Polypharmacy and Renal Toxicity in the Elderly Patient

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Polypharmacy and Renal Toxicity in the Elderly Patient:

Objectives

1. To provide current definitions & risk factors for:
   1. Polypharmacy in the Elderly
   2. Acute Kidney Injury (AKI) v. Chronic Kidney Disease (CKD) v. End Stage Kidney Disease (ESKD)

2. To describe the epidemiology of polypharmacy in the Elderly

3. To describe the aging kidney & its susceptibility to nephrotoxicity
   1. AKI & CKD
   2. Intrinsic v. Extrinsic Risk Factors

4. To identify the most commonly combined nephrotoxic drugs in the Elderly

5. To describe the mechanisms of action of nephrotoxic drugs

6. To recommend strategies for the prevention & control of polypharmacy & nephrotoxicity in the Elderly
Polypharmacy and Renal Toxicity in the Elderly Patient: Outline

1. **Introduction: The Aging US Population**
2. **Definitions: Polypharmacy, Elderly v. Old, Acute Kidney Injury (AKI), Chronic Kidney Disease (CKD), End Stage Kidney Disease (ESKD).**
3. **The Epidemiology of Polypharmacy in the Elderly**
4. **The Aging Kidney: An Increased Susceptibility to Nephrotoxicity**
7. **The Most Commonly Combined Nephrotoxic Drugs in the Elderly**
8. **The Mechanisms of Action of Nephrotoxic Drugs**
9. **The Prevention & Control of Polypharmacy & Nephrotoxicity in the Elderly**
10. **Conclusions**
Introduction: The Aging US Population

1. In 2008, persons aged ≥ 65 years represented 12.8% of the US population.

2. By 2030, there will be a 19.6% ↑ in this US population to 71 million persons.

3. By 2050, 1 in 5 adults in the US will be > 65 years old.

4. As the prevalence of the most important risk factors for CKD, HTN & DM, ↑, adults > 65 years old will become the most rapidly growing subset of the end stage kidney disease (ESKD) population.

   Source: US Census Bureau.
# Who are the Elderly?

<table>
<thead>
<tr>
<th>Group identities</th>
<th>Age ranges (years)</th>
<th>“Also known as the”</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young &amp; Restless Retirees</td>
<td>55-65</td>
<td>“Go-goes # 1”</td>
<td>Typically ex-military &amp; in good-to-excellent health</td>
</tr>
<tr>
<td>The Medicare Elderly</td>
<td>66-75</td>
<td>“Go-goes # 2”</td>
<td>New to Medicare with lower potential for polypharmacy</td>
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<tr>
<td>The Elderly-Elderly</td>
<td>76-85</td>
<td>“Go-slows”</td>
<td>Medicare Parts A, B, &amp; D enrollees with CV &amp; OTC polypharmacy</td>
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<tr>
<td>The Elderly-Old</td>
<td>86+</td>
<td>“No-goes”</td>
<td>In independent &amp; assisted living, with Alzheimer’s-dementia care, &amp; SNFs, &gt; 5 med polypharmacy.</td>
</tr>
</tbody>
</table>
What is Polypharmacy?

1. Polypharmacy has been defined as one patient taking 2 to 5 different medications concurrently with most studies accepting a definition of ≥ 5 or drugs (Jokanovic N et al, 2015).

2. Cardiovascular (CV) polypharmacy is defined as the use of 2 or more CV medications concurrently (Yong TY et al, 2012).

3. Both types of polypharmacy are increased by common comorbidities, especially hypertension & diabetes; both are common in elderly patients; & both are often associated with renal impairment with each additional CV medication increasing the risk for AKI by 30% (Chao CT et al, 2015).
The Epidemiology of Polypharmacy

1. The prevalence of polypharmacy is highest in the elderly, in long-term care clients, & in acute geriatric clinic attendees.

2. Significant risk factors for polypharmacy include: (1) neurological motor impairment, (2) endocrine & metabolic disorders, (3) comorbid circulatory diseases, (4) recent hospital discharge, & (5) increasing number of prescribing providers (Jokanovic N et al, 2015).

3. Hepatic cytochrome P450 polymorphisms of CYP2C9, CYP2C19, & CYP2D6 are very common in elderly hemodialysis patients (45%) & may be responsible for many adverse drug-related events (Parker K et al, 2016).
## Polypharmacy & Genetic Polymorphisms

<table>
<thead>
<tr>
<th>Hepatic cytochrome P450 enzymes with common genetic polymorphisms</th>
<th>% of all US drugs metabolized</th>
<th>Important classes of drugs metabolized</th>
<th>Major cytochrome inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 2C9</td>
<td>5%</td>
<td>NSAIDs, warfarin, phenytoin, losartan</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>CYP 2C19</td>
<td>15%</td>
<td>benzodiazepines, clopidogrel, proton pump inhibitors</td>
<td>SSRIs</td>
</tr>
<tr>
<td>CYP 2D6</td>
<td>25%</td>
<td>SSRIs, tricyclics, antipsychotics, antiarrhythmics, B-blockers</td>
<td>Fluoxetine, paroxetine</td>
</tr>
</tbody>
</table>
Acute Kidney Injury (AKI) v. Chronic Kidney Disease (CKD)

**Acute Kidney Injury (AKI)**
1. AKI, formerly acute renal failure (ARF), is an **abrupt onset of renal dysfunction** ranging from minor loss of function to failure.
2. AKI will develop in **4-7% of hospitalized patients** annually with a mortality rate of 20-35%.
3. The prevalence of AKI increases significantly with age.
4. AKI is often **superimposed on preexisting chronic kidney disease (CKD)**.

**Chronic Kidney Disease (CKD)**
CKD has now been defined by the National Kidney Disease Foundation Outcomes Quality Initiative (KDOQI) as:
1. Reduction of GFR to **< 60 mL/min/1.73m²**, and/or
2. Evidence of kidney damage, *e.g.*, proteinuria (**albuminuria > 30 mg/g creatinine**),
3. Glomerular or tubular (not urologic)-associated **hematuria**, or
4. Abnormal renal imaging with pathologic abnormalities persisting ≥ 3 months, irrespective of cause.
The Epidemiology of Aging & Susceptibility to AKI & CKD

The Epidemiology of Aging and AKI
1. In the 1950s, the mean age of AKI patients was 41.3 years of age (Turney et al, 1990).
2. By the 1980s, the mean age had increased to 60.5 years (Turney JH et al, 1990), & the mean age of those dying from AKI was 71.9 years (Rosenfeld JB et al, 1987).
3. The incidence of AKI is 3.5 times higher in those > 70 years old than those < 70 (Pascual J et al, 1990).
4. Patients older than 80 years are 5 times more likely to develop AKI than younger patients (Pascual J et al, 1990).
5. The most important risk factors for AKI in the elderly are preexisting CKD & polypharmacy.

The Epidemiology of Aging & CKD
1. The prevalence of CKD also increases with age.
2. NHANES compared the prevalence of non-HD-requiring CKD from 1988 to 1994 and from 1994 to 2004 & found a significant increase in the US prevalence of CKD from 10.3% to 13.1% with the greatest % increase in persons > 70 years of age, rising from a prevalence of 37% to 47%.
3. End stage kidney disease (ESKD) is Stage 5 of CKD in the KDOQI = GFR < 15 mL/min/1.73m^2, or a requirement for hemodialysis (HD).
4. The most important risk factors for CKD in the elderly are diabetes & hypertension.
The Aging Kidney: Risk Factors Increasing Susceptibility to AKI

Intrinsic v. extrinsic factors in AKI

Multifactorial etiologies responsible for the ↑incidence of AKI in aging may be divided into (Wang X et al, 2014):

1. **Intrinsic factors**: structural & functional changes of CKD with aging; & preexisting common comorbidities, especially DM, HTN, CAD, & CHF.

2. **Extrinsic factors**: polypharmacy with CV agents (CCBs, diuretics, ACEIs) + NSAIDs, ± antibiotics (aminoglycosides), ± radiographic contrast media.

What is known about AKI.

1. 35% of the elderly US population has Stage 3 CKD defined as a GFR of 30-59 mL/min/1.73m² (Coresh J et al, 2003).

2. AKI most often occurs on a background of CKD & such cases often progress to ESKD.

3. The hazard (odds) ratio of developing ESKD for patients with both AKI & CKD is 13.0 relative to those with only AKI (Ishani A et al, 2009).

4. The 2-year mortality rate for those with AKI + CKD is 54.3% (Ishani A et al, 2009).
The Aging Kidney & AKI: Intrinsic Risk Factors (80% etiology)

Structural changes with aging:
1. 20-25% loss of cortical kidney mass in glomeruli & nephrons
2. Glomerulosclerosis
3. Tubulointerstitial fibrosis
4. Nephrosclerosis

Functional changes with aging:
1. 0.75 mL/min/year decline in GFR
2. Decreased renal blood flow
3. Inability to maintain K homeostasis

Frequent comorbidities: HTN, DM, CAD.

Diffuse age-related glomerulosclerosis, (high power)
The Aging Kidney & AKI: Intrinsic Risk Factors (80% etiology)

Tubulointerstitial fibrosis

Nephrosclerosis

Tubulointerstitial Nephritis

Inflammatory cell infiltrate
- Mononuclear cells
- Eosinophils

Note: The presence of interstitial fibrosis imparts a worse prognosis

Normal glomerulus
Partial hyalinization of a glomerulus
Hyalinization within arterial wall
Tubules
Total hyalinization of a glomerulus
The Aging Kidney & AKI: Extrinsic Risk Factors (20% etiology)

Polypharmacy: ↑ AKI risks with combinations of the following drugs & agents (Chao CT et al, 2015):

1. **NSAIDs**: relative risk (RR) of AKI = 3.2.
2. **Calcium channel blockers**: RR = 7.8 when combined with NSAIDs.
3. **Diuretics**: RR = 11.6 when combined with NSAIDs.
4. **ACEIs**: Can also ↑ RR with NSAIDs.
5. **Aminoglycosides**
6. **Radiographic contrast agents**: most significant in hospitalized patients.

NSAID-induced chronic papillary necrosis, gross & microscopic
The Cellular & Molecular Level Mechanisms Underlying the Increased Susceptibility of the Aging Kidney to AKI. (Wang X et al, 2014)

#1. Hemodynamic changes: true hypovolemia (dehydration, diarrhea, etc.) & functional hypovolemia (liver disease, nephrotic syndrome); ↓ renal blood flow from ↑ sympathetic tone & ↑ RAA activity; ↑ vasoconstriction from ↓ NO production in peritubular capillaries. Overall, the aging kidney exhibits ↑ sensitivity to all vasoconstrictors & an impaired vascular response mechanism.
The Cellular & Molecular Level Mechanisms Underlying the Increased Susceptibility of the Aging Kidney to AKI 2. (Wang X et al, 2014)

2. **Oxidative stressors**: ↓ antioxidant responses, ↓ catalase levels, rapid glutathione depletion.

3. **Autophagy**: an inability to recycle damaged organelles, manifesting renally as an inability to remove damaged mitochondria and tubular cells.

4. **Inflammation**: chronic accumulation of lymphocytes & macrophages in renal interstitium that release damaging cytokines, esp. **TNF-α & monocyte chemoattractant protein-1 (MCP-1)**.

5. **Deficient repair mechanisms**: ↓ DNA synthesis, ↑ telomere shortening, ↓ growth factor expression (VEGF, epidermal GF, insulin-like GF), ↑ pro-fibrotic growth factor expression (TGF-β1, CT [connective tissue] GF), ↓ cell-cell adhesion from deficiencies in the cadherin/catenin complex (central protein complex that underlies synaptic plasticity & is responsible for learning & memory).
The Aging Kidney & CKD: Intrinsic Risk Factors: Chronic Diseases (Source: Maw TT et al, 2013)

**Intrinsic risk factors (80% etiology)**

1. **Comorbidities, especially HTN, DM, & preexisting AKI** are the most important intrinsic risk factors for CKD in the elderly.

2. **Elderly over 65 years of age** are the most rapidly growing subset of the ESKD population, especially those with preexisting AKI.

3. **Early evidence of CKD in the elderly may be overlooked because a declining muscle mass** may result in a serum creatinine in the high normal range; albuminuria may or may not be present; & GFR may be impacted by reduced cardiac hemodynamics.

4. **Symptomatic postural hypotension & a tendency to hypoglycemia** will hamper tight BP & glycemic control in elderly patients with CKD & CKD & DM respectively.

**Hypertensive nephropathy**
Intrinsic Risk Factors for CKD: **Diabetes**
Increasing Prevalence of DM by Age, US, 1980-2014 (Source: CDC)
The Aging Kidney & CKD:
Intrinsic Risk Factors: Chronic Diseases (Source: Maw TT et al, 2013)

Intrinsic risk factors, especially DM & HTN
(80% etiology)

Preventing CKD in the elderly

1. Early diagnosis will require the use of corrective formulas to measure renal function.

2. KDOQI Guidelines now recommend a target BP of **140/90** or less if albuminuria is < 30 mg/d, & **130/80** or less if albuminuria is > 30 mg/d.

3. Recommended antihypertensives should include either an ACEI or an ARB.

4. Conventional rather than tight diabetic control is recommended as RCTs have now confirmed more episodes of hypoglycemia & more weight gain in diabetic elderly with CKD managed with tight glycemic control.
The Aging Kidney & CKD:  
Extrinsic Risk Factors: Polypharmacy (Source: Maw TT et al, 2013) 

Extrinsic risk factors = polypharmacy  
(20% etiology)

1. The most important extrinsic risk factors for CKD in the elderly are the use of multiple medications (polypharmacy) known to increase the risks of AKI including NSAIDs, especially COX-2 inhibitors.

2. **Combinations**: NSAIDs, COX-2 inhibitors, & other medications & diagnostic X-ray procedures with significant risks of inducing AKI in the elderly, *e.g.*, aminoglycoside antibiotics and radiographic contrast agents; both of these should be avoided or limited in the elderly, if possible.
The Epidemiology of Drug-Induced Kidney Injury in the Elderly

Epidemiology of nephrotoxicity

1. Although most cases of AKI in the elderly result from multifactorial causes, nephrotoxic drugs are contributing factors in 19-25% of cases.

2. Although the use of potentially nephrotoxic medications in the elderly is often unavoidable, their use can be monitored, limited, & discontinued.

3. Accurate estimation of preexisting renal function should be based on age-adjusted formulas for GFR & other parameters before initiating potentially nephrotoxic drug therapy.
The Types of Drug-Induced Acute Nephrotoxicity

**Direct nephrotoxicity**

1. **AKI**: aminoglycosides, amphotericin B, vancomycin.
2. **Interstitial nephritis**: acute = penicillins; chronic = calcineurin inhibitors (cyclosporine, tacrolimus); papillary necrosis = NSAIDs.
3. **Osmotic nephrosis**: hydroxyethyl starch, IVIG, radiographic contrast agents.
4. **Obstructive uropathy**: acyclovir, indinavir, ciprofloxacin.
5. **Glomerular disease**: gold, penicillamine, some NSAIDs.

**Indirect nephrotoxicity**

Hemodynamically mediated: ACEIs, ARBs, NSAIDs.
The Mechanisms of Drug-Induced Acute Kidney Injury: Outline

Mechanisms of injuries

1. Nephrotoxic AKI (≤ 20%): aminoglycosides.
2. Interstitial nephritis (3-15%): other antibiotics, calcineurin inhibitors.
3. Osmotic nephrosis (≤ 20%): plasma volume expanders, IVIG, radiographic contrast agents.
4. Tubular obstruction (≤ 20%): HAART drugs.
5. Hemodynamicly mediated nephrotoxicity (≥ 20%): NSAIDs.
6. Glomerular vasculitis (≤ 3%).
The Pathophysiological Classification of Drug-Induced Kidney Injury

Mechanisms of injuries determine classification

(Pannu N et al, 2008)

1. Nephrotoxic AKI (formerly ATN, ≤ 20%): a dose-dependent, non-inflammatory condition caused by tubular excreted nephrotoxic drugs in predisposed elderly.

2. Interstitial nephritis (3-15%): an acute or chronic & typically inflammatory response to nephrotoxins.

3. Osmotic nephrosis (≤ 20%): an acute condition following the administration of hyperosmolar agents typically in the elderly with pre-existing AKI. Characterized by swollen proximal tubules & cytoplasmic vacuolization with glomerular sparing.

4. Tubular obstruction (≤ 20%): an acute obstructive uropathy caused by the crystalline precipitation of certain drugs in tubules & characterized by crystalluria & nephrolithiasis.

5. Hemodynamicly mediated nephrotoxicity (≥ 20%): indirect nephrotoxicity resulting from reduced intrarenal blood flow.

6. Glomerular vasculitis (≤ 3%): a rare, often autoimmune, condition characterized by glomerulonephritis.
Direct nephrotoxicity: Aminoglycoside (AG) AKI

1. AGs are indicated for tx of Gram-negative infections.
2. AGs are non-protein bound, not metabolized, & excreted by glomerular filtration.
3. Cationic charges facilitate binding to tubuloepithelial membranes in proximal tubules for active transport.
4. Intracellular accumulation within lysosomes of tubular cells interferes with cellular functions including protein synthesis & mitochondrial function resulting in cell death with release of proinflammatory cytokines.
5. Most-to-least toxic: neomycin > gentamicin > tobramycin > amikacin > streptomycin. Onset of AKI occurs within 5-10 days.
6. Risk factors: AG type, high peak AG levels, cumulative doses, treatment duration & frequency, hypoalbuminemia, preexisting renal &/or hepatic dysfunction, ↓ renal perfusion, concomitant nephrotoxins.
7. Pv: once-daily dosing, concomitant β-lactam antibiotics, drug level monitoring, Ca supplementation ± CCBs, antioxidants (vitamins E & C, selenium), deferoxamine. Few confirmatory RCTs conducted.
Direct nephrotoxicity: **Interstitial Nephritis (IN)**

1. **IN (3-15%)**: an acute or chronic & often inflammatory response to nephrotoxins.

2. Drugs most commonly associated with acute IN = NSAIDs + COX-2 inhibitors, penicillins, cephalosporins, rifampin, sulfonamides (TMP-SMX), ciprofloxacin, indinavir, thiazides, cimetidine, allopurinol, & PPIs (omeprazole & lansoprazole).


4. Treatment: **Prednisone**, 1 mg/kg/d for up to 1 month for bx-confirmed cases may accelerate recovery.

5. Prognosis: **Usually self-limited**, recovery over weeks-months.

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**Acute allergic interstitial nephritis, penicillin reaction**

*Acute Interstitial Nephritis*

- Drug-induced allergic interstitial nephritis (H&E stain). Note the diffuse interstitial infiltrate, many red-staining eosinophils, and sparing of the glomerulus (on the left).
1. In 2007, Sierra F et al were among the 1st to identify PPI-associated IN & reported 64 cases in elderly patients.

2. The mean age of case-patients was 78 years with 60% females.

3. The mean duration of PPI treatment duration before diagnosis (by kidney biopsy in 59 cases) was 13 weeks. Average recovery time was 36 weeks. One patient required permanent HD. There were no deaths.

4. PPI-associated acute IN is a rare idiosyncratic reaction, and a diagnosis of suspicion & exclusion.
Acute & Chronic Interstitial Nephritis: Calcineurin inhibitors (CIs)

1. Calcineurin is a Ca-dependent protein phosphatase that activates T-cells in graft v. host reactions. It is inhibited by the immunosuppressants, cyclosporine & tacrolimus, either of which can cause both acute & chronic interstitial nephritis.

2. Weeks to months after instituting organ transplant anti-rejection therapy with CIs, the CIs can cause AKI with ↓ GFR, hyperkalemia, HTN, RTA, & oliguria.

3. MoA is unknown, but believed to be related to afferent & efferent arteriolar vasoconstriction with ↓ renal plasma flow.

4. Dose reduction may reverse AKI & prevent CRD.

Calcineurin inhibitor nephropathy MoA?

Mechanism of CNI Nephrotoxicity

- Acute toxicity (reversible)
  - Afferent arteriolar vasospasm
  - Renal hypoperfusion
- Chronic toxicity (irreversible)
  - Renal hypoperfusion
  - Obliterative arteriopathy
  - Focal ischemia
    - Tubular atrophy
    - Interstitial fibrosis
    - Glomerulosclerosis

↓ GFR
Calcineurin inhibitors (CIs): Cyclosporine & Tacrolimus

Pathophysiologic Features of Chronic Calcineurin Inhibitor (CNI) Nephrotoxicity

- Intrarenal vasoconstriction (↑ alpha-adrenergic stimulation, thromboxane A₂, endothelin-1, angiotensin II & PDGF, ↓NO)
- Hypofiltration (↓GFR)
- Systemic hypertension
- Chronic glomerular ischemia
- Tubular damage
- Nephrocalcinosis
- Mesangial and vascular smooth muscle cell proliferation
- Thrombotic microangiopathy
- Impaired free-water excretion
- Impaired Na⁺, K⁺, phosphate, and Mg⁺⁺ excretion
Direct nephrotoxicity: **Cyclosporine Eye Drops in the Elderly**

1. The prevalence of **dry eye syndrome (DES)** is now 14% in persons age 65-85 years & is ↑ significantly as the population ages.

2. Risk factors: **older age, female gender (6% in women < 50 years old),** Asian ethnicity, LASIK refractive surgery, radiation therapy, autoimmune diseases, antihistamines, postmenopausal estrogens.

3. Metabolism: extensively metabolized by 3A4 > 3A9, 6% in urine.

4. Polypharmacy ↑ nephrotoxicity: aminoglycosides, antifungals, NSAIDs, H₂-blockers, CCBs, tacrolimus, methotrexate.

**DES is very common in women & elderly.**
1. **ON (≤ 20%):** acute condition following the administration of hyperosmolar agents typically in the elderly with pre-existing AKI.

2. Characterized by swollen proximal tubules & cytoplasmic vacuolization with glomerular sparing.

3. Most commonly associated with circulatory volume expansion with hyperosmolar agents: (1) hydroxyethyl starch volume expanders (Heta-starch®, Hespan®), (2) IVIG tx, & (3) hyperosmolar radiographic contrast agents.
Direct nephrotoxicity: IVIG-Osmotic Nephrosis

What is IVIG-osmotic nephrosis?
**Definition**: AKI following IVIG infusion.
**Epidemiology**: > 100 cases now reported.
**Risk factors**: (1) co-administration of any sucrose-containing products, (2) pre-existing AKI or CKD, especially in the elderly.
**Pathophysiology**: (1) ↑ osmolarity + ↑ blood viscosity = ↓ renal blood flow, (2) osmotic intake of sucrose causes tubular cell swelling that obstructs tubules, (3) immune complexes are deposited & incite local inflammatory reactions.
**Clinical**: in most cases, asymptomatic ↑ serum creatinine ranging to ARF & RRT.
**Prognosis**: typically spontaneous resolution within 4-8 days.
Osmotic Nephrosis: Contrast-Induced Nephropathy (CIN)

1. Definition: CIN is defined as an absolute ↑ serum creatinine of > 0.5 mEq/dL or a relative ↑ of 25% in serum creatinine above baseline 48-72 hours after contrast radiography.

2. Risk factors include: (1) an aging population with longer life expectancies; (2) more co-morbidities, especially diabetes, CV disease, renal disease; (3) large volumes of iodinated contrast agents; (4) greater demand for more accurate diagnostic & interventional radiographic procedures.

3. Prognosis: Most cases are mild & transient with complete recovery of renal function within 1-3 weeks. The elderly with co-morbidities are more likely to experience persistent decline in renal function & require RRT.
Direct nephrotoxicity: **Osmotic Nephrosis (ON)-Contrast**

## Classification of Contrast Dyes

<table>
<thead>
<tr>
<th>Type</th>
<th>Osmolality</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Osmolar Contrast Medium (HOCM)</td>
<td>Osmolality ≈ 1500 mOsm</td>
<td></td>
</tr>
<tr>
<td>Diatrizoate (Gastrografin, Hypaque, Urografin)</td>
<td></td>
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<tr>
<td>Iothalamate (Conray)</td>
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<tr>
<td><strong>Low-Osmolar Contrast Medium (LOCM)</strong></td>
<td>Osmolality ≈ 320-800 mOsm</td>
<td>Higher rate of AKI vs IOCM</td>
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<td>Iohexol (Omnipaque)</td>
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<td>Ioxaglate (Hexabrix)</td>
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<td>Ioversol (Optiray)</td>
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<td>Iomeprol (Imeron)</td>
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<td>Similar rate of AKI vs IOCM</td>
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<td>Iopromide (Ultravist)</td>
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<td>Iopamidol (Isovue, Iopamiro, Iopamiron, Niopam)</td>
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<td><strong>Iso-Osmolar Contrast Medium (IOCM)</strong></td>
<td>Osmolality = 290 mOsm</td>
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<td>Iodixanol (Visipaque)</td>
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Direct nephrotoxicity: Contrast ON Presumed Mechanisms
Direct nephrotoxicity: **Obstructive (Tubular) Uropathy (OU)**

1. Tubular obstruction (≤ 20%): an acute obstructive uropathy caused by the crystalline precipitation of certain drugs in tubules & characterized by crystalluria & nephrolithiasis.

2. Anti-HIV “HAART” meds have been associated with nephrotoxicity, especially the protease inhibitor, indinavir, and the reverse transcriptase inhibitor, tenofovir.

3. Indinavir has caused crystal-induced renal failure with nephrolithiasis & crystalluria-associated tubular obstruction.

4. Tenofovir has been associated with reversible tubular dysfunction, including Fanconi syndrome, nephrogenic DI, & AKI.

5. Fluoroquinoline antibiotics, e.g., ciprofloxacin, have also caused obstructive crystalline uropathies.

Obstructive uropathy, indinavir urine crystals (L); ciprofloxacin crystals in renal pelvis (R).

Increasing % of AIDS cases among elderly >

**Fig. 2 – Proportion of elderly diagnosed with AIDS, by year of diagnosis among all diagnosed at age 18 and above (1980 to June 2009).**
Indirect nephrotoxicity causing AKI & CKD: NSAIDs

1. The most important extrinsic risk factors for CKD in the elderly are multiple medications (polypharmacy) known to increase the risks of AKI including NSAIDs, especially COX-2 inhibitors.


3. Most-to-least nephrotoxic AIDs = Indomethacin > other NSAIDs > COX-2 inhibitors > ASA.

4. Risk factors: pre-existing AKI, liver disease, polypharmacy-AGs, ACEIs, & ARBs.
Indirect nephrotoxicity: Mechanisms of action of NSAIDs & ACEIs

NSAIDs can be harmful to the kidney:
PGs are the major determinant of afferent vasodilation. By inhibiting PG production, NSAIDs can cause afferent arteriole vasoconstriction & reduce GFR.

ACE-I’s are contraindicated in bilateral renal artery stenosis:
Ang II is the major determinant of efferent vasoconstriction. The Ang II effect helps to maintain GFR when renal perfusion is low (e.g. bilateral renal artery stenosis, volume depletion & elderly patients with CHF). Blocking the effect of Ang II with ACE-I’s & ARBs in these situations can cause acute renal failure.
1. **Identify elderly at high risk of kidney injury**: pre-existing CKD, hemodynamic instability, polypharmacy.

2. **Use age-adjusted formulas to assess GFR & other parameters of renal function**.

3. **Avoid nephrotoxins**, if safer alternatives exist, *e.g.*, amphotericin B.

4. **Ensure all drugs are dosed to estimated GFR & monitor & reevaluate renal function often**.

5. **Consult nephrologists** when in doubt.
Polypharmacy and Renal Toxicity in the Elderly Patient: **Conclusions**

1. Overall, the aging kidney exhibits **↑ sensitivity to all vasoconstrictors & an impaired vascular response mechanism.**
2. The most important risk factors for AKI in the elderly are **preexisting CKD & polypharmacy.**
3. The most important risk factors for CKD in the elderly are **diabetes & hypertension.**
4. AKI most often occurs on a **background of CKD & such cases often progress to ESKD.**
5. Although most cases of AKI in the elderly result from multifactorial causes, **nephrotoxic drug combinations (polypharmacy) are contributing factors in 19-25% of cases.**
6. Accurate estimation of preexisting renal function should be based on **age-adjusted formulas for GFR & other parameters** before initiating potentially nephrotoxic drug therapy.
7. Although the use of potentially nephrotoxic medications in the elderly is often unavoidable, their use can be **monitored, limited, or discontinued.**
Polypharmacy and Renal Toxicity in the Elderly Patient

References