In the name of " God”

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Nephrotoxins

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Acute Interstitial Nephritis
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Crystalluria/Nephrolithiasis
Altered Electrolyte Handling

Aminoglycosides

Aminoglycoside

gentamicin, tobramycin, dibekacin, amikacin, netilmicin, isepamicin and arbekacin

Incidence of nephrotoxicity of 7.3%

Aminoglycoside-induced nephrotoxicity

Tubular dysfunction

- **proximal tubular cell necrosis**

  in order from most toxic to least, is neomycin, gentamicin, tobramycin, and amikacin (dependent on the number of ion-izable amino groups), which affects brush-border six for neomycin, five for gentamicin, four for amikacin and kanamycin, and three for streptomycin

Glomerular dysfunction(AKI)

- GFR decrease angiotensin II–mediated afferent arteriolar vasoconstriction
- Kf (glomerular capillary ultrafiltration coefficient) is decreased because of a decrease in the number and density of glomerular capillary wall fenestrae

- it is rare, severe, sustained renal dysfunction has been described with peak serum creatinine levels at 3-10 days after cessation of aminoglycoside therapy and full recovery in weeks

Risk factors of aminoglycoside nephrotoxicity

Patient factors

- Age
- Pre-existing renal disease
- Magnesium, potassium, calcium deficiency, sodium depletion, hypoalbuminemia, diuretics
- acid-base disturbances
- hyperphosphatemia
- Intravascular volume depletion
- hypotension
- Hepatic syndrome(biliary obstruction or cholangitis)
- Sepsis syndrome

Aminoglycoside factors

- Recent aminoglycoside therapy
- Larger doses
- Treatment of 3 or more days
- Drug choice: e.g. gentamicin , amikacin vs Drug choice: e.g. tobramycin
- Frequent dosing interval

Concomitant drugs

Amphotericin B, Cephalosporins , Cisplatin, Clindamycin, Cyclosporine, Foscarnet, Furosemide, IV radiocontrast agents, Piperacillin ,Vancomycin

Prevent aminoglycoside-induced nephrotoxicity

Limit the duration of treatment to maximal 7 days

Choose the least toxic aminoglycoside

Adapt dose to renal function

Avoid concomitant administration of potentially nephrotoxic drugs

Determine clinical risk factors

thrice a day (TID) to once-day (QD)

clearance is slower during periods of inactivity such as sleep

Nephrotoxicity may be attenuated by

increased intake of dietary calcium

alkalinization of the urine

solute diuresis

use of calcium-channel blockers

captopril

Beta lactam anbiotics

Beta lactam anbiotics

- Penicillins
- Cephalosporins and cephamycins
- Carbacephems and carbapenems
- Monocyclic beta-lactams

Mechanisem

- Organic anion transporter(1,2,3) in PTC

Renal injury mechanism

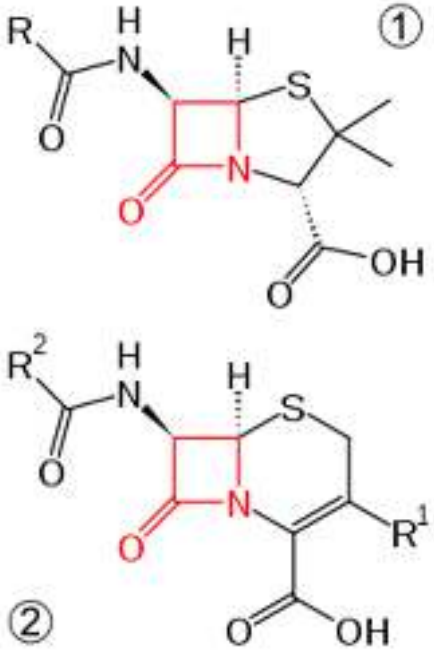
- Mitochondrial damage

Clinical characteristics

- ATN
- AIN(meticilline)
  - Fever, Rash, Oliguria, Artheralgia
  - Urine:Pyuria, eosinophiluria, pu, azotemia
  - therapy
  - Discountinuation
  - Glucocorticoids

prevention

- Administration of organic anion transporter inhibitors (probenecid) may help to prevent injury
- Drug dosage should be adjusted patient's renal function



core structure of penicillins (top) and cephalosporins (bottom). β-Lactam ring in red.

First generation (eg, cefazolin)

Second generation
- A. Subgroup with activity against *Haemophilus influenzae* (eg, cefuroxime)
- B. Cephamycin subgroup with activity against *Bacteroides* spp (eg, cefoxitin and cefotetan)

Third generation
- A. Subgroup with broad gram-negative activity but poor activity against *Pseudomonas aeruginosa* (eg, cefotaxime and ceftriaxone)
- B. Subgroup with broad gram-negative activity including good activity against *Pseudomonas aeruginosa* (eg, ceftazidime)

Fourth generation (eg, cefepime)

Fifth generation (eg, ceftaroline)

Vancomycin

Vancomycin

vancomycin-associated nephrotoxicity

Mechanism:mitochondri damage ,oxidative stress, autophagy,and apoptosis

AKI

incidence 5% to 43%

drug and patient factors

Patient-related risk factors include

obesity, CKD, severity of illness, and concurrent administration of other neph-rotoxic agents

Drug-related risk factors include

area under the curve (AUC) determinations(dose/exposure proxy),

Through level (<15mg/lit)

duration of therapy(<7 days), method of administration(continuous)

AIN

Prevention

Teicoplanin, quinupristin/dalfopristin and linozolid

vitamin E, vitamin C, N-acetylcysteine, caffeic acid phenethyl ester, and erythropoietin on vancomycin Nephrotoxicity(in rodent models)

Sulfonamides

Sulfonamide(+_Trimethoprim)

TMP-SMZ pathways of nephrotoxicity

tubulo-obstructive, tubulotoxic, and immunologic

sulfonamide-induced nephrotoxicity

- AKI, secondary to crystalluria
- acute interstitial nephritis
- necrotizing arteritis AKI
- hemoglobinuric AKI
- amiloride-like influence on the distal tubule(hyperkalemia and metabolic acidosis)

incidence

- crystalluria of 0.4 to 49%, hematuria (with or without flank pain) of 1 to 32%, oliguria, anuria, or azotemia of 0.4 to 29%, and renal stones of 0.4 to 20%, and the incidence of gross hematuria and microscopic Hematuria despite high fluid intake were 2-3% and 24%
- overall incidence of renal toxicity (excluding crystals) between 1 and 32%

risk factors associated with nephrotoxicity

- preexisting renal dysfunction, concomitant use of other drugs potentially nephrotoxic, advanced age, volume depletion, dose inappropriately adjusted for the level of renal function, and sepsis

prevention

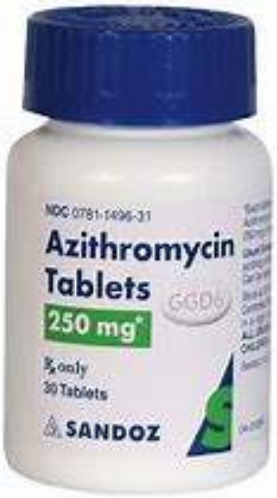
- reduction of dosage impaired renal function
- adequate hydration
- even with the use of preventive measures such as urine alkalinization, renal toxicity was 2%

Macrolide antibiotics

Macrolide antibiotics

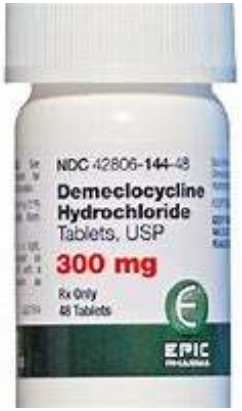
Macrolide antibiotics, including

erythromycin, clarithromycin, azithromycin, dirithromycin, inhibit the cytochrome P-450 isoenzyme CYP 3A4, which interferes with the metabolism of cyclosporin or tacrolimus and results in indirect renal toxicity



Tetracyclines

Tetracyclines



AIN(demeclocycline)

NDI(demeclocycline)

AKI(In cirrhotic patients)

Use of outdated tetracyclines can lead to

Fanconi syndrome(degradation product, anhydro-4-epitetracycline)

SIADH

phosphaturia

Polypeptide antibiotics

Polypeptide antibiotics

The polypeptide antibiotics polymyxin B, polymyxin E(colostin), bacitracin

Toxicity similar to that of aminoglycosides

This potential for nephrotoxicity has largely prevented their parenteral use

In United States only topical preparations remain available

Summery

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Beta lactam anbiotics
Vancomycin
Sulfonamides
Macrolide antibiotics
tetracyclines
Polypeptide antibiotics

Thanks