr在注射顯影劑三天後達到最高點，大部分在7 ~ 10 天回到基礎值
- ▶ 高危險族群，發生率可達20%

危險因子: 腎功能不全 ($\text{eGFR} < 60 \text{ ml/min}$)、糖尿病、體液不足、大於75 歲、尿蛋白、高血壓或低血壓、鬱血性心衰竭、肝硬化以及腎病症候群

接受顯影劑24 ~ 48小時內，Scr上升 $\geq 0.3 \text{ mg/dL}$ / 0.5 mg/dL 或25% / 7天內上升 ≥ 1.5 倍 baseline

顯影劑腎病變1: 血管攝影

Contrast-Induced Acute Kidney Injury (CI-AKI)

- ▶ Use **nonionic low-osmolal agents**. 非離子性低滲透壓
- ▶ 高風險病人 (At-risk patients) 採取預防措施: eGFR < 60 mL/min/1.73 m², proteinuria, diabetes, heart failure, liver failure, or multiple myeloma.
 - ✓ **Avoid volume depletion and NSAIDs.**
 - ✓ **Isotonic saline hydration**
 - ✓ **? bicarbonate/acetylcysteine/mannitol or other diuretics**

顯影劑腎病變2: 斷層掃描(CT)

- ▶ 高風險病人採取預防措施
 - Stable eGFR <30 mL/min/1.73 m² and not on dialysis.
 - Ongoing episode of AKI.
- ✓ intravenous fluid administration/oral hydration
- ✓ Use low- or iso-osmolar contrast agents.
- ✓ Metformin、非必要的潛在腎毒性藥物，停用48小時，至腎功能回復後再重新使用

MRI 磁共振造影檢查

- ▶ 含釷 (Gd^{3+}) 顯影劑 (Gadolinium-based contrast agents , GBCA)
- ▶ 腎因性全身性纖維化 (Nephrogenic systemic fibrosis, NSF) : 腎功能不佳的病人在使用 GBCA 的嚴重併發症，疾病的成因未明，主要表現為皮膚纖維化，可能併有心、肺、肝、肌肉等的全身性纖維化，造成多重器官衰竭與死亡。但並非每個腎功能不佳的病人都會發生 NSF

臨床處置

- ▶ AKI 或 $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ 或透析病人
不要使用gadolinium-based contrast agent (GBCA)
- ▶ 必須使用時，選用Group II GBCA – Associated with few or no verified unconfounded NSF cases (gadobenate, gadobutrol, gadoteridol, gadoterate meglumine).

二、顯影劑

建議強度	建議內容	證據等級
A	接受顯影劑時，在水分充足下可嘗試使用 N-acetylcysteine，但不確定其能有效預防顯影劑腎病變。	1++ 1+
B	含碘顯影劑造成腎臟傷害的危險因子包括腎功能不全（ $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$ ）、糖尿病、術前體液不足、年齡大於75歲、尿蛋白、高血壓或低血壓、鬱血性心衰竭、肝硬化及腎病症候群。	2++
B	在腎絲球過濾率 $< 30 \text{ ml/min/1.73m}^2$ 的病人使用含 gadolinium 的核磁造影顯影劑有機會造成腎因性全身纖維化 (nephrogenic system fibrosis)，使用上宜謹慎。	1++ 1-

感謝聆聽，敬請指教

