DOI: 10.30651/jqm.v8i02.20376

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

LITERATURE REVIEW

Acute kidney injury induced by beta-lactam antibiotics in children: A scoping review

Astalitha Lorel Tania[1*], Alya Ayu Tazkia[2]

1) Aisyiyah Hospital Bojonegoro
2) RSUD 45 Kuningan

ARTICLE INFO

Submitted : *14th October 2023*
Accepted : *30th March 2024*
Published : *25th July 2024*

Keywords:

Acute Kidney Injury, Children, Beta-lactam, Antibiotics

Correspondence:

lastalitha@gmail.com

ABSTRACT

Antibiotics are the agents that cause Acute Kidney Injuries (AKI) in children. A recent study has shown the incidence of nephrotoxicity by antibiotics reaches 16% in children. Beta-lactam types are not widely known for their nephrotoxic effect. This study aims to examine beta-lactam antibiotics' role in inducing children's renal failure. This search for a scoping review on the effect of beta-lactam antibiotics in children was carried out in December-January 2022-2023. We used some search engines with the year of publication 2012-2022 then extracted. The keyword combinations used are: "beta-lactams" OR "β-lactams" AND "acute renal failure" OR "acute renal injury" OR "nephrotoxic" OR "nephrotoxicity" AND "children" OR "pediatric" OR "neonate" NOT "adult". Studies were excluded if the: (i) adult; (ii) were a review, systematic review, or meta-analysis; (iii) written in a language other than English; (iv) not available in full text; (v) have kidney disease before (vi) in vitro or in vivo. The article selection process was based on PRISMA-ScR. From 4032 articles that met the search criteria, 3 studies met the inclusion criteria. The result shows that beta-lactam increases the risk of acute renal injury in children. This review emphasizes the importance of choosing kidney-safe antibiotics for children.

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

INTRODUCTION

Children and neonates have complex and unique physiological processes. Kidneys play an important role in regulating blood pressure, fluid, electrolyte balance, and excretion of metabolite by-products (Sulemanji & Vakili, 2013). Nephrogenesis, where the formation of nephrons occurs, is a process that transforms metanephric mesenchyme to the epithelium and involves a complex series of steps, which starts within 6 to 10 weeks after fertilization and completes by 36 weeks (Seely, 2017). Nephrogenesis proceeds from the deep to the outer cortex, and it is directed by a second, entirely different developmental process, the ductal branching of ureteric buds (Horster, Braun, & Huber, 1999). The study has shown that neonatal kidneys can maintain the capability to generate new nephrons until four days after birth (Kirita *et al*., 2016). Preterm neonates, who have incomplete nephrogenesis, have lower renal mass at birth (Black *et al*., 2013).

Pediatric patients are susceptible to bacterial infections and may require treatment with antibiotics. Beta-lactam antibiotics are commonly used in the population due to their broad-spectrum activity and favorable safety profile. Beta-lactam antibiotics have been associated with nephrotoxicity in children, often characterized by acute interstitial nephritis (Hammond *et al.*, 2017). The mechanisms of beta-lactam nephrotoxicity in children include transport into the tubular cell through the anti-luminal organic anion secretory carrier, acylation of target proteins, and inhibition of renal enzymes (Tune, 1997; Tune & Hsu, 1990). Beta-lactam antibiotics including penicillin, cephalosporins, and carbapenems have several structure-related compounds (Tune & Hsu, 1990). Where cephalosporins and carbapenems have been linked to nephrotoxicity(Patzer, 2008) and the concurrent administration of antipseudomonal beta-lactams with vancomycin has been found to increase the risk of acute kidney injury (AKI) (Bellos, Karageorgiou, Pergialiotis, & Perrea, 2020). However, there are several studies (Clifford *et al*., 2022) and (Rutter, Cox, Martin, Burgess, & Burgess, 2017) have shown that there is no evidence that a combination of piperacillin and tazobactam (PTZ) has a risk of nephrotoxicity and the combination of vancomycin and PTZ increases the rate of AKI (Rutter *et al*., 2017). Therefore, the use of beta-lactam antibiotics has been associated with nephrotoxicity, potentially serious adverse effects on the kidneys. Nephrotoxicity can lead to acute kidney injury, chronic kidney disease, also end-stage renal disease, which may significantly impact the long-term health and quality of life of affected individuals.

Ensuring sufficient trough plasma concentrations for broad-spectrum beta-lactams is essential when prescribing these classes for empirical or selective treatment of bacterial infections in children (André *et al*., 2022). AKI is a type of kidney injury that occurs due to the sudden loss of kidney function. It can lead to a reduction in the glomerular filtration rate (Brummer & Brophy, 2023). Adopting the Kidney Disease Improving Global Outcomes (KDIGO) criteria has decreased AKI incidence and mortality rates among pediatric patients (Brummer & Brophy, 2023). AKI in children and neonates is caused by multifactorial problems, but it is commonly divided into three categories; pre-renal, renal, and post-renal. Exposure to certain medications may contribute to pre-renal AKI. Antibiotics contribute to developing renal AKI because they induce Acute Tubular Necrosis (ATN). A recent study said that 18 - 70% of the epidemiology of AKI in the Neonatal Intensive Care Unit (NICU) is 18-70% based

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

on the studied on dependent on the studied population(Hanna *et al*., 2016). Based on (Al-Jebawi, Karalic, Shekhawat, & Mhanna, 2022) very low birth weight is a higher risk factor for having AKI, especially for those who receive antibiotics meropenem and vancomycin single use.

The number of cases of AKI in children has increased globally. According to a meta-analysis conducted worldwide, the incidence of AKI was estimated to be around 33.7% (Cleto-Yamane, Gomes, Suassuna, & Nogueira, 2019). In one study, the overall AKI incidence was reported to be 10.8%, while in another, the incidence of 9.7% was observed in a single center in Malawi (Bhojani *et al*., 2020; Bjornstad *et al*., 2020). Given the potential consequences of nephrotoxicity from beta-lactam antibiotics in pediatric patients, it is important to understand the current state of knowledge on this topic. This scoping review explores the current understanding of nephrotoxicity from beta-lactam antibiotics in children and neonates. In addition, the review will examine the impact of nephrotoxicity on long-term renal function and quality of life in pediatric patients receiving beta-lactam antibiotics. The results of this scoping review will provide valuable information for healthcare providers, patients, and families and inform future research directions to enhance the safe use of beta-lactam antibiotics in pediatric patients.

LITERATURE REVIEW

Method and Result

A. Identification of relevant studies

The medical literature review was carried out on PubMed, Google Scholar, EuropePMC, Cochrane, SpringerLink, and Science Direct databases using the Boolean search (beta-lactams OR β-lactams) AND (acute renal failure OR acute renal injury OR nephrotoxic OR nephrotoxicity) AND (children OR pediatric

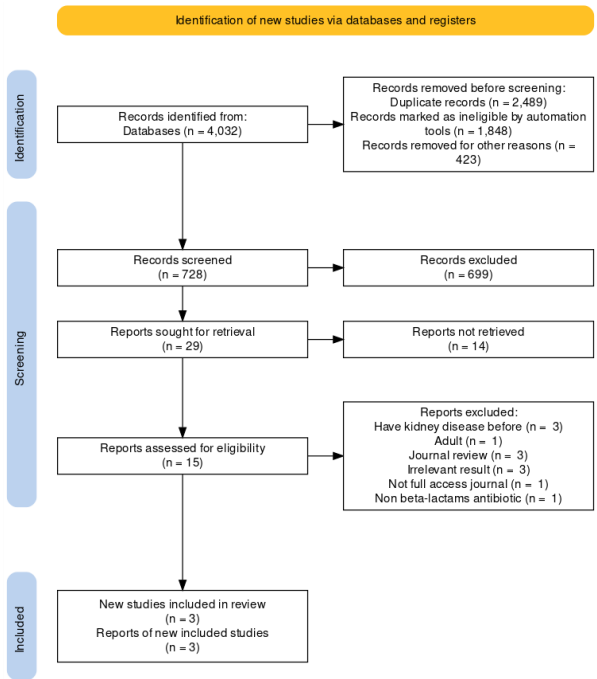

Figure 1. PRISMA Flowchart (Tricco et al., 2018)

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

OR neonate) NOT (adult). The limits applied to refer to the language (English) and years (2012 to 2022) of the articles of publication.

B. Study selection and eligibility criteria

For the analysis, all studies were selected independently by two researchers evaluating acute renal injury in pediatric patients caused by beta-lactam. All processes were performed according to the PRISMA statement (Preferred Reporting Items Systematic Reviews and Meta-Analyses), as shown in the flow chart (Fig.1)

The selection process for the articles in this scoping review uses a screening method with predefined inclusion and exclusion criteria. The inclusion criteria of this study are; a) journal articles in English; b) journal articles in the type of original articles or research articles; c) the research method used in the selected articles is RCT; d) journal articles between 2012-2022; e) in terms of intervention, the study involved intervention using the antibiotic beta-lactam only. Articles were excluded if studies (i) adult; (ii) were a review, systematic review, or meta-analysis; (iii) written in a language other than English; (iv) not available in full text; (v) have kidney disease before (vi) in vitro or in vivo.

C. Data Extraction

The data extraction process in the final reference of this study was carried out individually by two researchers. The results of data extraction will be carried out through comprehensive data mapping in Microsoft Office Excel software (Table 1). The mapping process is needed to facilitate the stages of reading all variables from the final reference in this study.

The initial search process is carried out using keywords that have been entered into scientific search engines such as PubMed, Google Scholar, EuropePMC, Cochrane, SpringerLink, and ScienceDirect. In the initial search process for article journals, a total of 4032 journal references were obtained. Then the identification process is continued by eliminating duplicate references obtained from different scientific search engines. This stage is followed by two screening phases, phase one and phase two. In the first phase of screening, namely, screening based on titles and abstracts on journal identities, 4017 journals were excluded due to topics that did not meet the established exclusion criteria. Then in the second phase of screening, 12 journals were excluded due to the non-fulfillment of the inclusion criteria that had been set. So that the final references for 3 journals will be extracted for the next step.

DISCUSSION

Several studies discussed the effect of acute kidney injury (AKI), which focuses on the antibiotic beta-lactam. Despite this, the discussion of beta-lactam causing AKI is still debatable. The most common uses of Beta-Lactam are ceftriaxone, piperacillin/tazobactam, cefepime and meropenem (Tang Girdwood *et al*., 2022). This can be characterized by several markers in the study. Antibiotics are the leading problem risk factor of AKI in children where the underdeveloped nephron causes AKI itself, especially in children who have a very low birth rate.

Based on (Shen *et al*., 2014) ages 5 months to 11 years who received ceftriaxone 1 gr for 5 days had oliguria and 10 days had anuria; all specimens were collected and analyzed by infrared spectrum, with results demonstrating that the main composition was ceftriaxone calcium. Supported by research conducted consecutively, ceftriaxone and calcium lead to disturbance reabsorption in the renal tubule, increasing calcium excretion in the urine (Shen *et al.*, 2014). Also, in the case-control study, cephalosporin 3rd ceftazidime, the same as ceftriaxone, was associated with a chance risk

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

of acute kidney injury in preterm(Cataldi *et al*., 2005). Another Cephalosporins group in 4th generation cefepime in the case reported >60 mg/dL after discontinuation and a concentration of 80 mg/L when experiencing neurotoxic symptoms (Hambrick *et al*., 2022). Therefore, the cephalosporin group has a high risk of nephrotoxicity in children.

In another conducted research by (Li *et al*., 2014) ceftriaxone can lead to crystallization in the urine where it adheres to tubular cells. It showed children had a history of consuming ceftriaxone for 5.2 days. These doses are 70 to 100 mg/kg/day, after 24 hours, the patient has onset anuria, flank pain, and vomiting. Other findings in ultrasonographic findings lead to hydronephrosis. Ceftriaxone-induced nephrolithiasis in congenital ureteropelvic junction obstruction has been reported (Dursun, Otunctemur, & Ozbek, 2013). (Stojanovic & Djuric Vijatov, 2009) demonstrated that with a given high dose ceftriaxone interacts with calcium to form crystals where it can be detected by ultrasonography. Other studies showed similarities with ceftriaxone associated with nephrolithiasis in 51 children (Avci *et al*., 2004) treated with 100/mg/kg/day and others given 50mg/kg/day intramuscular. Each underwent USG before and after ceftriaxone and also calculated with calcium oxalate, citrate, cystine, and uric acid where the result showed nephrolithiasis developed after 6.75 days with significant differences between the two groups.

However, penicillin is found to be rare for renal toxicity (Patzer, 2008). Retrospective review, comparing the beta-lactam group between meropenem, flucloxacillin, and piperacillin there was no difference in nephrotoxicity between groups. The Cmin between piperacillin and meropenem was high P<0.01 (Imani, Buscher, Marriott, Gentili, & Sandaradura, 2017) (8). Based on (Joyce, Kane-Gill, Priyanka, Fuhrman, & Kellum, 2019) parenteral and enteral were included in this research. It is shown in combination with piperacillin/tazobactam compared to other antibiotics vancomycin and cefepime and single cefepime, TZP has a higher risk of having AKI compared to other combinations of vancomycin and cefepime. Conversely, cefepime was not associated with AKI.

Retrospectively, research showed that beta-lactam antibiotics (Shabaan *et al*., 2017) were meropenem given to children in conventional and prolonged children in Egypt. Infants less than 28 days and has late-onset sepsis >72 hours. The risk of AKI in children after being given the meropenem treatment was more significant in conventional compared to infusion. (Jenkins *et al*.) reported a chat continuous group was given infusion with Klebsiella pneumoniae, which improved the eradication of infection and significantly lowered AKI compared to other adverse events. Based on (Cies, Ii, Shankar, & Chopra, 2014), antibiotics given to pediatric intensive care units between beta-lactam and vancomycin are not significantly different within an area under the curve (AUC) 15 mcg/mL; both antibiotics also receive vasoactive medications. Using GFR as estimated, it is shown that meropenem gives a low risk accumulation to children who have critically ill children. The meropenem and ertapenem are not hydrolysed by renal enzyme dehydropeptidase-1 (DHP-1), where it means it is safe to avoid nephrotoxicity (Linden, 2007).

However, some studies of beta-lactam monotherapy intend to have a risk of renal injury compared to a combination of beta-lactam and aminoglycoside. These studies showed that 170 pediatrics received antimicrobial therapy (19.3%) and developed AKI with combination therapy 135 (25.1%) compared with monotherapy 35 (10.2%). Despite this, there is some resistance among bacteria that need to be prescribed at least 1 type of antibiotic (Tamma *et al*., 2013).

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Table 1. Characteristics of the included study

Author	Population	Intervention	Result
Shen Xi, et al (2014)(Shen et al., 2014)	Fifteen cases including 12 males and 3 females were admitted to the study from July 2008 to July 2013. Their mean age of them was (4.76 ± 3.74) years. A complaint of anuria was presented in 12 (80.0 %) patients for 13 hours to 4 days and that of oliguria in three (20.0 %) patients for 20 h-10 days. All of them were diagnosed with postrenal AKI resulting from ceftriaxone-induced urolithiasis and underwent hospitalization.	Patients were admitted to emergency hospitalization and did the surgery. Nine patients performed double-J stenting with cystoscopy, and four patients ureteroscopy. Meanwhile, one patient did unilateral double-J insertion combined with contralateral percutaneous nephrostomy and another did open surgery	Different treatments were used in fifteen pediatric patients with ceftriaxone-induced urolithiasis. Most kids with sand-like stones got better on their own, but just one needed more treatment. The kidney function of all kids improved quickly after treatment. Tests showed the main stuff in the kidney stones was from ceftriaxone. After watching them for a few years, none of the kids had long-term kidney problems which seems like the treatments worked well.
Li N, Zhou X, et al (2014)(Li et al., 2014)	A retrospective study looked at 31 cases between 2003 and 2012 where children developed post-acute renal failure (PARF) after being treated with ceftriaxone. None of these kids had a history of kidney stones or kidney problem.	On average, the kidney issues occurred about 5.2 days after starting ceftriaxone	The main symptoms, besides not urinating, included flank pain (in kids older than 3, all 25 had it), excessive crying (in kids under 3, all 6 had it), and vomiting (in 19 out of 33). Ultrasound showed mild hydronephrosis in 25 out 31 case and

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

			stones in the tubes that connect the kidneys and bladder (ureteric calculi) in 11 out of 31 cases. Nine kids got better with medicine within 1 to 4 days, while 21 children resistant to medication underwent retrograde catheterization and after catheterization, normal urine flow was observed immediately, with symptoms subsiding. Only one child, for whom catheter insertion failed, required hemodialysis. The spectrometric analysis confirmed ceftriaxone as the primary component of the kidney stines in four children, all of whom experienced complete recovery
Shabaan AE., et al (2017)(Shabaan et al., 2017)	Prospective, randomized clinical trial was conducted in neonates with GN-LOS admitted to the neonatal intensive care unit (NICU), at Mansoura University	Patients were randomly assigned to receive either an intravenous infusion of meropenem over 4 hours (infusion group) or 30 minutes (conventional group) at a dosing	In comparing two groups, the infusion group exhibited a significantly higher rate of clinical improvement and microbiologic eradication within 7 days of starting meropenem treatment when

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Children's Hospital, between August 2013 and June 2015. A total of 102 infants (51 in each group) were recruited.	regimen of 20 mg/kg/dose every 8 hours and 40 mg/kg/dose every 8 hours in meningitis and Pseudomonas infection.	compared to the conventional group. Also, fewer people in the infusion group passed away, and they needed respiratory support for a shorter time compared to the regular group. Importantly, the risk of kidney issues after meropenem treatment was lower in the infusion group. This suggests that using an infusion for meropenem might be a better choice for patients, leading to improved outcomes and fewer side effects.

CONCLUSION

In conclusion, this scoping review provides a comprehensive overview of the existing knowledge regarding AKI induced by beta-lactam antibiotics in children. The findings underscore the need for a cautious approach in prescribing these antibiotics, especially in vulnerable children populations. Further research is warranted to refine our understanding of the risk factors, mechanisms, and optimal management strategies to mitigate the occurrence of beta-lactam-induced AKI in children. This knowledge will be instrumental in advancing pediatric nephrology practice and ensuring the well-being of pediatric patients receiving beta-lactam antibiotics.

REFERENCES

Al-Jebawi, Y., Karalic, K., Shekhawat, P., & Mhanna, M. J. (2022). The concomitant use of vancomycin and piperacillin-tazobactam is associated with acute kidney injury (AKI) in extremely low birth weight infants (ELBW). *Journal of Neonatal-Perinatal Medicine*, *15*(2), 303–309. https://doi.org/10.3233/NPM-210866

André, P., Diezi, L., Dao, K., Crisinel, P. A., Rothuizen, L. E., Chtioui, H., … Buclin, T. (2022). Ensuring Sufficient Trough Plasma Concentrations for Broad-Spectrum Beta-Lactam Antibiotics in Children with Malignancies: Beware of Augmented

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Renal Clearance! *Frontiers in Pediatrics*, *9*, 1599. https://doi.org/10.3389/FPED.2021.768438/BIBTEX

Avci, Z., Koktener, A., Uras, N., Catal, F., Karadag, A., Tekin, O., … Baskin, E. (2004). Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. *Archives of Disease in Childhood*, *89*(11), 1069–1072. https://doi.org/10.1136/adc.2003.044156

Bellos, I., Karageorgiou, V., Pergialiotis, V., & Perrea, D. N. (2020). Acute kidney injury following the concurrent administration of antipseudomonal β-lactams and vancomycin: a network meta-analysis. *Clinical Microbiology and Infection*, *26*(6), 696–705. https://doi.org/10.1016/J.CMI.2020.03.019/ATTACHMENT/FF1C1C5B-12FC-4B20-996C-0B2691FC374F/MMC1.DOCX

Bhojani, S., Stojanovic, J., Melhem, N., Maxwell, H., Houtman, P., Hall, A., … Milford, D. v. (2020). The Incidence of Paediatric Acute Kidney Injury Identified Using an AKI E-Alert Algorithm in Six English Hospitals. *Frontiers in Pediatrics*, *8*, 29. https://doi.org/10.3389/FPED.2020.00029/BIBTEX

Bjornstad, E. C., Muronya, W., Smith, Z. H., Gibson, K., Mottl, A. K., Charles, A., … Gower, E. W. (2020). Incidence and epidemiology of acute kidney injury in a pediatric Malawian trauma cohort: A prospective observational study. *BMC Nephrology*, *21*(1), 1–12. https://doi.org/10.1186/S12882-020-01755-3/TABLES/5

Black, M. J., Sutherland, M. R., Gubhaju, L., Kent, A. L., Dahlstrom, J. E., & Moore, L. (2013). When birth comes early: effects on nephrogenesis. *Nephrology (Carlton, Vic.)*, *18*(3), 180–182. https://doi.org/10.1111/NEP.12028

Brummer, H., & Brophy, P. D. (2023). Pediatric Acute Kidney Injury: Decreasing Incidence and Improving Mortality Disparities Worldwide. *Pediatrics*, *151*(2). https://doi.org/10.1542/PEDS.2022-059906

Cataldi, L., Leone, R., Moretti, U., De Mitri, B., Fanos, V., Ruggeri, L., … Cuzzolin, L. (2005). Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *90*(6), F514-519. https://doi.org/10.1136/adc.2004.060434

Cies, J. J., Ii, W. S. M., Shankar, V., & Chopra, A. (2014). Antimicrobial Renal Injury in a Pediatric Intensive Care Unit: β-Lactams vs. Vancomycin. *Pharmacy*, *2*(4), 276–286. https://doi.org/10.3390/pharmacy2040276

Cleto-Yamane, T. L., Gomes, C. L. R., Suassuna, J. H. R., & Nogueira, P. K. (2019). Acute Kidney Injury Epidemiology in pediatrics. *Jornal Brasileiro de Nefrologia*, *41*(2), 275. https://doi.org/10.1590/2175-8239-JBN-2018-0127

Clifford, K. M., Selby, A. R., Reveles, K. R., Teng, C., Hall, R. G., McCarrell, J., & Alvarez, C. A. (2022). The Risk and Clinical Implications of Antibiotic-Associated Acute Kidney Injury: A Review of the Clinical Data for Agents with Signals from the Food and Drug Administration's Adverse Event Reporting System (FAERS) Database. *Antibiotics*, *11*(10), 1367. https://doi.org/10.3390/antibiotics11101367

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Dursun, M., Otunctemur, A., & Ozbek, E. (2013). KIDNEY STONES AND CEFTRIAXONE. *Iranian Journal of Pediatrics*. Retrieved from http://files/126/Dursun *et al*. - KIDNEY STONES AND CEFTRIAXONE.pdf

Hambrick, H. R., Pavia, K., Tang Girdwood, S., Lazear, D., Taylor, J. M., & Benoit, S. (2022). Cefepime-Associated Neurotoxicity in a Pediatric Patient with Stage V Chronic Kidney Disease. *Journal of Pharmacy Practice*, 8971900221125000. https://doi.org/10.1177/08971900221125000

Hammond, D. A., Smith, M. N., Li, C., Hayes, S. M., Lusardi, K., & Bookstaver, P. B. (2017). Systematic Review and Metaanalysis of Acute Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam. *Clinical Infectious Diseases*, *64*(5), 666–674. https://doi.org/10.1093/CID/CIW811

Hanna, M. H., Askenazi, D. J., Selewski, D. T., Askenazi, D., Opin, C., & Author, P. (2016). Drug Induced Acute Kidney Injury in Neonates HHS Public Access Author manuscript. *Curr Opin Pediatr*, *28*(2), 180–187. https://doi.org/10.1097/MOP.0000000000000311

Horster, M. F., Braun, G. S., & Huber, S. M. (1999). Embryonic renal epithelia: Induction, nephrogenesis, and cell differentiation. *Physiological Reviews*, *79*(4), 1157–1191. https://doi.org/10.1152/PHYSREV.1999.79.4.1157/ASSET/IMAGES/LARGE/9J0490039015.JPEG

Imani, S., Buscher, H., Marriott, D., Gentili, S., & Sandaradura, I. (2017). Too much of a good thing: a retrospective study of β-lactam concentration–toxicity relationships. *Journal of Antimicrobial Chemotherapy*, *72*(10), 2891–2897. https://doi.org/10.1093/jac/dkx209

Joyce, E. L., Kane-Gill, S. L., Priyanka, P., Fuhrman, D. Y., & Kellum, J. A. (2019). Piperacillin/Tazobactam and Antibiotic-Associated Acute Kidney Injury in Critically Ill Children. *Journal of the American Society of Nephrology: JASN*, *30*(11), 2243–2251. https://doi.org/10.1681/ASN.2018121223

Kirita, Y., Kami, D., Ishida, R., Adachi, T., Tamagaki, K., Matoba, S., … Gojo, S. (2016). Preserved Nephrogenesis Following Partial Nephrectomy in Early Neonates. *Scientific Reports 2016 6:1*, *6*(1), 1–14. https://doi.org/10.1038/srep26792

Li, N., Zhou, X., Yuan, J., Chen, G., Jiang, H., & Zhang, W. (2014). Ceftriaxone and acute renal failure in children. *Pediatrics*, *133*(4). https://doi.org/10.1542/PEDS.2013-2103

Linden, P. (2007). Safety Profile of Meropenem. *Drug Safety*, *30*(8), 657–668. https://doi.org/10.2165/00002018-200730080-00002

Patzer, L. (2008). Nephrotoxicity as a cause of acute kidney injury in children. *Pediatric Nephrology*, *23*(12), 2159–2173. https://doi.org/10.1007/S00467-007-0721-X/TABLES/2

Rutter, W. C., Cox, J. N., Martin, C. A., Burgess, D. R., & Burgess, D. S. (2017). Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime. *Antimicrobial Agents and Chemotherapy*, *61*(2), e02089-16. https://doi.org/10.1128/AAC.02089-16

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Seely, J. C. (2017). A brief review of kidney development, maturation, developmental abnormalities, and drug toxicity: juvenile animal relevancy. *Journal of Toxicologic Pathology*, *30*(2), 125. https://doi.org/10.1293/TOX.2017-0006

Shabaan, A. E., Nour, I., Elsayed Eldegla, H., Nasef, N., Shouman, B., & Abdel-Hady, H. (2017). Conventional Versus Prolonged Infusion of Meropenem in Neonates With Gram-negative Late-onset Sepsis: A Randomized Controlled Trial. *The Pediatric Infectious Disease Journal*, *36*(4), 358–363. https://doi.org/10.1097/INF.0000000000001445

Shen, X., Liu, W., Fang, X., Jia, J., Lin, H., Xu, M., & Geng, H. (2014). Acute kidney injury caused by ceftriaxone-induced urolithiasis in children: a single-institutional experience in diagnosis, treatment and follow-up. *International Urology and Nephrology*, *46*(10), 1909–1914. https://doi.org/10.1007/S11255-014-0742-X

Stojanovic, V., & Djuric Vijatov, G. (2009). Nephrolithiasis Caused by Ceftriaxone in a 3-Year-Old Child with Ureteropelvic Junction Obstruction. *Case Reports in Medicine*, *2009*, 1–3. https://doi.org/10.1155/2009/365962

Sulemanji, M., & Vakili, K. (2013). Neonatal renal physiology. *Seminars in Pediatric Surgery*, *22*(4), 195–198. https://doi.org/10.1053/J.SEMPEDSURG.2013.10.008

Tamma, P. D., Turnbull, A. E., Harris, A. D., Milstone, A. M., Hsu, A. J., & Cosgrove, S. E. (2013). Less Is More: Combination Antibiotic Therapy for the Treatment of Gram-Negative Bacteremia in Pediatric Patients. *JAMA Pediatrics*, *167*(10), 903–910. https://doi.org/10.1001/jamapediatrics.2013.196

Tang Girdwood, S., Pavia, K., Paice, K., Hambrick, H. R., Kaplan, J., & Vinks, A. A. (2022). β-lactam precision dosing in critically ill children: Current state and knowledge gaps. *Frontiers in Pharmacology*, *13*. Retrieved from https://www.frontiersin.org/articles/10.3389/fphar.2022.1044683

Tune, B. M. (1997). Nephrotoxicity of beta-lactam antibiotics: *Mechanisms and strategies for prevention. Pediatric Nephrology*, 11(6), 768–772. https://doi.org/10.1007/S004670050386/METRICS

Tune, B. M., & Hsu, C. Y. (1990). Mechanisms of beta-lactam antibiotic nephrotoxicity. *Toxicology Letters*, *53*(1–2), 81–86. https://doi.org/10.1016/0378-4274(90)90098-7