Drug Nephrotoxicity & Pediatric AKI

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Introduction

The kidney and liver play central roles in the elimination of xenobiotic substances including drugs, environmental substances, food additives, and their metabolites.

In addition, several specific functions of the kidney (e.g., tubular transport, metabolism of xenobiotics, and concentration of urine) and changes in hemodynamics in the kidney may cause nephrotoxicity.

Introduction

- In clinical practice, it is not uncommon for nephrotoxicity to limit the usage of specific drugs. For example, **vancomycin**, a key drug for methicillin-resistant Staphylococcus aureus (MRSA), possesses potential nephrotoxicity ,and its inappropriate usage often causes severe acute kidney injury (AKI). The same is true for **cisplatin**, which has been used for solid tumors, such as seminoma, lung cancer, and ovarian tumors. However, cisplatin has very high nephrotoxicity and the total dose must be strictly limited. Thus, the consideration and knowledge of drug nephrotoxicity are essential in medical practice.

Mechanisms Underlying Nephrotoxicity of Substance

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- The kidney and liver are the final pathways for the excretion of xenobiotics and their metabolites, and most of the toxic substances ingested are finally excreted from the kidney and liver.
- In particular, hydrophilic drugs and/or their metabolites are preferentially excreted from the kidney.

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- During the transcellular transport of certain substances from the peritubular capillaries to the tubular lumen, their concentrations in the proximal tubular cells become very high transiently, they impair renal epithelial cells.
- In addition, some substances are taken up from the glomerular filtrate into tubular cells (drug transport systems).
- In addition, endocytosis mechanisms by which various substances including nephrotoxic compounds, such as aminoglycosides, are taken up into the proximal tubular cells.

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- The concentration of urine is one of the most important functions of the kidney. In adult, 180 L of plasma is filtrated from glomeruli in a day, whereas the final urinary output is only 1.0–1.5 L/day. Since more than 99 % of the fluid is reabsorbed through the nephron segments, the renal tissues are exposed to highly concentrated xenobiotics that are finally excreted into the urine.

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- The kidney consumes a large amount of **energy to transport ions, fluid, and organic substances** . The energy consumed in the tubular cells is mostly utilized by **Na+ , K+ -ATPase**. Alteration of the renal blood flow ultimately leads to **ischemia**. Ischemia causes ATP depletion in the tubular cells, which attenuates the function of Na+ , K+ -ATPase. Since Na+ , K+ -ATPase is essential for cellular function, the decreased activity of Na+ , K+ -ATPase results in profound **cellular damage.**

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- The kidney consumes a large amount of oxygen, so **oxidative stress** commonly occurs in the kidney. Several nephrotoxic agents, such as **cisplatin**, markedly induce oxidative stress.

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- Several drugs influence renal hemodynamics and alter the renal plasma flow (RPF) and glomerular filtrate rate (GFR). When these changes are severe and persistent, renal tissues are exposed to ischemic damage and kidney functions deteriorate.

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- Tubular cells possess metabolic enzymes including cytochrome P450 for phase I biotransformation and conjugating enzymes such as glucuronyl transferase for phase II biotransformation. In tubular cells, these enzymes occasionally produce toxic compounds.

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- Several compounds disturb the normal function of the endoplasmic reticulum (ER), called “ER stress.” ER stress in tubular cells may adversely affect cellular functions, which may result in cell injury or death.

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- Some drugs are highly concentrated in the tubular lumen and crystallize under specific urinary conditions, such as low pH. This can result in the obstruction of tubular lumens, leading to obstructive nephropathy.

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- Crystal nephropathy
- Disorder in renal function is also affected by medications that make insoluble crystals in human urine. The formation of insoluble crystals depends on the acidity of urine and drug concentration. Drugs that can cause crystal nephropathy are antibiotics such as ampicillin and antiviral agents such as acyclovir

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- Rhabdomyolysis
- Rhabdomyolysis is a condition in which muscle fiber contents are released into the bloodstream when skeletal muscle is destroyed due to some injury. As renal muscle cells disintegrate due to damage in muscle tissue, myoglobin and serum creatine kinase are released into the blood. Released myoglobin degrades and depresses the function of filtration in kidney resulting the acute tubular necrosis or renal failure . Major causes of rhabdomyolysis are drug abuses from heroin, methadone, methamphetamine, and statin as well as alcoholism .

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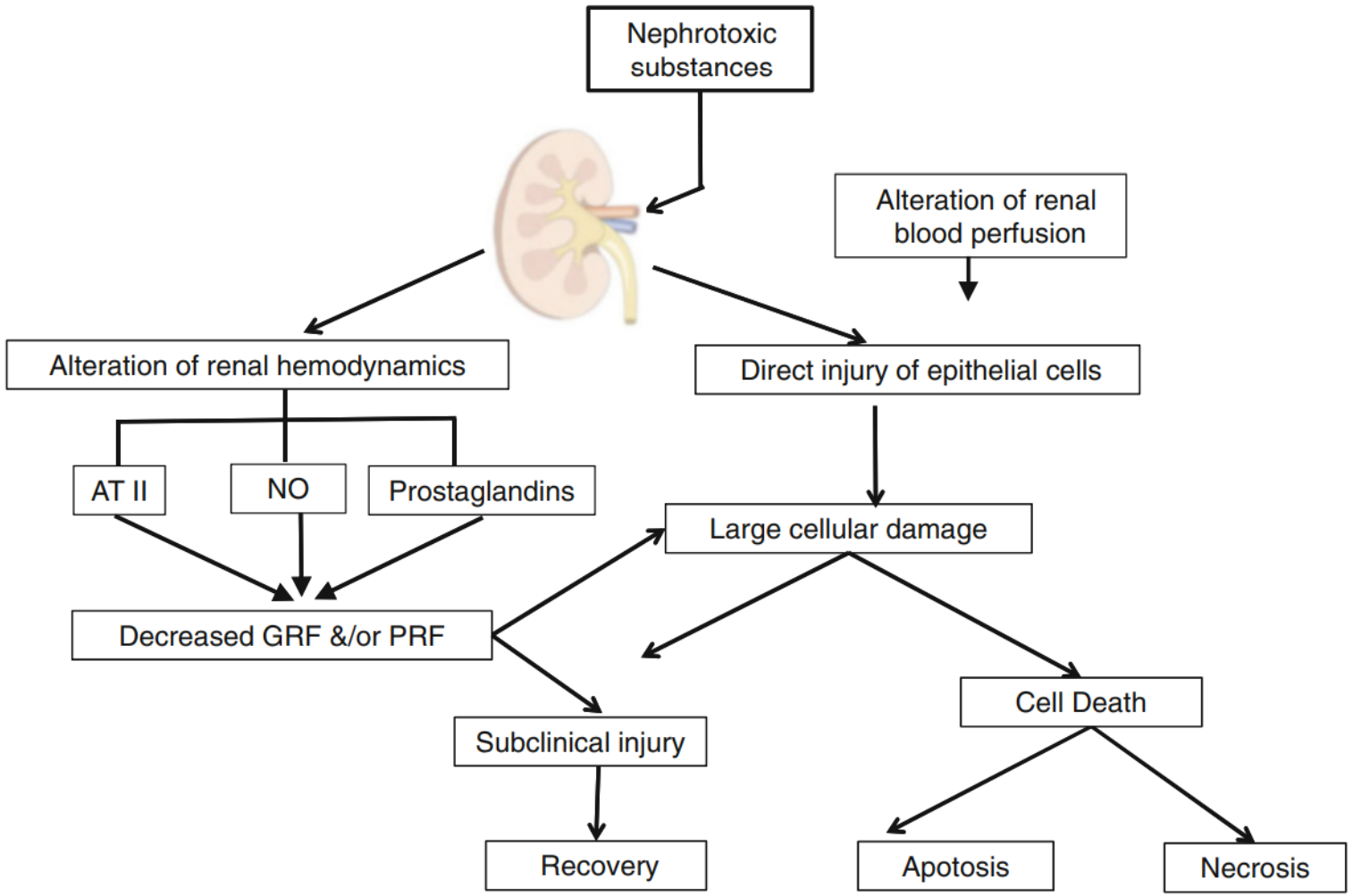
- Thrombotic microangiopathy
- Drug-induced thrombotic microangiopathy results from organ damage through inflammation or direct toxicity in renal epithelial cells .Antiplatelet agents including cyclosporin, mitomycin-C and quinine have been shown to cause thrombotic microangiopathy

Fate of Cells Exposed to Nephrotoxic Substances

- When renal cells are exposed to nephrotoxic substances, deleterious effects occur, such as ATP depletion and ischemia, resulting in considerable cell impairment. When the magnitude of impairment is within the range in which cells can **recover** from the damage, the cells will survive and re-differentiate and proliferate to normal cells. In contrast, when the magnitude of damage is beyond the threshold of cell viability, the cell death pathway is initiated. There are two types of cell death: **apoptosis** and **necrosis**.

- **Apoptosis: programmed death**. . Apoptosis is characterized by the fragmentation of nuclear DNA, followed by cell fragmentation and pinocytosis by phagocytes. Apoptosis is not accompanied by inflammation that affects neighboring cells. Thus, apoptosis is also called "**silent death**."
- **Necrosis: accidental death**.In necrosis, the cells with profound injury swell and finally rupture. Necrosis is accompanied by inflammatory reactions and can affect other cells.



The fate of renal cells following their exposure to nephrotoxic substances

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