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Preventing Drug Induced Acute Kidney Injury

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Abstract

Drug-induced acute kidney injury (AKI) is a serious complication caused by medications, affecting both hospitalized patients and those in critical care, including children[1,2,3]. The kidneys, responsible for filtering and concentrating drugs, are particularly vulnerable to damage. A variety of medications used in routine medical practice can also induce AKI. To prevent and treat AKI, it's essential to identify high-risk individuals, closely monitor kidney function, and adjust drug dosages as needed. Avoiding unnecessary nephrotoxic drugs, ensuring adequate hydration, and correcting volume depletion are also crucial preventive strategies.

Emerging innovations like pharmacogenetics and early warning systems offer promising approaches for personalized treatment and timely interventions, helping to mitigate the impact of drug-induced AKI. Despite these advances, preventing and managing AKI remains challenging due to the complex interplay of medication toxicity, patient-specific risk factors, and the necessity of certain nephrotoxic drugs in critical treatments. A multifaceted approach, including early diagnosis and individualized therapy, is crucial in mitigating the risk of AKI and improving clinical outcomes.

Keywords: Acute kidney injury (AKI), Drug-induced nephrotoxicity.

Introduction

Acute kidney injury (AKI) caused by medications is a significant concern in modern healthcare, particularly in hospitalized patients and those in critical care settings[1,2,3]. The kidneys are vulnerable to drug-induced injury due to their role in filtering and concentrating medications. Drug-induced AKI can result from several mechanisms, including direct tubular toxicity, immune-mediated inflammation, and

drug crystallization in the renal tubules[4]. These injuries often lead to impaired renal function, which, if not promptly recognized and managed, can result in severe outcomes, including the need for renal replacement therapy[5,6,7].

Certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACE-Is), aminoglycosides, and chemotherapeutic agents like cisplatin, are frequently implicated in AKI[4,5,6]. The incidence of drug-induced AKI varies but can account for up to 26% of adult cases, with critically ill patients at even higher risk[1,2]. The risk is compounded in patients with preexisting conditions such as chronic kidney disease, heart failure, or dehydration[8].

Prevention strategies are critical and include careful selection of medications, dose adjustments based on renal function, and close monitoring of at-risk patients. Deploying emerging technologies like pharmacogenetics may offer personalized approaches to minimize the risk of nephrotoxicity in vulnerable populations.

Review of Literature

Acute Renal Failure- Drugs can lead to acute renal failure (ARF) by inducing pre-renal, intrinsic, or post-renal toxicity.

Pre Renal Failure

Pre-renal failure arises from impaired glomerular hemofiltration, often due to reduced renal perfusion. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin- converting enzyme inhibitors (ACE-Is) impact vasomotor control in the afferent or efferent arterioles, leading to decreased glomerular filtration rate (GFR) and eventual renal failure. In patients with pre-existing conditions like heart failure or dehydration, this risk is particularly pronounced. Adequate intraglomerular pressure is maintained by prostaglandin-mediated afferent vasodilation and angiotensin II-mediated efferent vasoconstriction. ACE-Is and angiotensin receptor blockers (ARBs) interrupt this process by reducing angiotensin II-mediated vasoconstriction, whereas NSAIDs inhibit prostaglandin-induced vasodilation, resulting in reduced renal perfusion. These patients often present with oliguria, elevated urea to creatinine ratios, and low urinary sodium excretion.

Intrinsic Renal Failure

Drug-induced intrinsic renal damage frequently results from acute tubular necrosis, interstitial nephritis, or thrombotic microangiopathy. Aminoglycoside antibiotics and amphotericin B are commonly associated with acute tubular necrosis due to direct nephrotoxicity. Prolonged periods of impaired renal perfusion can also cause tubular damage. The diagnosis of tubular necrosis is made based on histological findings, such as degenerative and regenerative tubular changes.

Clinical manifestations include sudden elevations in serum creatinine and oliguria, with the presence of granular casts and renal epithelial cells in the urinary sediment.

Immune-Mediated Inflammation Caused By Drugs and Post Renal Causes

Another cause of drug-induced intrinsic renal failure is hypersensitivity reactions, accounting for about 15% of cases. Drugs, including NSAIDs and anticonvulsants, may induce renal inflammation through immune-mediated mechanisms. These reactions are triggered by the binding of drug metabolites to the tubular basement membrane or

interstitial matrix, forming antigenic complexes that lead to T-cell-mediated inflammation. Systemic symptoms like fever, rash, eosinophilia, or insidious manifestations such as malaise and back pain may accompany this form of renal toxicity. Proteinuria may develop due to cytokine release from T-cells, increasing glomerular permeability.

In addition, drugs like cyclosporine, tacrolimus, chemotherapeutic agents (e.g., bleomycin, cisplatin), and clopidogrel can cause thrombotic microangiopathy. This condition encompasses thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), presenting with microvascular thrombosis in the kidneys and other organs. The clinical presentation often includes fever, hemolytic anemia, thrombocytopenia, renal impairment, and neurological disturbances, with HUS predominantly involving renal dysfunction.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, a relatively new class of antidiabetic agents induce renal toxicity through various mechanisms. One potential mechanism of SGLT-2 inhibitor-induced renal toxicity is intraglomerular pressure reduction. Additionally, volume depletion due to osmotic diuresis is another contributor to renal toxicity. Another hypothesis suggests that SGLT-2 inhibitors may interfere with mitochondrial function, causing direct tubular injury. Although rare, instances of SGLT-2 inhibitor-associated acute tubular necrosis have been reported in the literature, underscoring the potential for direct nephrotoxic effects.

Renal Toxicity of Commonly Prescribed Drugs

Renal toxicity may often be caused by various drugs commonly used in medical practice. The kidneys play a vital role in filtering toxins from the bloodstream and maintaining homeostasis. Drug- induced renal damage can result in acute kidney injury (AKI), chronic kidney disease (CKD), or other forms of renal impairment. In this section we explore commonly prescribed drugs known to cause renal toxicity, discussing their mechanisms of action, clinical manifestations, risk factors, and strategies for prevention and management.

Analgesics[25]

Analgesics, especially nonsteroidal anti-inflammatory drugs (NSAIDs), are among the most frequently prescribed medications worldwide for the treatment of pain, inflammation, and fever. However, NSAIDs are also one of the leading causes of drug-induced renal injury, particularly when used chronically or in large doses.

The primary mechanism by which NSAIDs cause renal toxicity involves the inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. These enzymes are responsible for producing prostaglandins, which play a crucial role in maintaining renal blood flow by promoting vasodilation of the afferent arterioles. By inhibiting COX enzymes, NSAIDs reduce the production of vasodilatory prostaglandins, leading to renal vasoconstriction and a subsequent decrease in glomerular filtration rate (GFR).

Acute kidney injury due to NSAIDs can manifest as a sudden reduction in renal function, often associated with oliguria (decreased urine output) and elevated serum creatinine levels. Chronic NSAID use, on the other hand, can lead to more insidious forms of renal injury, such as chronic interstitial nephritis. Tubulointerstitial nephritis caused by NSAIDs may be characterized by proteinuria, which can sometimes

reach nephrotic-range levels, but it typically lacks the systemic signs of hypersensitivity (e.g., rash, fever) seen with other causes of nephritis.

Although COX-2 selective inhibitors (such as celecoxib) were initially developed to minimize renal side effects by sparing COX-1, they have not proven to be devoid of nephrotoxic effects. COX-2 inhibitors may still impair renal perfusion and have been linked to both acute and chronic kidney injury. Additionally, acetaminophen (paracetamol), another common analgesic, does not inhibit prostaglandin synthesis in the periphery but can cause acute tubular necrosis when taken in excessive doses, typically in cases of overdose.

The key to preventing NSAID-induced renal toxicity is cautious prescribing, especially in patients with pre-existing renal disease, heart failure, or hypovolemia. NSAIDs should be avoided in patients at high risk for renal injury, and alternative analgesics such as acetaminophen or opioid medications should be considered when appropriate. Regular monitoring of renal function in chronic NSAID users is also essential to detect early signs of nephrotoxicity.

Tenofovir[24]

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTI) used in the treatment of HIV and hepatitis B infection. While tenofovir is effective as part of antiretroviral therapy, it has been associated with significant renal toxicity, primarily affecting the proximal renal tubules.

Tenofovir-induced renal toxicity can manifest as Fanconi syndrome, a condition characterized by proximal tubular dysfunction. Patients with Fanconi syndrome present with features such as proteinuria, glycosuria (despite normal blood glucose levels), hypophosphatemia, and bicarbonate wasting, all of which reflect impaired tubular reabsorption. The exact mechanism by which tenofovir causes renal damage is not fully understood, but high intracellular concentrations of the drug within proximal tubular cells may lead to mitochondrial dysfunction and oxidative stress, resulting in tubular cell injury and apoptosis.

Risk factors for tenofovir-induced nephrotoxicity include pre-existing renal impairment, older age, low body weight, and concurrent use of other nephrotoxic drugs. However, tenofovir toxicity can also occur in patients without any obvious risk factors, making routine monitoring of renal function essential for all patients on tenofovir-based regimens.

Aminoglycosides[13]

Aminoglycosides, including drugs like gentamicin, tobramycin, and amikacin, are potent antibiotics used to treat serious gram-negative bacterial infections. Despite their efficacy, aminoglycosides are well-known for their nephrotoxic potential, with renal toxicity occurring in up to 20-30% of patients receiving these drugs.

The nephrotoxicity of aminoglycosides is largely due to their accumulation in the renal proximal tubular cells, where they induce oxidative stress, mitochondrial dysfunction, and apoptosis. Aminoglycosides are filtered by the glomerulus and then taken up by proximal tubular cells via the megalin-cubilin receptor complex. Inside the cells, aminoglycosides bind to phospholipids on the lysosomal membrane, disrupting lysosomal function and leading to cell death.

Clinically, aminoglycoside-induced nephrotoxicity presents as non-oliguric AKI, with a gradual rise in

serum creatinine levels and electrolyte disturbances such as hypokalemia and hypomagnesemia. Nephrotoxicity is dose-dependent, and the risk is higher with prolonged therapy, higher cumulative doses and the use of multiple daily dosing regimens. Other risk factors include advanced age, dehydration, and concurrent use of other nephrotoxic drugs.

Lithium[23]

Lithium is a mood stabilizer commonly used in the treatment of bipolar disorder. While highly effective in controlling mood swings, lithium carries a significant risk of nephrotoxicity, particularly with long-term use.

Lithium-induced nephrotoxicity can occur in both acute and chronic forms. Acute lithium toxicity may manifest as nephrogenic diabetes insipidus (NDI), a condition in which the kidneys become unresponsive to the actions of vasopressin (antidiuretic hormone), leading to impaired water reabsorption and polyuria. The mechanism underlying NDI involves lithium's accumulation in the renal collecting ducts, where it inhibits glycogen synthase kinase type 3β (GSK-3β), an enzyme involved in sodium and water reabsorption. As a result, patients with NDI experience excessive water loss and may develop symptoms such as dehydration and hypernatremia.

Chronic lithium use, especially over 10-20 years, can lead to progressive chronic tubulointerstitial nephritis, which may eventually cause CKD. Chronic lithium nephrotoxicity is characterized by gradual loss of renal function, with decreased GFR and the development of proteinuria.

Polymyxins[9] **(Colistin)**

Polymyxins, including polymyxin B and colistin, are antibiotics that have gained renewed interest in the treatment of multidrug-resistant gram-negative bacterial infections. However, these drugs are associated with high incidence rates of up to 60% nephrotoxicity.

The nephrotoxicity of polymyxins is due to their ability to increase the permeability of the renal tubular cell membranes, leading to cell edema and lysis. Polymyxins are particularly toxic to the proximal convoluted tubules, where they disrupt the integrity of the cell membrane. This damage results in AKI, often accompanied by electrolyte abnormalities such as hypokalemia and hypomagnesemia.

Polymyxin B may have a slightly lower incidence of nephrotoxicity compared to colistin, but both drugs require careful monitoring of renal function. The nephrotoxic effects of polymyxins are often dose-dependent, and adjusting the dose based on renal function can reduce the risk of toxicity.

Bisphosphonates[10]

Bisphosphonates, such as pamidronate and zoledronate, commonly used for the treatment of osteoporosis, Paget's disease, and hypercalcemia of malignancy are generally well-tolerated, however, they can cause renal toxicity in some cases.

Renal toxicity associated with bisphosphonates typically manifests as AKI or collapsing focal segmental glomerulosclerosis (FSGS). The mechanism of bisphosphonate-induced nephrotoxicity is thought to involve apoptosis of renal tubular cells, particularly when the drugs are administered via rapid intravenous infusion.

Clinically, bisphosphonate-induced AKI often occurs shortly after drug infusion and may present with proteinuria, elevated serum creatinine, and decreased GFR. Fortunately, most cases of bisphosphonate-

induced nephrotoxicity resolve after discontinuation of the drug, and long-term renal damage is rare.

Methotrexate[11]

Methotrexate is an immunosuppressant widely used in the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis, as well as in high doses for certain cancers. Methotrexate is known to cause nephrotoxicity, particularly when used in high doses (>500 mg/m2).

The primary mechanism of methotrexate-induced nephrotoxicity involves the formation of methotrexate crystals in the distal renal tubules. These crystals cause local inflammation and necrosis by generating free oxygen radicals, leading to tubular cell damage. AKI due to methotrexate can occur within days of high-dose therapy, particularly in patients with predisposing factors such as dehydration, drug interactions (e.g., with sulfas or beta-lactams), and pleural effusions.

Cisplatin[12]

Cisplatin is also a widely used chemotherapy agent, particularly for cancers of the lung, ovary, and gastrointestinal tract. However, its use is associated with a significant risk of nephrotoxicity, with studies reporting an incidence of AKI in up to 34% of patients.

Cisplatin-induced nephrotoxicity primarily affects the proximal tubules, where the drug is internalized via organic cation transporters (OCTs). Once inside the tubular cells, cisplatin causes DNA damage, oxidative stress, and cell death. In addition to AKI, cisplatin can cause electrolyte disturbances such as hypomagnesemia and hypokalemia.

Sodium-Glucose Cotransporter-2 (Sglt-2) Inhibitors[21,22]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, are a class of drugs used in the management of type 2 diabetes mellitus. Unlike many other antidiabetic drugs, SGLT-2 inhibitors have been found to have a protective effect on the kidneys but it may cause renal injury through different mechanisms.

Volume depletion- SGLT-2 inhibitors increase urinary glucose and sodium excretion, leading to osmotic diuresis and natriuresis. This can cause dehydration and volume depletion, contributing to renal hypoperfusion and AKI.

Reduced intraglomerular pressure- These drugs lower afferent arteriolar tone, reducing intraglomerular pressure and decreasing the glomerular filtration rate (GFR). This may lead to AKI, especially in patients with pre-existing conditions like hypotension or heart failure.

Hypotension- The diuretic effect can exacerbate hypotension, leading to reduced renal perfusion and AKI. This is particularly concerning in patients on antihypertensive medications.

Pathogenesis of Drug-Induced Renal Injury

The kidneys are particularly vulnerable to drug-induced injury due to their role in the filtration, reabsorption, and excretion of various substances. One common mechanism is the formation of crystals[14,15] from medications that aggregate in a symmetrical structure. The kidney's unique environment makes it a prime site for crystal deposition[16,17,18]. There are several contributing factors to this:

1. **High Drug Concentration in the Tubules:** As drugs traverse through the renal tubules, their

concentration can increase significantly, leading to supersaturation of the drug substrate. This promotes crystal nucleation, especially in conditions that favor drug precipitation.

2. **Nature of the Crystals:** Crystal-forming drugs, due to their physical and chemical properties, can easily precipitate and deposit within kidney tissues. Supersaturation combined with the injured cell membranes found in the renal tubules provides a conducive environment for crystal formation.
3. **Crystal Nucleation and Adhesion:** Injured tubular cells upregulate surface molecules that create a favorable environment for crystal nucleation. Crystals adhere to these damaged membranes, acting as a nidus for further crystal growth. The deposition of these crystals can obstruct the renal tubules, leading to acute kidney injury (AKI), though obstruction is less of a concern than the direct cytotoxic effects of crystals on kidney cells.
4. **Cytotoxicity and Inflammation:** Crystals within the kidney can trigger several harmful cellular responses. For instance, they activate intracellular signaling pathways that promote necrosis. Drug crystals that resist digestion can destabilize lysosomes, causing the release of harmful enzymes like cathepsin-B, which further disrupts cellular homeostasis. This leads to necrosis through processes such as autophagy and necroptosis.
5. **Release of Damage-Associated Molecular Patterns (DAMPs):** Crystal-induced necrosis releases DAMPs into the extracellular space, including histones, demethylated DNA, RNA, and mitochondrial DNA. These molecules are capable of engaging with death receptors on neighboring cells, amplifying the extent of kidney damage by promoting additional cellular necrosis.
6. **Inflammatory Pathways:** Crystals not only damage tubular cells directly but also initiate inflammation, exacerbating renal injury. Once tubular cells are damaged, there is complement activation and leukocyte invasion, which intensifies the inflammatory response. Additionally, the crystals can activate the NLRP3 inflammasome, leading to secretion of IL-1β, further driving intrarenal inflammation.

Crystals can also engage toll-like receptor 4 (TLR4), activating the NF-κB pathway, which upregulates the expression of proinflammatory cytokines and chemokines. These cytokines promote further damage to the renal tissue. Crystals may also induce lipid sorting on the cell surface, activating the tyrosine protein kinase Syk, which stimulates B cells, perpetuating the immune response.

Pyroptosis, an inflammatory form of cell death, can be triggered by NLRP3 inflammasome production, while necroptosis results from the damaging effects of proinflammatory cytokines like TNF-α. Together, these processes create a cycle of crystal-induced inflammation and kidney injury.

Principles To Minimize Drug-Induced Renal Injury[19,20]

To minimize the risks of drug-induced renal injury, several principles should be followed, particularly when managing high-risk patients:

1. **Identification of At-Risk Patients:** Certain patient populations are more susceptible to nephrotoxicity, such as those with pre-existing

kidney disease, diabetes, advanced age, or those taking other nephrotoxic medications. Before prescribing potentially nephrotoxic drugs, clinicians should thoroughly assess the patient's risk factors and weigh the nephrotoxic potential against the therapeutic benefit.

2. **Drug-Specific Precautions:** Depending on the drug being used, specific precautions can be taken to mitigate its nephrotoxic effects such as-
   - Amphotericin B: This antifungal agent can cause significant renal toxicity. To minimize its effects, it should be administered to patients who are normovolemic. Liposomal formulations of amphotericin B are less nephrotoxic and should be used whenever possible.
   - Aminoglycosides: Nephrotoxicity from aminoglycosides can be reduced by closely monitoring their trough concentrations and renal function. Adjusting the dose based on renal function or switching to alternative drugs with a lower nephrotoxic profile may help reduce the risk.
   - ACE Inhibitors (ACE-I): A drop in glomerular filtration rate (GFR) shortly after starting an ACE-I could indicate bilateral renal artery stenosis, and in such cases, ACE-I should be avoided.
3. **Frequent Monitoring of Renal Function:** Early detection of drug-induced renal injury is key to preventing irreversible damage. Frequent monitoring of renal function should be part of the management strategy, particularly in high-risk patients. Serum creatinine levels are commonly used to monitor renal function, but it is important to note that normal creatinine levels in the reference range may not always reflect normal kidney function. A subtle increase in creatinine, especially after initiating potentially nephrotoxic drugs, should be investigated promptly.
4. **Avoiding Combinations of Nephrotoxic Drugs:** The simultaneous use of multiple nephrotoxic drugs should be avoided whenever possible, as this can increase the likelihood of renal injury. If the use of such combinations is unavoidable, it is crucial to monitor renal function closely and adjust dosages based on renal performance.
5. **Hydration and Fluid Management:** Maintaining adequate hydration is crucial in reducing the risk of drug-induced renal injury, particularly in patients taking drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), contrast agents, or high-dose diuretics. Volume depletion can exacerbate the nephrotoxic effects of these drugs by reducing renal perfusion and enhancing drug concentration in the renal tubules. Ensuring that patients are well-hydrated before administering these drugs can help protect against kidney damage.
6. **Drug Dosing Adjustments Based on Renal Function:** Dose adjustment based on renal function is essential to reduce nephrotoxicity. Many nephrotoxic drugs require dose reduction or extended dosing intervals in patients with impaired renal function. Using accurate measurements of GFR to adjust dosing can significantly reduce the risk of renal injury.
7. **Patient Education:** Educating patients on the importance of hydration, recognizing early symptoms of renal impairment (such as reduced

urine output, swelling, or confusion), and adhering to follow-up schedules can play a vital role in preventing drug-induced renal injury.

By integrating these principles into clinical practice, healthcare professionals can mitigate the risk of nephrotoxicity while maintaining the therapeutic efficacy of medications. Proactive identification of high-risk patients, vigilant monitoring, appropriate hydration, and cautious use of nephrotoxic agents are critical to protecting renal function during drug therapy.

Discussion

The evolution of modern medicine, characterized by the development of potent therapeutic agents, has greatly improved the management of critical illnesses such as infections and cancer. However, these advances come with an increased risk of side effects, among which nephrotoxicity remains a significant concern due to its morbidity and prevalence. The primary objective in clinical practice is to minimize renal damage associated with drug toxicity. This makes early diagnosis and intervention crucial.

Recent research has highlighted the utility of electronic alert systems that notify nephrologists when laboratory results indicate a rise in serum creatinine, irrespective of the use of nephrotoxic medications. These systems enable timely nephrological assessments, allowing for the early implementation of protective measures such as dose adjustments, reduction or discontinuation of non-essential or highly nephrotoxic drugs, and correction of conditions like hypovolemia.

Pharmacogenetics has emerged as a promising area of investigation in this context. It is well- established that certain individuals possess genetic predispositions to adverse drug reactions, including nephrotoxicity. For example, mutations in drug transporters located in the proximal convoluted tubule (PCT), such as organic anion transporters (OAT) and multidrug resistance protein (MRP), have been linked to more severe renal cell damage. Understanding these genetic factors can inform personalized treatment decisions, helping clinicians identify patients who may require closer monitoring when exposed to potentially nephrotoxic drugs. In the future, pharmacogenetics may also provide therapeutic targets for drug development. An example of this is the creation of medications like tenofovir alafenamide, which has been designed to achieve lower intracellular concentrations within tubular cells, thereby reducing its nephrotoxic potential.

No drug is entirely free of adverse effects; therefore, the management of nephrotoxicity is centered on identifying at-risk populations, ensuring early detection, and employing general measures that mitigate kidney damage. These measures include adjusting drug dosages based on the patient's renal function, an intervention that is simple yet frequently overlooked. Additionally, replacing nephrotoxic drugs with less harmful alternatives, correcting hypovolemia and electrolyte imbalances, reducing treatment duration when feasible, monitoring drug serum levels, and avoiding highly toxic drug combinations are all cost-effective strategies that can significantly lower the incidence of drug- induced renal injury.

Conclusion

In conclusion, drug-induced acute kidney injury (AKI) remains a significant clinical concern, particularly in hospitalized and critically ill patients. The kidneys' vulnerability to nephrotoxicity is due to their central

role in drug metabolism and excretion, with various drugs causing renal injury through pre-renal, intrinsic, and post-renal mechanisms, as discussed above.

Preventive measures and management strategies as enumerated earlier are critical to mitigating the impact of drug- induced AKI. Emerging fields like pharmacogenetics offer promise for personalizing treatment to reduce nephrotoxic risks, although these approaches require further validation in clinical practice.

Despite advancements in early diagnosis and preventive strategies, challenges remain in balancing therapeutic efficacy and minimizing renal toxicity. The integration of multidisciplinary approaches, combining pharmacological innovations and patient-centered care, will be key in reducing the global burden of drug-induced AKI.

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