ISCHEMIC &NEPHROTOXIC ATN

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Epidemiology

- AKI is a common complication in critically ill patients, with ARF requiring renal replacement therapy (RRT) developing in 5 to 10% of intensive care unit (ICU) patients.
- Epidemiological studies have demonstrated that ARF is an independent risk factor for mortality.
- Interventions to prevent the development of ARF are currently limited to a small number of settings, primarily radiocontrast nephropathy and rhabdomyolysis.

Epidemiology

- A multinational, multicenter, epidemiological study of 54 centres in 23 nations in North and South America, Europe, Asia and Australia assessed 29.000 patients hospitalized in intensive care. The incidence of AKI over 16 months was 5.7% (1.4%-25.9%) with 58.9% of patients hospitalized for medical and 41.1% for surgical problems.
- AKI is very common after cardiac surgery, representing 25.2% of all cases.
- Overall, hospital mortality was 60.3%, 52% in those patients that required intensive care support and 13.8% from the survivor group required renal replacement therapy after discharge.

- recent study provide epidemiologic data
- In elderly patients, a 3-year observational study that included 325 ασθενείς ≥ 60 years reached the following conclusions:

- Pre-renal AKI in hospitalized patients is responsible for 58% of all AKI cases
- In the community, post-renal causes of AKI are Commoner
- Overall mortality in this age group is 54%
- Mortality is higher (59%) when patients develop AKI during hospitalization compared to AKI in the community (%۴۱)
- Increased mortality was observed when concomitant heart disease was present, in patients with cancer, sepsis, neurological or haematological disease and in case with oliguria.

CAUSE OF ACUTE KIDNEY INJURY

- Critically ill patients with AKI may have several causative factors that should all be determined by starting with a careful review of the history, medical record, and physical examination.
- **Sepsis, major surgery** (particularly coronary artery bypass surgery), and **uncompensated heart failure** are the most common causes of AKI in the ICU, with sepsis accounting for more than 50% of cases.
- **Trauma**, **hemorrhagic pancreatitis**, and h**ypovolemia** are other causes .
- Another frequent contributing causeis exposure **to** **nephrotoxic drugs** and **intravenous contrast dye**.

CAUSE OF ACUTE KIDNEY INJURY

- Drugs are the primary or associated cause of AKI in up to 25% of ICU patients
- Current and past medication lists should be reviewed and any potentially nephrotoxic drugs should be replaced or eliminated.
- The comorbidities that most notably increase the risk for drug-induced nephrotoxicity are
  - **CKD**
  - **cirrhosis and liver failure**
  - **acute or chronic left heart failure**
  - **pulmonary artery hypertension with/without right heart failure**
  - **malignancy.**
- In addition, several major surgical procedures, such as
- **cardiac surgery, aortic surgery, and major intra-abdominal surgery**, enhance the risk of nephrotoxic drugs as well as the risk of AKI.

Risk factors in people with acute illness :

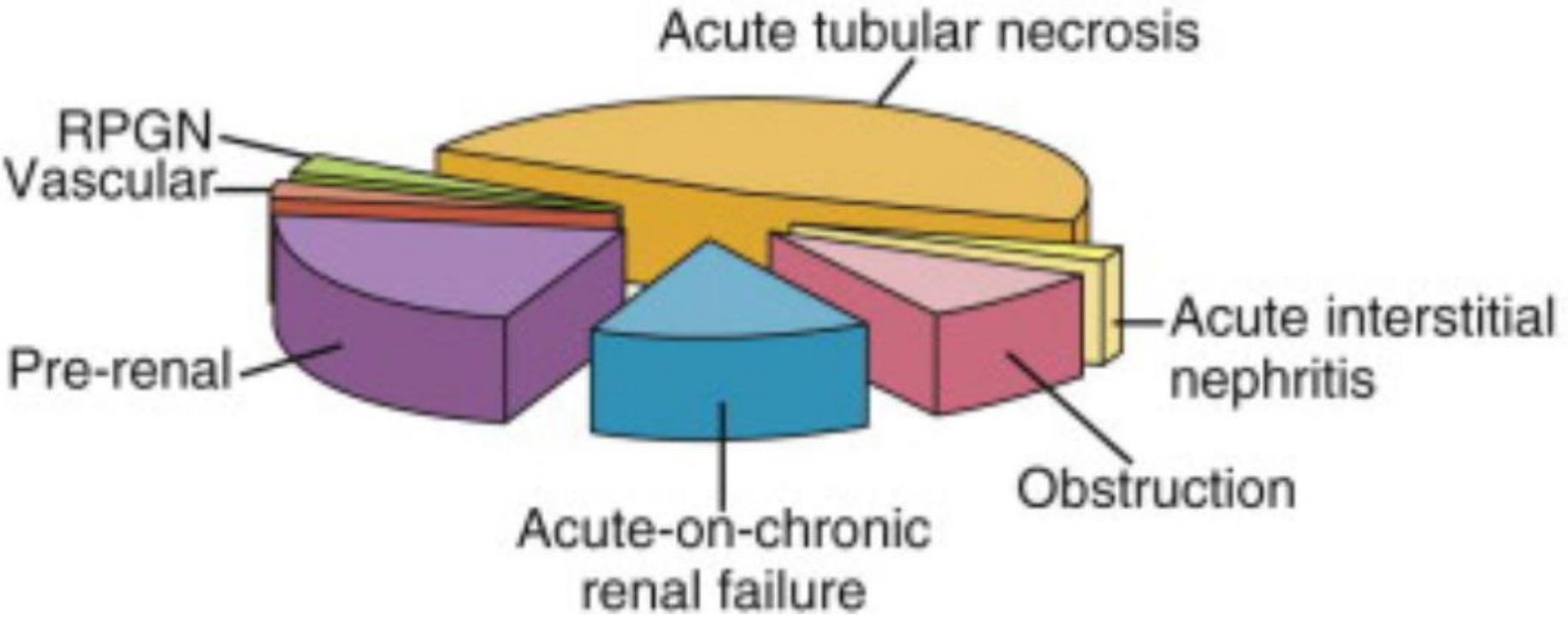
1. Age ≥65 years.
2. Heart failure.
3. Liver disease.
4. Chronic kidney disease (particularly if eGFR <60).
5. Past history of AKI.
6. Diabetes.
7. Anemia
8. Dehyration
9. Hypovolaemia.
10. Haematological malignancy.
11. Symptoms or history of urological obstruction, or a risk factor for it.
12. Sepsis.
13. Use of iodinated contrast agents within the previous week.
14. Current or recent medication with nephrotoxic potential

CAUSE OF ACUTE KIDNEY INJURY

- Impaired renal blood flow secondary to hypotension, shock, and loss of autoregulation within the nephron causes imbalances in oxygen delivery, nutrient delivery, and metabolic demand, particularly within the renal tubule.

- This normally low oxygen tension in the outer renal medulla makes this area at highest risk to ischemic injury. Hypoxic injury leads to structural damage to tubular cells, which subsequently forms casts that obstruct tubules and cause back-leak of filtrate.

Causes of AKI in Hospital Setting



- Ischemic acute renal failure spans the range from prerenal azotemia to acute tubular necrosis (ATN) and accounts for most cases of ARF seen in the community and for approximately three quarters of hospital-acquired cases of acute renal failure.

- Prerenal azotemia may be completely reversible if the underlying causes are corrected,
- but prolonged or untreated prerenal azotemia often progresses to ATN, which continues to have substantial morbidity and mortality rates. Although ischemic AKI is frequently associated with multiple-organ failure, the presence of AKI carries an independent risk for death.

PRERENAL AZOTEMIA

- Prerenal azotemia is caused by an absolute or relative reduction in renal perfusion, effecting a modest reduction in glomerular filtration rate (GFR) .It is generally, but not exclusively, accompanied by oliguria .
- This disorder occurs as a physiological response to lowered renal perfusion, which may result from a globally or regionally reduced blood flow to the kidney .
- Regardless of the cause, the initial compensatory mechanisms correct renal blood flow (RBF) and bring GFR toward normal.

- the renal microvasculature exhibits a highly efficient, autoregulatory behavior such that steady-state renal blood flow, GFR, glomerular pressure, proximal tubule pressure, and peritubular capillary pressure remain relatively unchanged over a wide range of renal arterial perfusion pressures.

- It is believed to be partly mediated by an intrinsic **myogenic response** to changes in renal arterial perfusion pressure, allowing a gradual **vasodilation of the preglomerular arteriole**, and partly to the **tubuloglomerular feedback** mechanism, both of which stabilize GFR and fluid delivery to the distal nephron

- In addition to engendering renal autoregulation, global hypotension or hypoperfusion stimulates **the baroreceptors in the carotid sinus and aortic arch**.

- This initiates activation of the **sympathetic nervous system** and **RAAS** and also stimulates release of **vasopressin** from the posterior pitu itary ,so that autoregulation of RBF and GFR takes place in a milieu of generalized vasoconstriction and an upregulated RAAS, which also serve to normalize systemic blood pressure during hypotension.

- If hypoperfusion continues, **vasoconstriction at the postglomerular arteriole** also takes place under the influence of angiotensin II, maintaining a constant glomerular capillary hydrostatic pressure.
- During this phase, a number **of intrarenal and extrarenal vasodilators** are also activated, mitigating the effects of unrestricted renal vasoconstriction and further adding to the maintenance of RBF and GFR.
- The vasoconstrictive effects of angiotensin II are counteracted locally by the intrarenal production of **prostaglandins and nitric oxide (NO),** which in the systemic circulation are direct vasodilators but, within the renal circulation, probably mediate their activity as antagonists of the vasoconstrictor effects of angiotensin II and renal adrenergic nerve activity.
- The effects of both angiotensin II and NO are complex within this context, and although NO generally antagonizes the effects of angiotensin II, it also stimulates the RAAS, so that chronic reductions in NO activity can result in reduced intrarenal generation of angiotensin II.

- In hypotension secondary to congestive heart failure, atrial stretch receptors stimulate the **release of atrial natriuretic peptide (ANP)** prohormone, which in its active forms attenuates the production of renin, angiotensin II, angiotensin II–stimulated aldosterone release, and sympathetic nervous system activity.

- ANP also inhibits Na ,K -ATPase by enhancing the production of intrarenal prostaglandin E .
- The gene for the ANP prohormone is present in the kidney as well as the cardiac atria and is upregulated in early renal failure;

- In prerenal azotemia, this balance of vasoconstrictor and vasodilator regulatory systems maintains RBF and GFR at the expense of increased water and urea resorption under the influence of vasopressin

- the picture may be confused in patients in whom there are renal concentrating defects or in catabolic states such as burns, trauma, and postoperative recovery, in which the obligatory excretion of urea causes polyuria

- **Surgical patients** are particularly predisposed to AKI because of the physiological insult induced by major surgical procedures, preexisting comorbidity, and sepsis.

- Patients at risk for development of perioperative ARF include those with **reduced renal functional reserve, arterial hypertension, cardiac disease, peripheral vascular disease, diabetes mellitus, jaundice, and advanced age.**

- The **type of surgery** is also an important determinant.
- Other risk factors are hypothermia, hypoxia, unstable hemodynamics, and cardiopulmonary bypass.

- Etiologically, ARF can be divided into three categories:
- prerenal azotemia,
- postrenal azotemia, and
- intrinsic renal failure.

- *Prerenal azotemia* , defined as reversible renal failure caused by decreased effective arterial blood flow to the kidney, accounts for 60% of inpatient cases of AKI.
- Anesthesia, blood and volume losses, volume overload and heart failure, and peripheral shunting of blood due to vasodilatation from sepsis are all common causes of prerenal azotemia in the perioperative period.

- Obstructive nephropathy accounts for 10% of inpatient cases of AKI.
- Intrinsic causes, finally, account for approximately 30% of inpatient cases of AKI. Ninety percent of cases of intrinsic ARF in adults are due to acute tubular necrosis (ATN), and ischemic ATN is the most common cause of intrinsic renal failure in the surgical setting.

ACUTE ISCHEMIC RENAL FAILURE

- As noted previously, the duration or intensity of ischemia required for the transition from prerenal azotemia to ATN is unknown in humans.

- Clinical ischemic ARF is somewhat different. It is often multifactorial, and seemingly minor deviations from baseline perfusion may result in renal failure in particular populations of patients, especially the elderly, diabetic patients, and patients with some prior renal dysfunction.

- The key sign of clinical ischemic ARF is a rapidly progressive and profound reduction in GFR, which has been noted to continue and even progress after the return of renal perfusion to baseline.

- During prerenal azotemia, renal tubules and microvasculature remain intact; in ischemic ATN, marked pathophysiological changes occur in both the tubules and the renal vasculature.

- In the early phase of ischemic ARF **(*initiation phase*),** autoregulatory mechanisms, which were effective in prerenal azotemia, begin to fail, and RBF declines with GFR while adenosine triphosphate (ATP) stores become depleted.
- Inappropriate and selective **renal vasoconstriction** occurs in response to sympathetic nervous system stimulation and to RAAS. There is heightened sensitivity of the vascular endothelium to these two systems and a number of other vasoconstrictors, such as thromboxane, endothelin, and leukotrienes.
- Furthermore, vasorelaxation in response to stimuli that normally generate endothelium-dependent vasodilators is also inhibited

PATHOLOGY AND PATHOGENESIS

- The process underlying ischemic ATN occurs in multiple phases, including prerenal (impairment in renal perfusion), initiation of injury, extension of injury, maintenance, and repair .
- The major histologic changes in ATN are
- effacement and loss of proximal tubule brush border,
- patchy loss of tubule cells,
- focal areas of proximal tubule dilatation,
- distal tubule casts, and
- areas of cellular regeneration that appear during the phase of recovery of renal function

- In addition to observable tubule obstruction and cell death, other factors may contribute to the decline in glomerular filtration rate (GFR)
- Tubules from multiple nephrons drain into a single collecting tubule. As a result, obstruction in a relatively small number of collecting tubules may lead to failure of filtration in a large number of nephrons.
- The combination of continued glomerular filtration and impaired proximal and loop reabsorptive function leads to increased sodium chloride delivery to the macula densa in individual nephrons. This activates the tubuloglomerular feedback mechanism, causing afferent arteriolar constriction, which lowers the GFR in an attempt to reduce tubule flow rate .
- Back leak of filtered tubular fluid into the vascular space may occur across the damaged tubule epithelium
- Apoptosis occurs in both proximal and distal tubule cells
- Peritubular capillaries in the outer medulla may be congested with leukocyte accumulation that impairs local renal blood flow .
- A number of processes contribute to the pathogenesis of ATN, including endothelial and epithelial cell injury, intratubular obstruction, changes in local microvascular blood flow, and immunologic or inflammatory processes

Strategies for prevention of AKI

- 1. Haemodynamic management to prevent septic AKI:

- sepsis is one of the most common causes of AKI. The main factors contributing to septic AKI are microcirculatory dysfunction, inflammation and bio-energetic adaptive responses to injury, including downregulated metabolism and cell-cycle arrest .
- Under certain circumstances blood pressure may also directly influence kidney perfusion and glomerular filtration. However, the exact mean arterial pressure (MAP) and perfusion targets to prevent AKI in individual patients are not known. In patients with septic shock a higher blood pressure in patients with pre-existing hypertension appears to be associated with less AKI.
- The practice of fluid resuscitation to improve renal perfusion and function in sepsis is particularly controversial. Although intravascular fluid administration is important in volume-depleted patients, it can be counterproductive and harmful once intravascular volume has been restored. Restricted fluid management (i.e. fluid administration only in case of severe tissue hypoperfusion) resulted in less AKI progression compared to standard fluid administration (i.e. fluid boluses as long as circulation continued to improve) .

Strategies for prevention of AKI

- 2.Haemodynamic management in surgery-associated AKI: recent large studies confirmed an association between the severity and duration of intraoperative hypotension and the development of AKI . Perioperative haemodynamic optimization may effectively protect renal function in surgical patients. Several inotropic drugs have been studied in cardiac surgery patients , but no single agent can be recommended with regard to renoprotection.
- 3. Non-haemodynamic measures: several pharmacological and non-pharmacological interventions to prevent AKI have been studied, including selective renal vasodilators, adenosine, endocrine and antiinflammatory strategies and remote ischaemic preconditioning None of them have shown consistent benefit or are routinely utilized in clinical practice.
- 4. Avoidance of nephrotoxicity: It is evident that whenever possible nephrotoxic substances should be replaced by non-nephrotoxic equivalents. On the other hand, essential substances should not be withheld if important for the management of the patient

drug-induced acute kidney injury In icu pateint

- a wide range of toxins can provoke AKI or contribute to its onset and severity.
- Drug-induced nephrotoxicity accounts for more than 2% of cases of ARF in patients admitted to the hospital and for 15% of cases in those in intensive care units (ICUs).).
- Beside the risk factors already mentioned, drug interactions should be considered an important risk factor. The mechanisms involved are an increase in blood and/or tissue half-life of the nephrotoxic drug (through interference with its metabolism and/or elimination) and/or an additive nephrotoxicity.

Altered Renal Hemodynamics

- GFR can be modulated by changes in the resistance of the afferent and efferent glomerular arterioles: Vasoconstriction of the former and vasodilatation of the latter lowers the intraglomerular pressure, whereas the reverse situation raises it.
- Angiotensin II predominantly causes vasoconstriction of the efferent arteriole, thus preserving GFR in cases of lowered renal blood flow, whereas prostaglandins act as vasodilators of the afferent arteriole.

- *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*.
- In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function. However, in situations in which renal perfusion may be diminished (decreased effective circulating volume), which are relatively common with critically ill patients, the inhibition of prostaglandininduced vasodilation with the use of NSAIDs may further compromise renal blood flow and exacerbate ischemic injury.
- The renal effects of NSAIDs do seem to be dependent on the type, dose, and duration of treatment .
- Indomethacin is thought to be the most likely drug to impair renal function, and aspirin the least likely .
- Patients at high risk of NSAID-induced nephrotoxicity include

➢ patients with preexisting renal dysfunction,

➢ severe cardiovascular or hepatic failure, or

➢ the concomitant use of other potentially nephrotoxic medications, such as aminoglycosides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers .

✓ The requirement for NSAIDS should be considered carefully in high-risk critically ill patients. If used, indomethacin should be avoided and consideration should be given to using NSAIDs with shorter half lives, such as sulindac.

- *Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers*. Intraglomerular pressure and consequently glomerular filtration rate (GFR) are normally regulated by the vasomotor tone of the afferent (preglomerular) and the efferent (postglomerular) arterioles. In situations of decreased renal blood flow, intraglomerular pressures are maintained by vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole.
- ACE I and ARB decrease intraglomerular pressure by selective inhibition of angiotensin II–mediated vasoconstriction at the efferent arteriole.
- As a consequence, the serum creatinine may increase by as much as 30% after initiating angiotensinconverting enzyme inhibitors or angiotensin receptor blockers without being a cause for concern, a reflection of angiotensin II inhibition . This apparent decline in GFR is seen 3–5 days after initiating therapy and stabilizes within 7 days. This action is beneficial in proteinuric renal disease or diabetic renal disease in which high intraglomerular pressures are associated with progression of renal disease; however, in situations involving a reduction in renal perfusion (bilateral renal artery stenosis, shock of any cause, or decreased intravascular volume) these drugs will further decrease intraglomerular pressure, precipitating prerenal failure.

- *Calcineurin inhibitors* may also cause an acute, functional, and dose-dependent decrease in renal blood flow and GFR. The current hypothesis is that calcineurin inhibitors cause
- predominantly afferent arteriolar vasoconstriction and thereby alter renal hemodynamics.
- The vasoconstriction is, in part, related to an imbalance of prostaglandin E (vasodilation) and thromboxane A (vasoconstriction).
- In addition, cyclosporine may interfere with the production of nitric oxide and
- increase systemic vascular resistance through activation of the sympathetic nervous system.

- *amphotericin B* may induce changes in renal hemodynamics. By
- changing vascular smooth muscle cell permeability,
- amphotericin B may cause cell depolarization with the resultant opening of voltage-dependent calcium channels and muscle contraction.
- Higher intracellular calcium concentration may activate arachidonic acid metabolism and lead to the accumulation of vasoactive substances with a net vasoconstrictive effect.
- Renal vasoconstriction appears to play a major role in the amphotericin B–induced reduction in GFR

Drug-Induced Acute Tubular Necrosis

- *Aminoglycosides.*
- AGs continue to be commonly used for the management of severe Gram-negative infections, despite well established ototoxicity and nephrotoxicity. AKI as defined by a 0.5–1 mg/dL increase in serum creatinine values is a relatively common complication of treatment with a reported frequency ranging between 10% and 20%.
- Aminoglycosides are non–protein bound drugs that are not metabolized and are primarily excreted by glomerular filtration. The cationic properties of these agents facilitate binding to the tubuloepithelial membrane in the proximal tubule,
- Neomycin is associated with the most nephrotoxicity; gentamicin, tobramycin, and amikacin are intermediate, and streptomycin is the least nephrotoxic .
- Intracellular accumulation of AG within lysosomes is thought to interfere with normal cellular function, such as protein synthesis and mitochondrial function, eventually leading to cell death . AGs also are known to stimulate the calciumsensing receptor on the apical membrane, which induces cell signaling and cell death

- Risk factors for aminoglycoside nephrotoxicity include the type of AG, high peak serum levels, cumulative dose, the duration and frequency of administration, and patient-related factors such as age, pre-existing renal dysfunction, hypoalbuminemia, liver dysfunction, decreased renal perfusion, and the use of concomitant nephrotoxic drugs .
- Severalm investigators have demonstrated that calcium supplementation reduces the nephrotoxic effect, likely through competitive inhibition of calcium channels in the proximal tubule .
- Similarly, calcium channel blockers also have been shown to attenuate aminoglycoside nephrotoxicity .
- The protective effect of concomitant use of B lactam antibiotics has been recognized for several years, although the mechanism by which this may occur is somewhat unclear .
- Aminoglycoside therapy induces the generation of reactive oxygen intermediates and the release of iron by cortical mitochondria .Antioxidants such as vitamins E and C , selenium , and probucol , as well as deferoxamine , have shown protective effects in animal studies;
- Once-daily dosing of aminoglycosides is the only clinical approach that is commonly used to reduce nephrotoxicity
- . Aginduced acute renal failure is generally nonoliguric, and may be associated with decreased urine-concentrating ability and urinary magnesium wasting. It is generally reversible after discontinuation of the drug; however, supportive renal replacement therapy may be required. We recommend that alternative antimicrobials should be considered when possible in patients at high risk for AG nephrotoxicity

Allergic Interstitial Inflammation

- AIN is associated with a wide variety of drugs, many of which are commonly used in the critical care setting , and accounts for 3% to 15% of all drug-induced acute renal failure .
- Renal dysfunction usually occurs 7–14 days after exposure, but may occur earlier in a previously sensitized individual.
- Systemic symptoms may be associated with B lactam antibiotics and sulfa drugs including fever, eosinophilia, and rash. Renal manifestations include sterile pyuria, eosinophiluria, and characteristic findings of an inflammatory infiltrate in the renal interstitium, as well as granulomas on renal biopsy.
- Acute interstitial nephritis usually occurs on an allergic basis in an idiosyncratic and non–dose-dependent manner. The pathogenesis of the majority of cases involves a cell-mediated hypersensitivity reaction.
- AIN is usually self-limiting, and spontaneous recovery occurs after withdrawal of the offending drug.

Vasculopathy

- **antineoplastics,**
- **immunotherapeutics,**
- **antiplatelet agents,**

➢ have been associated with thrombotic microangiopathy.

- the likely mechanisms by which these agents lead to a thrombotic microangiopathy include either an immune-mediated phenomenon involving the ADAMTS13 metalloprotease (quinine/quinidine, ticlopidine, and clopidogrel) or direct endothelial toxicity (mitomycin C and calcineurin inhibitor).

Obstructive Tubulopathy

- acyclovir,
- sulfonamides,
- methotrexate,
- indinavir, and
- triamterene—

➢ areassociated with the production of crystals that are insoluble in human urine. Intratubular precipitation of these crystals can lead to acute renal insufficiency through obstructive tubulopathy.

➢ Many patients who require treatment with these medications have additional risk factors, such as true or effective intravascular volume depletion, underlying renal insufficiency, and metabolic perturbation (acidosis and electrolyte depletion), that increase the likelihood of drug-induced intrarenal crystal deposition.

➢ Major preventive measures include adequate (pre)hydration and induction of high urinary flow rates (100-150 mL/hr), dose adjustment for renal function, and slowing down of the infusion rate.

- Tenofovir has been associated with a
- reversible proximal tubule dysfunction, including the development of a
- Fanconi syndrome,
- nephrogenic diabetes insipidus, and
- AKI.
- Although low-grade proteinuria has been described, nephrotic range proteinuria is rare.
- The onset is usually within 5–12 months after initiation of therapy, and recovery usually occurs within a few months following the discontinuation of tenofovir .

Osmotic Nephrosis

- Osmotic nephrosis is a distinct pattern of acute tubular injury observed after parenteral infusion of hyperoncotic solutions. Cellular injury begins with the uptake of nonmetabolizable molecules by pinocytosis into proximal tubule cells. The molecules create an oncotic gradient, leading to the accumulation of intracellular water, severe cytoplasmic swelling and vacuolization, and disruption of cellular integrity.
- Several therapeutic agents have been associated with osmotic nephrosis. They include sucrose, mannitol, intravenous immunoglobulin, radiocontrast agents, dextran, and hydroxyethyl starch (HES).
- HES is a volume expander that is increasingly used in the perioperative and intensive care setting. These characteristics determine the toxicity profile because they affect the time to elimination from the intravascular space and the degree of macromolecule accumulation

- IVIG is often prescribed for the management of immune-mediated disorders in the intensive care unit. The basis for IVIG nephrotoxicity is speculated to be the sucrose that is added to these solutions as a stabilizing substance. More than 50 cases of IVIG nephrotoxicity have been reported . IVIG-related nephrotoxicity appears to follow a predictable clinical course. Most reported patients have had pre-existing renal impairment and are elderly, which may be a surrogate for unrecognized renal impairment. Renal failure develops within 2–4 days of administration and tends to be oliguric and reversible, although renal replacement therapy has been required in approximately one third of reported cases. Renal biopsy shows a distinctive pattern of injury: swollen proximal tubular cells with cytoplasmic vacuolization, and narrowing and occlusion of the tubular lumen from cellular edema with characteristic sparing of the glomeruli. While no studies specifically have addressed the issue of reducing nephrotoxicity, the administration of IVIG over a longer duration may reduce its nephrotoxic potential.

- guide us to avoiding these complications in critical illness:

- 1) Identify patients at high risk of kidney injury (the elderly, pre-existing chronic kidney disease, hemodynamic instability, sepsis).
  2) Avoid nephrotoxins in high-risk patients if alternatives exist.
- 3) Ensure all medications are dosed to estimated GFR and carefully monitor and re-evaluate renal function.
- 4) A clinical pharmacist in the critical care setting can reduce dosing errors and may prevent or limit nephrotoxin exposure .
- 5) When in doubt about the nephrotoxic effect of a medication, hold all potentially offending drugs.

- Consider AIN in your differential diagnosis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