RESEARCH ARTICLE

Renal-pulmonary Crosstalk in Patients with Chest Disease in ICU: Role of Flouroquinolones in AKI Development

Ahmed Waheed Ahmed[1], Mohy Eldeen H[1], Mohamed O. Abdelaziz[1], Mostafa Ahmed Abu Elela[2]

[1]*Department of Internal medicine, Faculty of Medicine, Minia university*
[2]*Department of Clinical pathology, Faculty of Medicine, Minia University*

Received: 19th July 2024; Revised:3rd Aug, 2024; Accepted:11th Aug, 2024; Available Online: 31st August, 2024

ABSTRACT

Acute kidney injury is a prevalent consequence in studied cases who have acute pulmonary insult, in many studies reported incidence rates of up to 35%. AKI and ARDS together ensure a worse prognosis, including increased death. Describing the risk factors that make AKI more common in these studied cases is necessary. Understanding these factors could aid physicians in better managing these conditions, ultimately reducing mortality Hypertension, diabetes, high BMI, and mechanical ventilation, drugs (antimicrobials such as fluroquinolones, NSAIDS, RAAS blockers and diuretics) are significant predictors of AKI in patients with respiratory diseases. These findings underscore the importance of monitoring and managing these factors to mitigate the Occurrence of AKI in critical care settings. Antibiotic resistance is a common factor in the development of AKI. studied cases receiving antibiotics are frequently predisposed to an increased risk of AKI because of underlying medical conditions & the severity of their illness. In addition, certain medicines can have direct effects on the kidneys.

Keywords: Acute kidney injury-Acute Respiratory distress syndrome - Risk factors-Mechanical ventilation- Intensive care unit-Body Mass Index

How to cite this article: Ahmed Waheed Ahmed,Mohy Eldeen H.,Mohamed O. Abdelaziz,Mostafa Ahmed Abu Elela. Renal-pulmonary Crosstalk in Patients with Chest Disease in ICU: Role of Flouroquinolones in AKI DevelopmentInternational Journal of Pharmaceutical Quality Assurance. 2024;15(3): 2059-2065. DOI: 10.25258/ijpqa.15.3.143

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

In critically ill patients, the interaction between the kidneys and lungs has received a lot of attention. (1). Both organ injuries and dysfunctions are common and linked to considerable morbidity and mortality (2) Acute kidney injury is a major complication with high mortality rates in hospital and ICU units, affecting up to 20% of all hospitalized studied cases and 57% of ICU patients, with approximately 13% requiring renal replacement therapy (RRT) (3). Due to hemodynamic, neurohormonal, and inflammatory consequences, patients with acute respiratory failure or acute respiratory distress syndrome (ARF/ARDS), particularly those requiring invasive mechanical ventilation, are more likely to develop AKI. (4) A multicenter ICU study found that 44.3% of ARDS patients developed AKI within two days of ARDS onset and mechanical ventilation (5)Acute respiratory failure can lead to renal damage through several mechanisms: hypoxia can reduce renal blood flow & reduce glomerular filtration, while hypercapnia can cause renal vasoconstriction and systemic vasodilation due to high PaCO2 levels (6) Additionally, systemic proinflammatory mediators released from injured lungs are linked with AKI(7). Although the most common consequence in studied cases with acute respiratory distress syndrome is acute kidney injury (AKI), it's crucial to describe the main risk factors for AKI in these studied cases. Knowing these factors will help doctors better manage these diseases, which will eventually lower mortality. (8) Potential nephrotoxic drugs make up one-fourth of all prescriptions administered in hospitals. According to estimates, hospitalized patients' Medication is one of the most frequent reasons for AKI in ICU studied cases, accounting for nineteen percent to twenty-six percent of all occurrences of AKI.(9)

Acute Kidney Injury

The description of acute renal injury, formerly known as acute renal failure, as measured by glomerular filtration rate, is an abrupt & usually reversible decline in kidney function(10). Sometimes, however, blood urea nitrogen (BUN) or creatinine (Cr) values immediately following a renal insult could be within normal limits, & the only sign of AKI could be a decrease in urine output. AKI may cause salt, water, and other metabolic products to build up. Additional electrolyte problems can also be caused by AKI. In hospitalized patients in particular, AKI is a common illness that affects up to seven percent of admissions, & thirty percent of admissions in intensive care units. Numerous criteria, including RIFLE, AKIN, and KDIGO criteria, have been applied to diagnose AKI. KDIGO is the most modern and widely utilized. KDIGO describes AKI as the existence of any one of the following (table1) (11)**:** For classification, the criterion with the greatest impairment is

Author for Correspondence: dr.awa5500@gmail.com

Table1: KDIGO's criteria for acute kidney injury (12)

Stage	Rise in serum creatinine	Urine output
1	≥0.3mg/dL (26.5μmol/L) in 48h or 1.5–1.9times baseline in 7days	<0.5mL/kg/h for six to twelve hour
2	2.0–2.9times baseline in 7days	<0.5mL/kg/h for ≥twelve hour
3	≥three times baseline, or ≥ 4.0mg/dL (354μmol/L) increase in 7days or initiation of RRT or in studied cases <18years of age, reduce in estimated GFR to <35mL/min/1.73m^2	<0.3mL/kg/h for ≥twenty-four hour or Anuria ≥twelve hour

employed. When baseline Cr is unknown, a baseline GFR among seventy-five & one hundred mL/min is assumed, or an estimated baseline Cr can be determined using the Modification of Diet in Renal Disease equation. The RIFLE criteria identify three types of impairment—risk, damage, & failure—as well as two categories of long-term renal outcome. (13). (**table 2)** Also known as the "modified RIFLE" criteria, the AKIN criteria have been derived from the RIFLE criteria. All three systems are similarly good in predicting in-hospital mortality, even though RIFLE and KDIGO are more sensitive than AKIN.(11).

Etiology of AKI

Numerous factors can lead to AKI, but its primary causes are higher energy demands (from cellular stress) and a focused mismatch in the delivery of nutrients & oxygen to the nephrons because of compromised microcirculation. Classifying AKI patients into 3 primary categories—pre-renal, intrinsic, & post-renal—was the foundation for diagnosis and treatment for a long time. **(Figure 1)**(15).

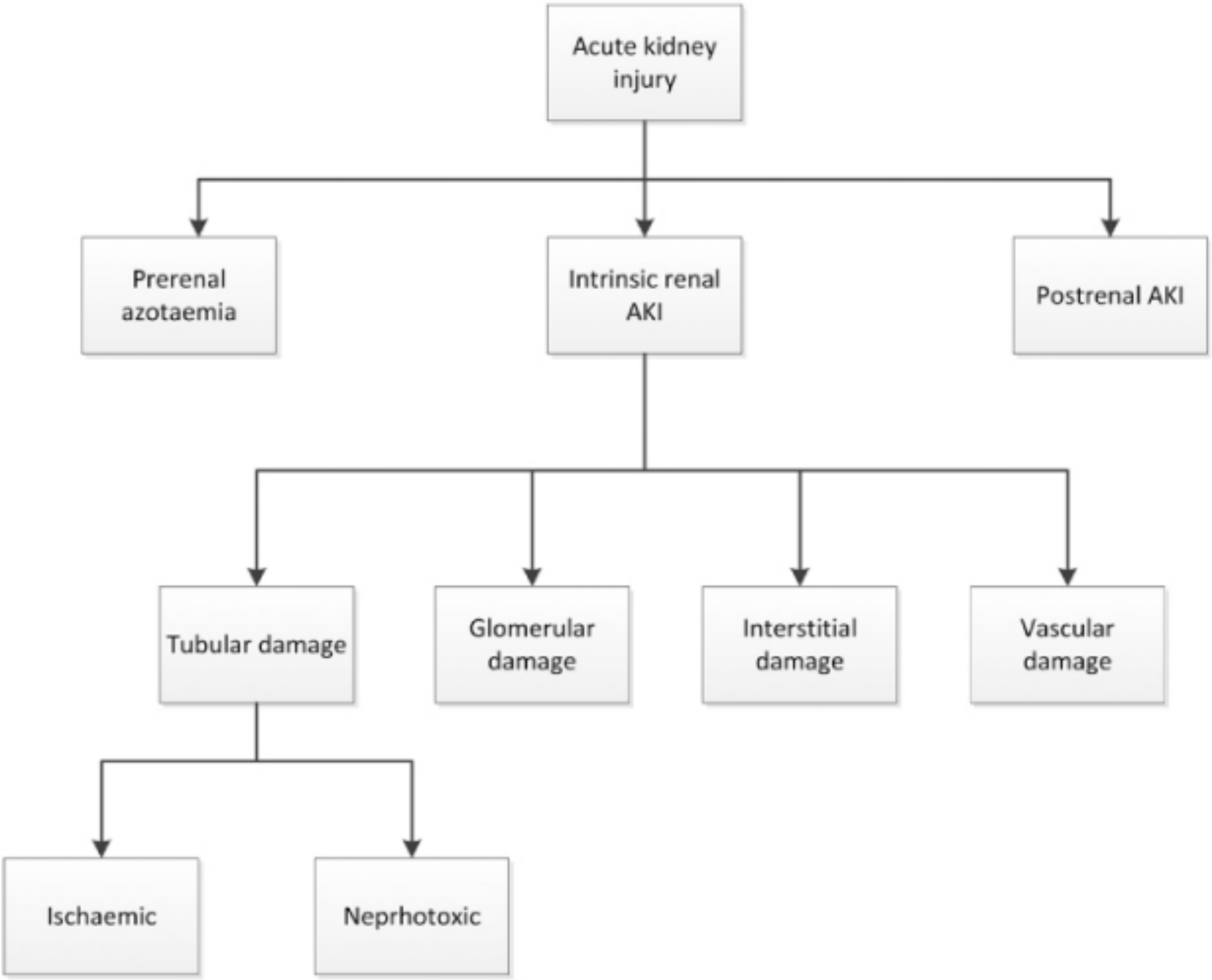

Figure1: Etiologies of acute kidney injury(16).

Table 2: RIFLE criteria(14).

Stage	Creatinine / GFR	Urine output
R (isk)	**1.5-fold rise** in serum creatinine / GFR decrease of twenty-five percent or more	< **0.5**ml/kg/h for at least **6hours**
I (njury)	**2-fold rise** in serum creatinine / GFR decrease of fifty percent or more	< **0.5**ml/kg/h for at least **12hours**
F (ailure)	**3-fold rise** in serum creatinine / GFR decrease of seventy-five percent or more	< **0.3**ml/kg/h for at least **24hours**
L (oss)	**persistent renal failure** (after week four)	
E (SRD)	**chronic kidney disease** (after month three)	

Risk factors for AKI

AKI risk factors include exposures and patient vulnerabilities. (17) (**table 3).**

Epidemiology

Hospitalized patients are often found to have AKI; in the US, 1% of all admissions had AKI at the time of admission. Up to sixty-seven percent of studied cases permitted to the intensive care unit experience AKI. & account for approximately 2% to 5% of acute kidney injury incidence during hospitalization.(18).

Pathogenesis

Due to its numerous etiologies and risk factors, AKI has a very complex pathophysiology. Sepsis, shock, major heart or transplant surgeries, and other diverse conditions can all lead to it. The process primarily depends on vascular, tubular, & inflammatory damage mechanisms as well as the subsequent repair processes, even though the precise mechanism is unknown. These processes can either generate progressive fibrotic alterations that contribute to chronic kidney disease or they can restore normal function.(19)**.** Although the traditional view of the etiology of AKI is pre-renal, intrinsic, & obstructive, which is more anatomical, immunological systems are crucial for both epithelial layer repair and injury or modulation of the inflammatory response. (20)**.**Depending on what causes the AKI, the mechanism causing it can vary. AKI is still primarily caused by renal ischemia, which can be brought on by a variety of factors like the production of enzymes, cytokines, & oxygen-free radicals; leukocyte adhesion & endothelial activation; activation of the coagulation system; & apoptosis induction. It is generally accepted that intrinsic renal failure can be caused by glomerular or tubular disorders, renal ischemia, or diminished renal perfusion from any source. The afferent and efferent arterioles, which keep blood flow & filtration fraction constant in an 80–180 mm Hg range of mean arterial blood pressure, are responsible for the remarkably good autoregulation of renal perfusion. The renin-angiotensin-aldosterone system, the tubuloglomerular feedback mechanism via the macula densa, & the myogenic activity of the afferent arterioles are the main autoregulation mechanisms of renal blood flow.(21)**.** The maintenance of glomerular filtration requires afferent arteriolar vasodilation in response to hypotension. Prostaglandins and nitric oxide are secreted along with activation of the renin-angiotensin-aldosterone system and other vasodilators. Afferent arteriolar vasoconstriction during hypertension is caused by a variation of mediators, comprising adenosine, sympathetic nerve activation, endothelin-1, angiotensinII, thromboxane A2, prostaglandin H2, leukotrienes, & efferent arteriole dilatation to stabilize RBF & GFR. The risk of acute kidney injury escalates when any cause, such as the use of Non-steroidal anti-inflammatory medications & angiotensin-converting enzyme inhibitors, inhibits these autoregulatory systems. (22)**.** Acute kidney injury frequently manifests as hypotension brought on by bleeding, dehydration, sepsis, compromised heart function, or the use of vasoactive medications. Systemic hypotension may not necessarily be required, though, as variations in regional renal flow might lead to regional renal hypoperfusion. Normally, the kidneys receive 25% of the heart's output. The peritubular arteries & vasa recta renis, which are crucial for the reabsorptive function, are where the kidney's glomerular afferent & efferent arterioles branch. This function is highly energy-dependent; adenosine triphosphate is produced by oxidative metabolism in the cortex, while the medulla receives approximately thirty-three percent of its energy from glycolysis, making it vulnerable to ischemia. The medulla's

Table 3: Risk factors for acute kidney injury (17)**.**

AKI Risk Factors	
advanced age	Shock
Diabetes	Sepsis
High blood pressure	Nephrotoxins
persistent renal illness	(NSAIDs, ARB, ACEi, contrast)
Heart-related conditions	Operation
persistent liver damage	elevated uric acid
Long-term obstructive lung disease	Low blood sugar
HIV infection	elevated blood sugar
Being overweight	Anemia

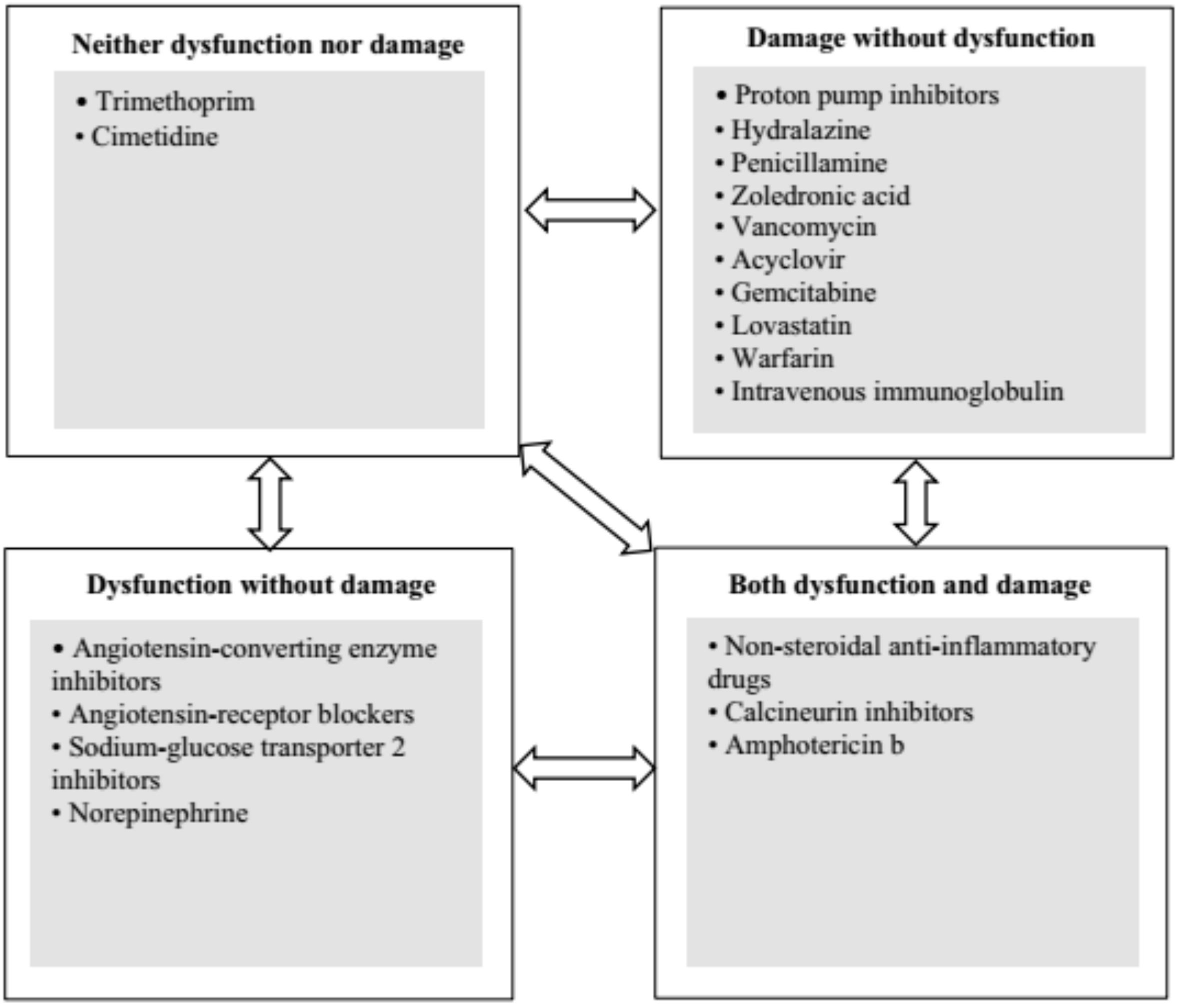

Figure 2: Drug-induced kidney injury classification scheme based on damage & functional biomarkers (31)**.**

partial pressure of oxygen decreases from 70mm Hg in the cortex to 20mm Hg because of the tubular saltwater reabsorption function's high oxygen requirement. The medulla is hence highly susceptible to hypoxia and damage(23)**.** The breakage of tight connections between cells caused by tubular ischemia damage or necrosis allows glomerular filtrate to flow back, significantly lowering effective GFR. Compared to the distal tubular cells, which may use glycolysis for metabolism, the proximal tubules rely on aerobic metabolism, making them more susceptible to mitochondrial malfunction. Additional hypothesized processes behind tubular damage include endothelial cell activation, endothelial enlargement, and increased adhesion molecule expression accompanied by glycocalyx denuding. Leukocyte stimulation, platelet aggregation, red cell entrapment, & activation of the coagulation cascade are other processes that result in vascular congestion & further ischemia damage. As the dying cells produce cellular debris that sloughs off into the tubules, obstructive casts form, further lowering GFR & leading to the loss of functional nephrons. Another theory about the mechanism of tubular damage is induced autophagy(21)**.** According to the ischemia-reperfusion theory, ischemic injury causes the epithelial cells to lose their polarity, changing where adhesion molecules and Na/K ATPase are located. This is followed by either necrosis or apoptosis, which is the final stage of cell death. The viable epithelial cells are unable to properly adhere to the basement membrane because of this change in adhesion molecule placement, and ultimately the healing process fails. Certain researchers propose that in cases of severe and protracted injury, the epithelial cell might undergo fibroblast transformation, which would then trigger fibrosis-based repair. Because fibrosis will make it harder for nutrients and oxygen to reach the tubules, tubular stress, and epithelial cell damage will increase. (24)**.**

Clinical Feature

Individuals with AKI do not have symptoms that are unique to the illness. On the one hand, they might exhibit symptoms of the underlying illness, such as thrombotic microangiopathy, sepsis, heart failure, or systemic vasculitis. The normal course of AKI has 4stages: (I) initiation, (II) oligo-anuria, (III) polyuria, & (IV) restitution, if renal function is compromised. Stage 2 (oligo-anuria) of this dynamic process is when clinical indications of renal impairment first appear. (20)**.** 70% of AKI patients have reduced urine production, which may lead to fluid retention, heightened hypertension, & heart failure with pulmonary edema. The entire organism is impacted by decreased excretion of electrolytes & endogenous & exogenous waste products. Such a toxification has been referred to as uremia, and it is linked to a wide range of symptoms such as pruritus, neurological symptoms, nausea & vomiting, diarrhea, anorexia-related appetite loss, cardiac arrhythmia, and sleeplessness (25**.** Furthermore, the patients are more vulnerable to bleeding problems and infections. Uremia is significant since it usually means that dialysis treatment is required. Stage three (polyuria) usually marks the beginning of the recovery of renal function, but it may affect significant losses of water, salt, & potassium. The latter could cause arrhythmia in the heart. AKI becomes chronic kidney disease, or CKD, if the renal healing process takes longer than three months(26)**.**

Drug-induced kidney disease

About twenty-five percent of all drugs administered in hospitals have the potential to be nephrotoxic(27). It is believed that 19–26% of hospitalized patients' cases of AKI are caused by DIKD.(28)**,** with one of the most frequent reasons for AKI in ICU studied cases being medication(29). Studies have sought to incorporate temporality & the mechanism of injury into the evaluation of DIKD, and have employed a variety of the previously described classification systems. (30). Based on clinical presentation and injury mechanism, Mehta et al. (2015) proposed four phenotypes of DIKD: glomerular disease, nephrolithiasis, tubular dysfunction, & AKI. Considering conceptual frameworks about the temporal course of occurrences, DIKD had been further classified into acute (one to seven days), subacute (eight to ninety days), & chronic (> ninety days) (28). A new framework for classifying tables (2 by 2) was recently presented by a panel of experts at the twenty third ADQI conference, which took place in Rome, Italy in April 2019. **(Figure 2)** (31). As a result, the main mechanism(s) of nephrotoxicity as well as functional and damage biomarkers have been combined to categorize drugs into the following 4 groups: dysfunction with damage, dysfunction and damage combined, dysfunction without damage, & neither dysfunction nor damage**(Figure 2)** (31)**.**

Fluoroquinolones & Nephrotoxicity

Broad-spectrum antibiotics, known as fluoroquinolones, are used to treat respiratory infections, some gram-positive bacteria, & intestinal gram-negative bacteria. But AKI is linked to some FQs, namely ciprofloxacin, & less frequently, levofloxacin & moxifloxacin (32). Given that the risk of AKI is far lower in FQs like gatifloxacin, norfloxacin, & gemifloxacin, the risk of AKI does not seem to be class-related (33) Fluoroquinolones have been linked to AKI in a nested cohort research (rate ratio 2.19, 95% CI 1.74–2.73) (33). On the other hand, 6.5 incidents increased the absolute incidence of AKI for every 10,000person-years of fluoroquinolone use. Additionally, a self-controlled case series discovered no meaningful correlation (34). The AKI from FQs usually results in AIN, but it can produce ATN when taken in excess, & in rare cases, it can cause crystalluria & granulomatous interstitial nephritis (35). Alkaline urine (pH > 6.8), concurrent use of renin-angiotensin system blockers, & precipitation-related characteristics such as low urine volume & high medication concentrations are risk factors for developing crystalluria (36). The distal tubules are frequently where the crystals form, which obstructs urine output & causes interstitial inflammation. The crystals that have been recovered from urine samples have a stellate appearance, are birefringent under polarized light, &, according to biopsies, are needle-shaped in the tubules (37). Like other antibiotics, AIN derived from FQs is usually nonoliguric & could or could not exhibit conventional inflammatory impacts (e.g., pyuria, eosinophilia). On the other hand, anuria may result from AKI from ATN. FQs-related crystalline nephropathy frequently manifests as an abrupt rise in creatinine & oliguria without any other symptoms. Maintaining adequate hydration, avoiding alkaline urine, and utilizing FQs that are less frequently linked to AKI, like norfloxacin or moxifloxacin, are preventative approaches (32). Treatment options involve tapering down the antibiotic or using a different medication (38).

REFERENCES

1. M J, Lg F, Sj K, Pm H, K K, M O, et al. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive care medicine [Internet]. 2020 Apr [cited 2024 Jul 19];46(4). Available from: https://pubmed.ncbi.nlm.nih.gov/31820034/
2. Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med [Internet]. 2015 Aug 1 [cited 2021 Jul 4];41(8):1411–23. Available from: https://doi.org/10.1007/s00134-015-3934-7
3. Park BD, Faubel S. Acute Kidney Injury and Acute Respiratory Distress Syndrome. Crit Care Clin [Internet]. 2021 Oct [cited 2024 Jul 19];37(4):835–49. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8157315/
4. Marchiset A, Serazin V, Ben Hadj Salem O, Pichereau C, Lima Da Silva L, Au SM, et al. Risk Factors of AKI in Acute Respiratory Distress Syndrome: A Time-Dependent Competing Risk Analysis on Severe COVID-19 Patients. Can J Kidney Health Dis [Internet]. 2023 Jan 10 [cited 2024 Jul 25];10:20543581221145073. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9834615/
5. Darmon M, Clec'h C, Adrie C, Argaud L, Allaouchiche B, Azoulay E, et al. Acute respiratory distress syndrome and risk of AKI among critically ill patients. Clin J Am Soc Nephrol. 2014 Aug 7;9(8):1347–53.
6. Husain-Syed F, Slutsky A, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. American journal of respiratory and critical care medicine. 2016 Jun 23;194.
7. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased

immune response and lower survival. Kidney Int [Internet]. 2010 Mar [cited 2024 Jul 19];77(6):527–35. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2871010/

8. Shebl E, Zake LG, Mowafy SM, Abd El-Hameed AR. Risk of acute kidney injury in patients with acute respiratory distress syndrome and its effect on the outcome. The Egyptian Journal of Chest Diseases and Tuberculosis [Internet]. 2020 Dec [cited 2024 Jul 14];69(4):671. Available from: https://journals.lww.com/ecdt/fulltext/2020/69040/risk_of_acute_kidney_injury_in_patients_with_acute.12.aspx
9. Karimzadeh I, Barreto EF, Kellum JA, Awdishu L, Murray PT, Ostermann M, et al. Moving toward a contemporary classification of drug-induced kidney disease. Crit Care [Internet]. 2023 Nov 9 [cited 2024 Aug 31];27(1):435. Available from: https://doi.org/10.1186/s13054-023-04720-2
10. Muroya Y, He X, Fan L, Wang S, Xu R, Fan F, et al. Enhanced renal ischemia-reperfusion injury in aging and diabetes. Am J Physiol Renal Physiol. 2018 Dec 1;315(6):F1843–54.
11. Pereira M, Rodrigues N, Godinho I, Gameiro J, Neves M, Gouveia J, et al. Acute kidney injury in patients with severe sepsis or septic shock: a comparison between the ‘Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease’(RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. Clinical kidney journal. 2017;10(3):332–40.
12. Hertzberg D, Rydén L, Pickering JW, Sartipy U, Holzmann MJ. Acute kidney injury—an overview of diagnostic methods and clinical management. Clinical kidney journal. 2017;10(3):323–31.
13. Ephraim RKD, Darkwah KO, Sakyi SA, Ephraim M, Antoh EO, Adoba P. Assessment of the RIFLE criteria for the diagnosis of Acute Kidney Injury; a retrospective study in South-Western Ghana. BMC nephrology. 2016;17(1):1–6.
14. Patschan D, Müller GA. Acute kidney injury. Journal of Injury and Violence Research. 2015;7(1):19.
15. Gonsalez SR, Cortês AL, da Silva RC, Lowe J, Prieto MC, da Silva Lara L. Acute kidney injury overview: from basic findings to new prevention and therapy strategies. Pharmacology & therapeutics. 2019;200:1–12.
16. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. The clinical biochemist reviews. 2016;37(2):85.
17. Gameiro J, Fonseca JA, Outerelo C, Lopes JA. Acute kidney injury: from diagnosis to prevention and treatment strategies. Journal of clinical medicine. 2020;9(6):1704.
18. Kirkley MJ, Boohaker L, Griffin R, Soranno DE, Gien J, Askenazi D, et al. Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database. Pediatric Nephrology. 2019;34:169–76.
19. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Comprehensive Physiology. 2012;2(2):1303.
20. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nature reviews Disease primers. 2021;7(1):52.
21. Kulkarni AP, Bhosale SJ. Epidemiology and pathogenesis of acute kidney injury in the critically ill patients. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2020;24(Suppl 3):S84.
22. Dalal R, Bruss ZS, Sehdev JS. Physiology, renal blood flow and filtration. 2018;
23. Andonovic M, Curle J, Traynor JP, Shaw M, Sim MAB, Mark PB, et al. Impact of acute kidney injury on major adverse cardiovascular events in intensive care survivors. BJA open. 2023;8:100243.
24. Soares ROS, Losada DM, Jordani MC, Évora P, Castro-e-Silva O. Ischemia/reperfusion injury revisited: an overview of the latest pharmacological strategies. International journal of molecular sciences. 2019;20(20):5034.
25. Manzoor H, Bhatt H. Prerenal Kidney Failure. 2020;
26. van Eck van der Sluijs A, Abrahams AC, Rookmaaker MB, Verhaar MC, Bos WJW, Blankestijn PJ, et al. Bleeding risk of haemodialysis and peritoneal dialysis patients. Nephrology Dialysis Transplantation. 2021;36(1):170–5.
27. Kane-Gill SL, Smithburger PL, Kashani K, Kellum JA, Frazee E. Clinical Relevance and Predictive Value of Damage Biomarkers of Drug-Induced Kidney Injury. Drug Saf. 2017 Nov;40(11):1049–74.
28. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerda J, et al. Phenotype standardization for drug-induced kidney disease. Kidney Int. 2015 Aug;88(2):226–34.
29. Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Crit Care Med. 2010 Jan;38(1):261–75.
30. Awdishu L, Mehta RL. The 6R’s of drug induced nephrotoxicity. BMC Nephrol [Internet]. 2017 Apr 3 [cited 2024 Aug 31];18:124. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5379580/
31. Ostermann M, Bellomo R, Burdmann EA, Doi K, Endre ZH, Goldstein SL, et al. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2020 Aug;98(2):294–309.
32. Perazella MA, Rosner MH. Drug-Induced Acute Kidney Injury. Clin J Am Soc Nephrol [Internet]. 2022 Aug [cited 2024 Sep 15];17(8):1220–33. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9435983/
33. Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JAC. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ. 2013 Jul 9;185(10):E475-482.

34. Rennie TJW, De Souza N, Donnan PT, Marwick CA, Davey P, Dreischulte T, et al. Risk of acute kidney injury following community prescription of antibiotics: self-controlled case series. Nephrol Dial Transplant. 2019 Nov 1;34(11):1910–6.
35. Morales-Alvarez MC. Nephrotoxicity of Antimicrobials and Antibiotics. Adv Chronic Kidney Dis. 2020 Jan;27(1):31–7.
36. Hajji M, Jebali H, Mrad A, Blel Y, Brahmi N, Kheder R, et al. Nephrotoxicity of Ciprofloxacin: Five Cases and a Review of the Literature. Drug Saf Case Rep. 2018 Apr 18;5(1):17.
37. Khan M, Ortega LM, Bagwan N, Nayer A. Crystal-induced acute kidney injury due to ciprofloxacin. J Nephropathol [Internet]. 2015 Jan [cited 2024 Sep 15];4(1):29–31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4316583/
38. Campbell RE, Chen CH, Edelstein CL. Overview of Antibiotic-Induced Nephrotoxicity. Kidney Int Rep [Internet]. 2023 Aug 25 [cited 2024 Sep 15];8(11):2211–25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10658282/