Acute kidney injury due to gentamicin nephrotoxicity and specific miRNAs as biomarkers

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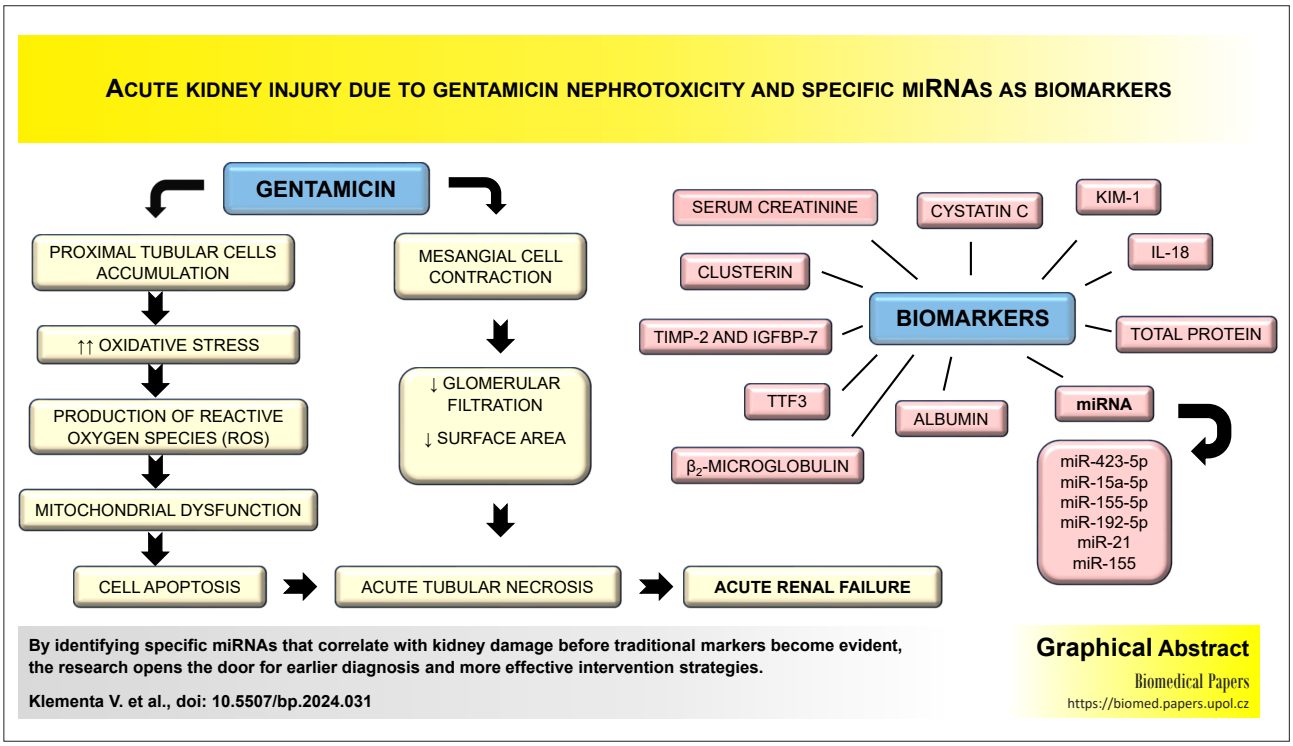
Acute kidney injury (AKI) due to gentamicin nephrotoxicity is a significant concern in clinical medicine, particularly in patients receiving prolonged or high-dose gentamicin therapy. Gentamicin is an aminoglycoside antibiotic frequently used in the treatment of a range of bacterial infections. However, its use is associated with nephrotoxicity which can manifest as AKI. Due to this, it is crucial to diagnose promptly and manage treatment effectively. Ongoing studies are therefore focusing on non-protein-coding RNAs as potential biomarkers for AKI. Numerous microRNAs (miRNAs) have been implicated in gentamicin-induced nephrotoxicity and AKI. They participate in pathways associated with inflammation, cell death, and oxidative stress and each of these factors play critical roles in the development of gentamicin-induced kidney injury. Research studies have demonstrated changes in the expression levels of these miRNAs in response to gentamicin exposure both *in vitro* and in *in vivo* models, as well as in human clinical trials involving patients receiving gentamicin therapy. The dysregulation of these miRNAs correlates with the severity of kidney injury and may serve as sensitive biomarkers for early detection and monitoring of AKI induced by gentamicin.



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INTRODUCTION

MicroRNAs are a class of non-coding RNA molecules that have a significant impact on controlling how genes are expressed. The first miRNAs were discovered in 1993 by a group led by Ambros and this includes Lee and Feinbaum[1]. They are typically about 20–25 nucleotides long and are found in all living organisms and some viruses. MiRNAs have been identified as essential participants in various biological mechanisms, such as cell growth, differentiation, cell death and reactions to stress. The wide range of changes observed in miRNA patterns during diseases holds significant promise for the use of miRNAs as diagnostic biomarkers. In the context of kidney disease, miRNAs have been recognized as important regulators and biomarkers of various pathological conditions, including acute kidney injury (AKI). To date, over 2,000 miRNAs have been identified in humans, and it is believed that together they control around a third of the genes found in the human genome. miRNAs are also associated with a large number of human diseases and are being actively explored as targets for clinical diagnosis and treatment[2].

Acute kidney injury

Acute kidney injury is defined as a sudden and rapid decline in kidney function which can occur from a few hours to a few days. It is a frequently occurring and serious issue linked with higher rates of illness and death, particularly among critically ill septic patients. The incidence of acute kidney injury (AKI) is as much as 15% in hospitalized patients and more than 50% in intensive care units[3]. An important cause of AKI is nephrotoxicity induced by antibiotics, especially aminoglycosides such as gentamicin. Gentamicin-induced nephrotoxicity is characterized by renal tubular cell apoptosis, inflammation, and oxidative stress, ultimately leading to impaired renal function.

Definition of acute kidney injury

Acute kidney injury is generally defined as a sudden decline in kidney function linked to a reduction in glomerular filtration rate and characterized by the accumulation of waste products from nitrogen metabolism, as well as reduced urine production or both The Kidney Disease Improving Global Outcomes (KDIGO) 2012 classification led to description of any of the following: increase in serum creatinine (S_{crea}) by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; increase in S_{crea} to ≥ 1.5 times baseline, which is known or presumed to have occurred within the 7 days prior; urine volume < 0.5 mL/kg/h for 6 hours. Based on severity, we classified AKI into three grades. Stage 1 AKI is described as a rise of S_{crea} 1.5–1.9 times from baseline or ≥ 0.3 mg/ dL (≥ 26.5 mmol/L) and/ or a reduced urine production to < 0.5mL/kg/hour for 6–12 hours. Stage 2 is described as a rise of S_{crea} 2.0–2.9 times from baseline and/or a reduced urine production to < 0.5mL/kg/hour for ≥ 12 hours. Stage 3 AKI is described as an increase in S_{crea} of 3.0 times from baseline or ≥ 4 mg/dL (≥ 353.6 μmol/L) or need for initiation of RRT (renal replacement therapy) and/or a reduced urine production to < 0.3mL/kg/hour for ≥24 hours or anuria for ≥12 hours[4].

Gentamicin

Gentamicin is an aminoglycoside antibiotic agent with a bactericidal effect on Gram-negative bacterial pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus sp*. and *Klebsiella sp*. The primary way this antibiotic is removed from the human body is through renal elimination, specifically by passing through the glomerular filtration process[5].

The basic pharmacokinetic parameters of gentamicin can be substantially affected in the critical condition due to its hydrophilicity and low plasma protein binding, ranging between 0–30% depending on the method of testing[6].

The volume of distribution (V_d) for gentamicin is generally equal to the extracellular body weight, which means that it tends to decrease with age. In adults with healthy kidneys, the elimination half-life of gentamicin is fairly short, usually in the range of 2 to 3 hours[7]. The median clearance (CL) of this antibiotic in adults with normal function of kidneys (creatinine clearance [CL_{CR}] > 60 mL/min) is approximately 4.58 L/h/70 kg with range 4.31–5.12 L/h/70 kg (ref.[8]). Gentamicin distributes throughout the extracellular fluid compartment, the V_d in non-critically ill adult patients with normal kidney function is roughly 19.5 L/70 kg (ref.[9,10]). Gentamicin is a concentration dependent antimicrobial with optimal required C_{max}/MIC ratio (maximum serum concentration to minimum inhibitory concentration of pathogen) 8–10:1.

A typical initial dose of gentamicin, ranging from 5–7 mg/kg based on total body weight (adjusted in overweight patients) appears to be the best approach to increase the probability of target attainment (PTA) after the first dose in adults and children over one month old, even in critically ill patients. Higher loading doses may further increase the PTA but there is insufficient evidence that the treatment is more effective in clinical settings while the probability of kidney damage is expected to increase. Establishing the ideal dosing interval for each patient is crucial in minimizing the risk of nephrotoxicity. The best way to achieve this is therapeutic drug monitoring (TDM), targeting a C_{min} under 2 mg/L but preferably < 1 mg/L. In patients with AKI the gentamicin should be administered optimally at 24hour intervals. TDM to optimize the probability of pharmacokinetic/ pharmacodynamic (PK/PD) target attainment is advised especially for patients with widely varying drug metabolism rates. This includes individuals who are critically ill, such as the elderly, children, newborns, and those undergoing intermittent hemodialysis[11].

The incidence of acute renal failure after gentamicin treatment may be present in approximately 10–20% of all cases[12]. Acute nephrotoxicity is very often reversible but it can also be fatal. According to some clinical studies, the incidence of kidney damage has been shown to vary depending on the target population, suggesting that certain people possess a higher level of sensitivity than others. The most relevant risk factors include reduced re-

nal function, older age, dehydration, hepatic dysfunction, metabolic acidosis and lack of sodium. The risk of kidney damage may be also affected by the dose, frequency, and duration of nephrotoxic therapy. Concomitant treatment with other nephrotoxic drugs e.g. NSAIDs (non-steroidal anti-inflammatory drugs), diuretics, vancomycin, cisplatin, cyclosporin, cephalosporins, amphotericin, etc. is another relevant risk factor for the gentamicin toxicity[13,14].

Gentamicin – induced nephrotoxicity – pathophysiology

The nephrotoxic effects of gentamicin involve a complicated physiological process that affects both the kidney tubules and glomeruli. A major aspect of aminoglycoside nephrotoxicity is their tubular toxicity, which consists in the selective drug accumulation in renal proximal convoluted tubules that leads to loss of brush border integrity[15].

In experimental animal studies, it has been proven that aminoglycoside treatment can cause both apoptosis and necrosis of renal tubular cells[16-18]. Apoptosis is a regulated process requiring ATP (adenosine triphosphate) as a source of energy. When the cellular ATP reserve is reduced, the controlled cell death loses the typical characteristics of apoptosis and acquires markers of necrosis. This may also depend on the interaction of some inducing or predisposing factors. One of these may be, for example, the level of ischemia[19].

The toxic effects of gentamicin on the kidneys are observed in the specific types of cells where the drug accumulates. These are epithelial cells located in the cortex, primarily found in the proximal tubule of both experimental animals and humans, as well as in the distal and collecting ducts[20]. The higher accumulation of gentamicin in these cells is consistent with the expression of a protein and cation transporter, specifically a large endocytic complex consisting of megalin and cubilin, which is restricted to the proximal tubule. This complex has been identified as facilitating the transportation of gentamicin into kidney cells through endocytosis[21]. Gentamicin moves through the endosomal compartment and tends to gather predominantly in lysosomes, the Golgi apparatus, and the endoplasmic reticulum. It also attaches to phospholipids in cell membranes, changes their turnover and metabolism. Once the level of aminoglycoside inside endosomal structures reaches a certain threshold, their membranes are destroyed, and their contents enter the cytosol along with the drug, where it affects mitochondria and triggers the internal process of programmed cell death, disrupts the energy production process in cells by halting the respiratory chain, decreases ATP synthesis, and generates oxidative stress through elevated levels of superoxide anions and hydroxyl radicals, which further contributes to cell death[19]. Furthermore, the lysosomal content also carries highly active proteases called cathepsins, which can be responsible for cell death[22].

Gentamicin – induced nephrotoxicity – biomarkers

Whereas there is an interest in finding new biomarkers of gentamicin induced AKI. Urinary biomarkers clusterin, KIM-1 (kidney injury molecule-1), Cystatin C and NGAL were compared with serum BUN (blood urea nitrogen) and creatinine for early identification of progression from minimal to moderate kidney injury in gentamicin-treated animals. As expected, all of these biomarkers exhibited signs of onset earlier than the commonly utilized serum BUN and creatinine in diagnosing AKI (ref.[23]). In the review study by Fuchs et al. dozens of potential biomarkers of AKI were identified. The most promising of these were Cystatin C, clusterin, KIM-1, TTF-3 (trefoil factor-3), β_2-microglobulin, albumin and total urine protein[24].

The studies are also focused on finding miRNA specific for disclosure of gentamicin nephrotoxicity. In a research trial focusing on kidney damage caused mainly by certain drugs affecting either tubular (like gentamicin and cisplatin) or glomerular (such as puromycin and doxorubicin) functions, researchers identified miR-143-3p and miR-122-5p as possible indicators of tubular injury, while miR-3473 was suggested as a potential marker for glomerular damage[41]. In study by Sun et al. authors selected six promising microRNAs (*miR-15b*, *miR-15b-3p, miR-16, miR-30a, miR-30a-3p,* and *miR-30c-2-3p*). The diagnostic effectiveness of these six potential microRNAs were better than the conventional serum biomarkers (all $P<0.05$). Of these six molecules, the most promising seem to be *miR-15b* and *miR-30a* as markers for renal toxicity[42].

Engagement of specific miRNAs in gentamicin-induced AKI is still under investigation. However, *miR-155* was found to be notably increased in rats experiencing kidney damage, whether caused by gentamicin exposure or resulting from ischemia[43]. In both mouse kidneys and a rat kidney cell line, the levels of miR-122 dropped following exposure to gentamicin (also after cisplatin and doxorubicin). Since gene *FOXO3* is a verified target of *miR-122*, *FOXO3* stimulated downstream activation of *p53* in the absence of *miR-122* and resulted in progression of programmed cell death and damage to the kidneys[44]. In the study by Ramachandran et al., was identified miRNAs that can significantly differentiate patients with AKI from individuals without AKI. The average values of *miR-21* ($P=0.0005$), *miR-200c* ($P<0.0001$), and *miR-423* ($P=0.001$), in the urine were considerably higher in patients with AKI than in the patients without AKI, whereas *miR-4640* ($P=0.0355$) was considerably lower in the AKI group compared with the non-AKI group[45]. In the prospective animal study by Xiaobing et al. the findings indicated that the levels of four specific miRNAs (*mmu-miR-138-5p*, *mmu-miR-1971*, *mmu-miR-218-1-3p*, and *rno-miR-489*) were continuously increased in urine samples a few days after gentamicin administration. This increase was not mirrored by conventional markers like S_{crea} and BUN. Receiver operator characteristics analysis indicated that the effectiveness of these miRNAs, which showed increases corresponding to either time or dosage, was similar to established biomarkers (i.e. S_{crea} and BUN). This suggests that the collection of urinary miRNAs could serve as promising biomarkers for identifying gentamicin-induced AKI in rats[46]. In summary, further investigation into the involvement of miRNA in the development of drug-induced kidney injury could lead to the development of miRNA-based therapeutics, which appears hopeful considering the present discoveries and outcomes observed in related fields.

Table 1. Overview of the most promising biomarkers for the detection of nephrotoxicity. Modified by Fuchs et al.[24].

Biomarker	Pathophysiology	Marker of	Experimental evidence	Clinical evidence	Ref.
Cystatin C	Glomerular filtration, reabsorption, and lysosomal degradation by proximal tubule cells	Decrease glomerular filtration, proximal tubule damage	Levels rise in rats with diabetes and in reaction to partial kidney removal. Increase during chromium- induced kidney damage	Elevated in humans with AKI or with tubular dysfunction	25–27
Clusterin	Participating in cell attachment, the reuse of membranes, restructuring of tissues, controlling the cell cycle, programmed cell death, and repairing DNA	Proximal tubule damage, distal tubule damage	Increased increased in response to ischemia, postrenal AKI or as reaction to numerous toxins, e.g., increased miRNA expression in kidneys of rats treated with gentamicin	Excessively expressed in human kidney disorders.	28–30
KIM-1	Transmembrane protein expressed by tubule epithelial cells in reaction to insult	Proximal tubule damage	Upregulated due to gentamicin administration.	Increased in patients after kidney transplant and patients with AKI of many causes	27, 28, 31, 32
IL-18	synthesized as a precursor by monocytes, macrophages, and proximal renal tubular epithelial cells	Proximal tubule damage	Triggered by caspase-1, leading to ischemic damage and inflammation in the nearby renal tubules, subsequently eliminated through urine	marker for predicting AKI, primarily in pediatric patients	33
[TIMP-2]* [IGFBP-7]	Raised due to improved filtering, increased discharge through the tubules, and reduced reabsorption within the tubules	Tubular damage	Both markers have been suggested to improve the accuracy of diagnosing AKI.	The potential to predict bad prognosis of AKI	34,35
TTF3	Peptide hormones of limited size that are released by cells producing mucus, as well as by epithelial cells found in various tissues	Tubular damage	The heightened decline following gentamicin treatment	N/A	36,37
β_2-microglobulin	Glomerular filtration and reabsorption by proximal tubule cells	Proximal tubule damage	Elevated in reaction to ochratoxin A, depleted uranium, cisplatin, chlorotrifluoroethylene, 1,1-dichloro- 2,2-difluoroethylene	High values in patients with idiopathic membranous nephropathy; elevated in drug induced kidney damage	26,38
Albumin	Its dimensions and negative electric charge exclude it from excretion in the glomerulus	Glomerular damage	Greater contact between proximal tubular cells and albumin can trigger cell death through fatty acid boundary. This is heightened as a reaction to cisplatin (Platinol) and gentamicin.	In patients with type 1 diabetes, a decrease in albuminuria is linked to reduced levels of markers indicating tubular injury, specifically KIM-1 and NAG.	36,39
Total protein	The glomerulus didn't filter out big, highly charged proteins. On the other hand, small proteins passed through the glomerular barrier easily and were taken back in by the proximal tubular cells.	Glomerular damage, Proximal tubule damage	Increased levels were observed following the introduction of cisplatin, gentamicin, vancomycin, tacrolimus, puromycin, and doxorubicin.	Proteinuria serves as an indicator for prediction kidney-related outcomes and the risk of death in individuals with chronic kidney disease	26,40

AKI, acute kidney injury; DNA, deoxyribonucleic acid; KIM-1, kidney injury molecule; IL-18, interleukin-18; IGFBP-7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor metalloproteinase-2; TTF3, trefoil factor 3; T1DM, type 1 Diabetes mellitus; CKD, chronic kidney disease; NAG, urinary *N*-acetyl-β-D-glucosaminidase.

Table 2. microRNAs in humans involved in septic acute kidney injury and gentamicin induced nephrotoxicity.

	Target gene regulation	Biochemical pathway regulation	Pathophysiological process	Ref.
miR-423-5p	*GSTMI1*	increasingly activated due to induced stress within the endoplasmic reticulum and reactive oxidative stress by suppressing *GSTMI1*	ischemia, apoptosis	48
	DDIT4	Expressed more in reaction to hypoxia-inducible factor 1; controles the production, is activated by DNA damage as a target of p53	inflammation	49
	PRG2	participating in defense against parasites as a cytotoxin, they also possess strong abilities to fight against microbes	inflammation	50
	MAFF	participating in the reaction of cells to stress	inflammation	50
	FOXA1	enhanced as inflammation and fibrosis advance	inflammation	51
miR-15a-5p	*XIST-CUL3*	participating in the initiation of programmed cell death in kidney cells	ischemia, inflammation, nephrotoxicity	52
	TNIP2	participating in the inflammatory response during sepsis through the activation of the NF-κB pathway	inflammation	53
	VEGFA *VEGFC* *MYLK*	negative regulation of IKK-α and inhibition of genes encoding VEGFA, VEGFC and myosin light chain kinase, raising vascular permeability in sepsis	inflammation	54
miR-155-5p	*IRF2BP2-NFAT1*	in animals, reducing the activity of miR-155-5p improves the condition of acute lung injury caused by lipopolysaccharide by controlling the expression of these specific miRNAs	inflammation	55
miR-192-5p	*XIAP* *Bax* *P21* *P53*	upregulation of pro-inflammatory cytokine in sepsis production, association of *miR-192-5p* with regulation of the *miR-192-5p XIAP* axis in this condition has been investigated in animals	Inflammation, nephrotoxicity	56
miR-21	*ARG2* *BECN1 CFDP1* *COQ6* *ERC1* *FAM134B FKBK1B*	controlling various kidney processes crucial for and involved in ischemia/ reperfusion injury such as inflammation, apoptosis, proliferation, and fibrosis, promote proliferative responses by upregulating the survival factor *Bcl-2* and downregulating the tumor suppressor gene-Pdcd4.	inflammation, apoptosis	43
miR-155	*PTGS2*	produced by different types of kidney cells when they are triggered by inflammatory signals such as TNF-α, IL-6, IL-1β, TGF-β.	inflammation	43

AKI, acute kidney injury; Bax, B-cell lymphoma 2 Asociated X, Apoptosis Regulator, *DDIT4,* DNA damage–inducible transcript 4; DNA, deoxyribonucleic acid; *FOXA1*, forkhead box protein A1; GSTM1, glutathione-S-transferase M1; *IFR2BP2-NFAT1,* interferon regulatory factor 2 binding protein 2–nuclear factor of activated T cells 1; IKK, inhibitory-κB kinase; IL-1β, interleukin-1β; IL-6, interleukin 6; *MAFF,* MAF basic leucine zipper transcription factor F; miR, micro RNA; *MYLK*, myosin light chain kinase; Pdcd4, tumor suppressor gene-programmed cell death 4; *PRG2,* proteoglycan 2, pro eosinophil, major basic protein; p21, p21 gene; p53, p53 gene; NF-κB, nuclear factor kappa B; TGF-β, Transforming Growth Factor-β; TNF-α, tumor necrosis factor-alpha; *TNIP2*, TNFAIP3 interacting protein 2 gene; VEGFA, vascular endothelial growth factor A gene; VEGFC, vascular endothelial growth factor C gene; XIAP, X-linked inhibitor of apoptosis; XIST-CUL3, X inactive specific transcript – cullin 3 gene.

The most of above studies were all performed in animal models, there is still a lack of papers investigating specific miRNAs in humans. In our prospective clinical study by Petejova et al. were recognized four circulating miRNAs- *miR-15a-5p, miR-155-5p, miR-192-5p, and miR-423-5p* in septic patients treated by nephrotoxic antibiotic agents (vancomycin or gentamicin) (ref.[47]). Another prospective study by Saikumar et al., authors showed that *miR-21* and *miR-155* were among the highest upregulated miRNAs in the kidney following ischemic reperfusion injury. The increase in these miRNAs in the kidney was noticed in various AKI models, but there was no such observation after liver damage. This highlights how reliable, consistent, and specific the miRNA reaction is. Additionally, the urinary excretion patterns of *miR-21* and *miR-155* in urine could successfully distinguish patients with AKI and those without it[43].

Management and prevention of nephrotoxic acute kidney injury

Key in prevention of AKI is identification of risk factors – recognize patients at higher risk for nephrotoxic AKI, including those with preexisting kidney disease, elderly individuals, and patients on potentially nephrotoxic medications. Whenever possible, physicians should avoid or minimize exposure to substances known to be nephrotoxic, including certain medications (e.g., NSAIDs, aminoglycoside antibiotics, contrast agents), environmental toxins, and illicit drugs as well as adjust medication dosages based on renal function to minimize the risk of neph-

rotoxicity. Important is also to consider using alternative medications or adjusting dosing intervals in patients with impaired kidney function and maintain adequate hydration, especially in situations where dehydration may exacerbate the toxic effects of substances on the kidneys. The following steps are advised: encourage fluid intake and administer intravenous fluids, when necessary, to monitor renal function through serum creatinine and urine output measurements, particularly in patients at risk of nephrotoxic AKI, and to identify promptly any signs of kidney injury for early intervention[57].

The management of nephrotoxic AKI is based on several important issues. The most important thing to start with is discontinue the use of the nephrotoxic therapy as soon as possible. We should try to maintain or restore intravascular volume with isotonic crystalloid fluids to optimize renal perfusion and support kidney function. Monitor fluid status closely to prevent volume overload. Correct electrolyte imbalances and acid-base disturbances promptly to prevent further renal injury. The next steps consist of ensuring adequate blood pressure and hemodynamic stability to support renal perfusion, using vasopressors if necessary to maintain organ perfusion. In severe cases of nephrotoxic AKI, we should consider RRT initiation, especially if there is oliguria, fluid overload, or severe electrolyte disturbances presented. RRT may help remove toxins and maintain fluid and electrolyte balance. Provide supportive care to manage complications associated with AKI, including infection prevention, nutritional support, and management of other organ dysfunctions. Identify the underlying cause of nephrotoxic AKI and address it accordingly. Further diagnostic evaluation may be needed to determine the specific toxin or medication responsible for kidney injury. Implement strategies to prevent recurrence of nephrotoxic AKI, such as avoiding nephrotoxic agents, optimizing medication management, and addressing modifiable risk factors[4].

In complex cases or when renal replacement therapy is required, involvement of a nephrologist for specialized management and guidance is appropriate. By implementing these preventive measures and management strategies, we can effectively reduce the incidence and severity of nephrotoxic AKI and improve patient outcomes.

CONCLUSIONS

Drug induced kidney injury is still a large problem in clinical medicine. Despite the promising outcomes observed with miRNA biomarkers, it is important to note that the field encounters various fundamental obstacles that impede the seamless progress of qualifying and validating biomarkers. One major obstacle in clinical miRNA biomarker research is assessing their effectiveness compared to S_{crea} which serves as the established gold standard for defining AKI. Although in preclinical studies renal histopathological examination is the most reliable method for diagnosis of drug induced kidney injury, S_{crea} continues to be commonly employed in clinical evaluations. In fact, moderate performances of new AKI biomarker candidates are often seen in clinical studies, where AKI is mostly defined based on increased S_{crea} levels. One possible approach to studying drug-induced kidney injury is to compare the effects of the nephrotoxic drug itself against other treatments. Another obstacle arises from the absence of uniformity not just in the methods used to isolate and measure miRNA, but also in the way samples are collected, processed, and stored. While miRNAs hold promise as biomarkers and therapeutic targets, their use in clinical practice, especially for conditions like AKI, is hindered by issues of specificity and sensitivity (miRNAs often show similar expression patterns across different diseases. For example, miRNAs involved in AKI can also be altered in other kidney diseases or conditions involving inflammation and stress, leading to potential misdiagnoses), technological challenges, regulatory hurdles, and variability in expression patterns. Addressing these challenges requires ongoing research to improve the accuracy, reliability, and practicality of miRNA-based applications in healthcare. Large-scale prospective studies are required to assess their sensitivity, specificity, and predictive value in different patient populations and clinical settings. Additionally, standardized protocols for miRNA detection and quantification need to be established to facilitate their translation into routine clinical practice. Despite these challenges, miRNAs hold promise as valuable biomarkers for the early detection and management of gentamicin-induced AKI, potentially improving patient outcomes through timely intervention and dose optimization.

Search strategy and selection criteria

A search was performed on PubMed for the terms “miRNA” OR “microRNA” AND “acute kidney injury” AND “gentamicin”. The objective of this review is to provide an overview of possible biomarkers of acute kidney injury related to nephrotoxic antibiotic treatment, which is a severe complication often occurs in critically ill patients with sepsis. In recent years, attention has been focused on new and promising biomarkers, including miRNA. In our study, we focused on miRNA specific for gentamicin nephrotoxicity in septic patients. The publications were evaluated for potential applicability.

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