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Original Article

Pediatric Amikacin Therapy: Unveiling Adverse Drug Reactions through a Pharmacovigilance Study at AIIMS, Bathinda

Gazal Gagneja[a], Navdeep Singh Dhoat[b], Abhinav Kanwal[a]*

[a]*ADR Monitoring Centre, Department of Pharmacology, All India Institute of Medical Sciences, Bathinda-151001, India,* [b]*Department of Pediatric Surgery, All India Institute of Medical Sciences, Bathinda-151001, India.*

Abstract

Amikacin is commonly prescribed to pediatric patients as a bactericidal antibiotic. However, limited scientific data is available to determine safe and toxic levels in this population. This study aims to raise awareness among healthcare professionals about the adverse drug reactions associated with Amikacin therapy in pediatric patients and improve patient care and safety. The study involved a pharmacovigilance awareness program for healthcare professionals at the Pharmacovigilance unit of All India Institute of Medical Sciences (AIIMS), Bathinda. Patients reported adverse drug reactions (ADRs) through various means, such as phone or WhatsApp. The ADR reports were evaluated for demographic and ADR attributes such as date of onset, management description, causality, and overall event outcome. The causality of each ADR was determined using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale and Naranjo algorithm, and the severity was determined using the Modified Hartwig and Siegel Scale. Out of 60 pediatric patients given Amikacin, 5 reported adverse drug reactions. Most patients reporting ADRs were female, with a median age of 9 years and a median duration of one day. The adverse drug reactions were primarily skin-related and non-serious. The study highlights the need for a national-level control of preventable adverse drug reactions and a pediatric pharmacovigilance system in healthcare facilities. The data collected from this study will be used by the National Coordination Centre, Pharmacovigilance Programme of India, to create a drug alert and improve patient care and safety at the national level.

Keywords: Adverse drug reaction; Amikacin; Pediatric patients; Antibiotics; Intramuscular; Awareness.

1. Introduction

One of the biggest plights in today's pediatric practices is the emerging threat of pediatric diseases. By definition, children are growing, maturing, developing, and learning new things. In addition, when a child is exposed to an illness, develops a disease, or receives treatment, numerous enzymatic, endocrine, and metabolic systems and processes have not yet been fully developed. Some studies are evincing that absorption, distribution, metabolism, and elimination (ADME) works

Corresponding Author: Dr. Abhinav Kanwal, Assistant Professor, Department of Pharmacology, All India Institute of Medical Sciences, Bathinda-151001, Punjab, India.
Email: abhinavkanwal@gmail.com.

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distinctly in pediatric populations at various ages [1].

The likelihood that an exposure during infancy or early childhood may not manifest the adverse effects for years after the exposure, when typically some other maturation event, such as puberty, was to occur, further complicates this issue [1].

A child's range of responses is restricted to physical manifestations, including crying, somnolence, vomiting, diarrhea, and physiological manifestations like abnormalities of the heart and lungs. It is understandable why parents or other caretakers for these demographic characteristics would only find a small number of seriously detrimental impacts. A younger verbal child's lexicon knowledge for expressing discomfort or suffering is constrained. Parents or caretakers may be bewildered or believe a child's changing behavior is normal when it could be a reaction to therapy because behavior is prone to change. These standard processes in the pediatric population make investigations of the adverse effects occurring after the treatment even more complicated when compared with the adult groups. This is specifically relevant to identify events occurring after post-marketing [2].

Therefore, drug formulations are always a strenuous task to obtain in pediatric issues. The attempts to make the pediatric formulations are usually expensive and burdensome, and even sponsors are not usually exuberant to develop these or market them. Eventually, over-dosing, under-dosing, and an increase in the frequency of medication errors may happen because of the paucity of age-appropriate pediatric therapies leading to AE [3].

As per previous literature, adverse drug reactions (ADR) in the pediatric age group have not just led to prolonged hospitalization but have shown serious, life-threatening, and fatal outcomes as well [2]. Most of the pediatric population is susceptible to Amikacin, a bactericidal antibiotic with a narrow therapeutic range belonging to the aminoglycoside group [1]. As per the WHO definition, the assessment of medication concentrations in blood is the focus of the clinical chemistry and clinical pharmacology branch, which is known as therapeutic drug monitoring. Its primary emphasis is on medications having a limited therapeutic window. However, the therapeutic drug monitoring of amikacin is not being carried out among newborns regularly [1]. Several dosing regimens have been used in children, but safety and efficacy have not been established in infants [4].

Amikacin is vital in treating gram-negative bacterial infections in pediatric patient’s resistant to gentamicin and tobramycin. It explicitly addresses lung exacerbations associated with cystic fibrosis, often caused by *Pseudomonas aeruginosa*. Factors like decreased protein binding and organ failure, can affect amikacin efficacy in critical cases. Due to significant pharmacokinetic variability, optimizing amikacin dosing is essential in pediatric CF [5, 6].

Close monitoring of blood levels is essential to minimize ototoxicity risks. Despite placental transfer, it generally does not harm the fetus. For breastfeeding, minimal amikacin in milk poses low risks. The drug, excreted through the renal glomerulus, shows favorable half-lives in pediatric cases [6].

Amikacin doses are 15 mg/kg once daily (OD) and 7.5 mg/kg twice (BD) in infants and 20- 40 mg/kg OD in children has been prescribed, and it is favorably administered once daily because it produces lower trough and higher peak concentrations, which curtails the potential of toxicity and raises peak concentration, which boosts therapeutic efficacy. The absorbance rate of the amikacin is rapid after the intramuscular injection, where its peak concentration after the injection of 7.5 mg/kg reaches 20 µg/ml. The mean half-lives of amikacin vary with different age groups. It is 6.0 hours for infants in the first weeks of life and 1.9 hours for children aged up to 6 years [7, 8].

However, its diffusion is not appropriate into the cerebrospinal fluid because of its polar nature, and therefore, the serum peak to amniotic fluid ratio is 0.03. Its excretion is through the renal glomerulus route, and elimination half-lives are 7-14 hours in infants with a postmenstrual age of less than 30 weeks and 4-7 hours at a postmenstrual age of 40 weeks. Studies on the pharmacokinetics of amikacin have extensively been done in infants and children, and prominent differences in the pharmacokinetic levels have been shown. There is a fluctuation in the half-life ($t_{1/2}$) and clearance (Cl) data in the infancy and maturation stage [7]. The single intramuscular 7.5 mg/kg dose of amikacin has different concentrations in biological fluids or body parts, as shown in **Table 1** [9].

Table 1: Concentration of amikacin in the biological fluid or body part (with a single intramuscular dose of 7.5 mg/kg).

Biological part	Amikacin concentration
Serum	14.9
Skeletal muscle	2.2
Fat tissue	1.9

Note: Table 1 is based on data from [9].

Therefore, there is an exiguity of scientific data that could assist in demarcating the safe and toxic levels of amikacin in the pediatric population, which makes it extensively hard to amend the dosage regimen for them. [1, 10]. Hence, the risk of having side effects with the use of amikacin is high and can be serious as well. Amikacin treatment commonly causes nephrotoxicity and ototoxicity [11, 12]. Aminoglycosides concentrate in the proximal convoluted tubule of the nephron, leading to apoptosis and necrosis in mitochondria and inhibiting transporters in the proximal tubule, causing damage to the glomerular filtration rate, reduction of blood flow to the renal, and damage to the proximal tubule [13, 14]. Amikacin therapy also causes ototoxicity by binding to bacterial ribosomal subunits, resulting in apoptosis, oxidative stress, programmed cell death, and hearing loss at sharp frequencies. Continuous damage can result in hearing impairment [15–17]. Amikacin therapy ranges with the span and dosing regimens. It can occur after a few days or weeks of the treatment or even six months after treatment completion. This corresponds to the total dose received and extended exposure to the remedial treatment [18]. In this research, we have done a study to investigate the adverse drug reactions occurring in the pediatric population that has been administered with one of the drugs of the Aminoglycosides group, i.e., amikacin. The study aims to create awareness among healthcare professionals regarding the side effects of the above-said drug. This has been done by evaluating the reactions prevailing in the younger age groups so that one should monitor them for the safety of the patient's health and to limit the treatment cost.

The primary aim of this study is to raise awareness among healthcare professionals about the adverse drug reactions associated with Amikacin therapy in pediatric patients. This study aims to gather and evaluate reports of ADRs from patients, track the incidence and prevalence of ADRs and their management, and conduct future investigations to improve patient care and safety. The data collected in this study will be further assessed by India's Pharmacovigilance Programme, which will create a drug alert for manufacturing companies to prevent such reactions.

2. Materials and Methods

2.1. Study design

An observational research case study was carried out at the Pharmacovigilance unit of the ADR Monitoring Centre, Department of Pharmacology, All India Institute of Medical Sciences, Bathinda. (AIIMS-Bathinda). AIIMS-Bathinda has worked as an ADR Monitoring Centre under India's Pharmacovigilance Programme since 2021. The National Coordination Centre- Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission has provided technical professionals trained in pharmacovigilance. The Pharmacovigilance ADR Monitoring Centre offers pharmacovigilance awareness workshops for the institute's healthcare personnel, including doctors, nurses, medical students, and pharmacists, to train them regarding the importance of reporting ADR, considering the under-reporting of adverse drug reactions (ADRs).

Suspected ADR reporting forms were made available for inpatient, outpatient, and intensive care units to make it simple for doctors and other healthcare professionals to submit the reports; even for the convenience of getting the form, it has been made available on the official website of the AIIMS Bathinda. Detailed guidance to the healthcare workers is being provided to help them fill out the form with the help of presentations and illustrations to encourage them to report the ADRs. They are all directed to submit the reports to the ADR monitoring Centre or can directly report to the pharmacovigilance center over the phone. ADRs were gathered from patients in the outpatient setting during visits and reported to the pharmacovigilance center via WhatsApp groups or telephone conversations.

2.2. Inclusion Criteria

The study specifically includes pediatric patients who have experienced adverse drug reactions (ADRs) within the past three months. The primary focus is on ADRs associated with Amikacin, the causative agent in multiple cases. Ethical committee approval has been obtained for this study.

2.3. Exclusion Criteria

The study excludes adult patients and is limited to pediatric patients. ADRs caused by drugs other than Amikacin are not considered in this study, as they have been observed in one patient only, in contrast to Amikacin-related ADRs, which have occurred in multiple patients within the past three months.

2.4. Evaluation of ADR data

The Pharmacovigilance Coordinator and Associate at the ADR Monitoring Centre

examines each unique identified ADR report [2]. The reports were compiled, documented, and examined for demographic proficiency, including initials, gender, age at the event or date of birth, and weight (in kg) [16]. Subsequently, a comprehensive assessment of the patient's medical history and conditions was conducted, encompassing vital components, including Chief Complaints, detailing the primary reasons for the patient seeking medical attention, and an extensive review of Past Medical History and Family History [20, 21].

Also, the ADR attributes like the date at which the AE started and its recovery date if the reaction has been stopped; additionally, the description of reaction management with details (if any), data on dechallenge which includes the action taken after the reaction like if the drug has been withdrawn or its dose has been increased, reduced or not changed and rechallenge, which is performed to check the reaction if it reappears after the reintroduction of suspected medication. Then, the length of hospital stay kind of ADRs, the system affected by the ADRs, the result of those ADRs, and the medications used to manage the AE were evaluated [22]. Then, the therapy details, including dosage, pharmaceutical dose form, route of administration (oral, intradermal, intravenous, intramuscular), frequency (OD/BD/TDS), dates therapy started and stopped, indications of the suspected medications, its name, batch number, manufacturer and expiry date if known were taken into consideration [23]. The overall event outcome and the reporter's information were also noted. The factors like recovering, recovered, not recovered, or recovered with sequelae and fatal were noted in the outcome. The causality of the case (i.e., the relationship between the suspected ADR and the drug) and results were collected from the Suspected ADR reports for evaluation [19]. The causality of each suspected ADR was determined using the WHO-UMC scale and Naranjo algorithm [24]. Naranjo scale is made up of a questionnaire with ten questions and the answers yes, no, and does not know, along with a score for each answer[the total scores range from 4 to 13; the reaction is considered Definite if the score >8, probable 5-8, possible 1-4, and doubtful 0), [19] as well as the WHO-Uppsala Monitoring Centre, Sweden (the suspected ADR is assessed as certain, probable, possible, unlikely, and unclassified/unclassifiable) [25,26]. The Modified Hartwig and Siegel Scale was used to determine the severity of the ADRs, which can be classified as mild (level 1,2), moderate (level 3,4,5), or severe (level 6,7) [2,26]. ADR suspicions were further divided into serious and non-serious categories. Serious ADR was defined as any ADR that was deadly, life-threatening, permanently or significantly debilitating. The necessity of early or extended hospitalization resulted in a congenital disability or required intervention to stop the long-term impairment or harm [22,27]. This evaluation is based on the ADR reports collected from October 1, 2022, to December 19, 2022.

The administration of Amikacin during the specified period encompassed diverse formulations from different pharmaceutical brands and dosages. The study specifically utilized Amikacin sulfate injections "Nkacin-250" and "Nkacin-500" from Abbott Healthcare Pvt Ltd at 0.5 ml and 0.1 ml, respectively.

Furthermore, Amikacin injections at a dosage of 250 mg from Aristo Laboratories Pvt Ltd were administered, with varying volumes of 0.1 ml or 0.5 ml.

This study has received formal approval from the Institutional Ethical Committee, denoting compliance with ethical standards and ensuring participant rights and safety. The approval code is AB/RESCELL/2023/00229, validating the study's ethical clearance.

3. Results and Discussion

In this study, the pediatric patients in the inpatient department were actively observed in October, November, and December 2022 for developing ADRs using amikacin antibiotics until they were discharged from the hospital. During this study period, a total number of 60 patients had received a dose of amikacin. Among these, five patients reportedly had ADRs. Of five patients, 3 (60%) were female and 2 (40%) were male. The gender-wise distribution of the area is shown in **Figure 1**.

Of these, three patients have shown only one ADR. Among them, one was female, and 2 were male patients. The other two patients showed 2 ADRs, and both were females. The age of the patients lies in the age group of 9 months to 12 years, the youngest being nine months and the eldest being 12 years. Age groups 0-3 years and 3-6 years have shown only one ADR. The age group 9-12 years has shown two ADRs, and the age group 12-15 has shown one ADR (**Fig. 2**).

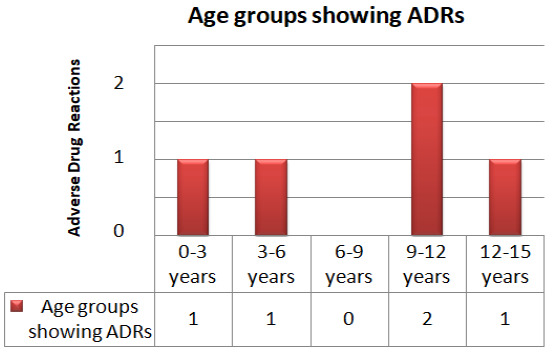

Figure 2. Number of ADRs shown by different age groups.

The median age of the patients was nine years. The age of the patients ranges from 9 months to 12 years. The demographic details are shown in **Table 2a**.

Table 2a: Demographic details of the patients showing ADRs after receiving amikacin.

Demographic details	ADR with Amikacin
Female (%)	60
Male(%)	40
Age group	9 months-12 years
Weight range	6.5 kg- 35.5 kg

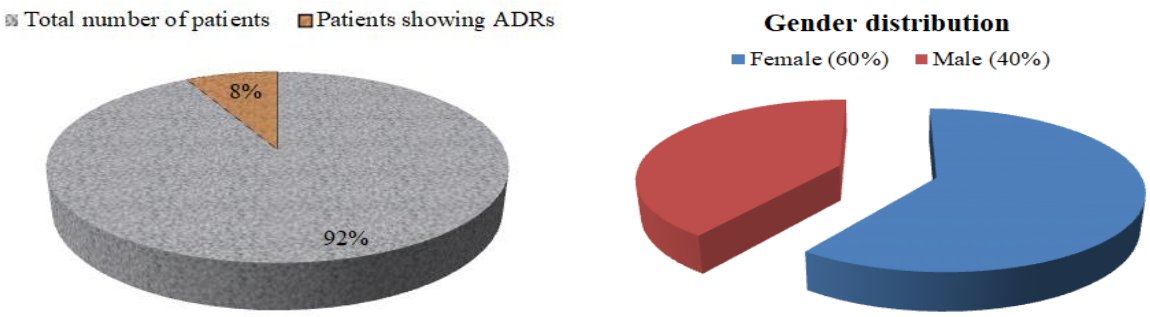

Figure 1. Pediatric population showing ADRs and the gender-wise distribution of ADRs received.

The ADRs seen with the antimicrobial susceptibility test (0.1 ml intradermally) of amikacin, including redness, rashes, and tenderness, were categorized as non-serious and had no severity. Redness was seen in 80% of the patients, rashes in 40%, and tenderness in 20% (**Fig. 3a**).

All the reactions were non-serious and had recovered without any medication. The median duration of ADR is one day. Along with their suspected medications, 40% of the patients took concomitant medications. Notably, one patient received a 6 mg IV OD Vitamin K injection along with 0.1 ml ID of Amikacin, and another received an Injection of Ceftriaxone, 0.1 ml ID OD, alongside 0.1 ml ID of Amikacin. These patients exhibited adverse drug reactions (ADRs), such as redness and tenderness, respectively (**Fig. 3b**).

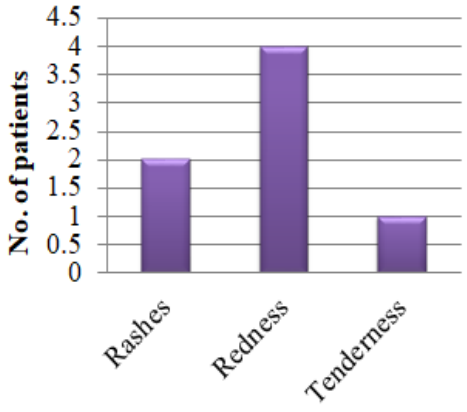

Figure 3a. ADR pattern in pediatric patients.

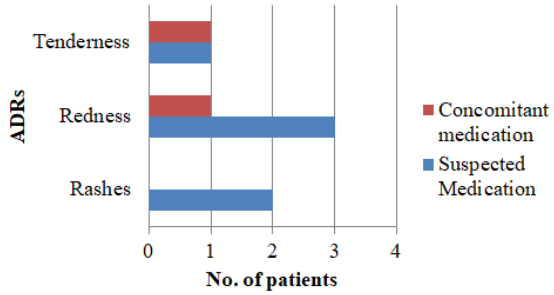

Figure 3b. ADRs in patients having therapy with suspected and concomitant medication.

The dose of amikacin was given to pediatric patients for the treatment of arteriovenous malformation, localized peritonitis, small bowel obstruction, chronic constipation, and cystitis. **Table 2b** shows the indication of amikacin and the ADRs seen in those patients.

Table 2b: Indication of amikacin and the ADRs seen in pediatric patients.

No.	Indication for Amikacin	ADRs seen
1	Arteriovenous malformation	Redness
2	Localized peritonitis	Redness and rashes
3	Small bowel obstruction	Redness and rashes
4	Chronic constipation	Tenderness
5	Cystitis	Redness

According to the WHO-UMC Causality Assessment scale, 80% of the ADRs were possible, and 20% were unlikely (**Fig. 4**).

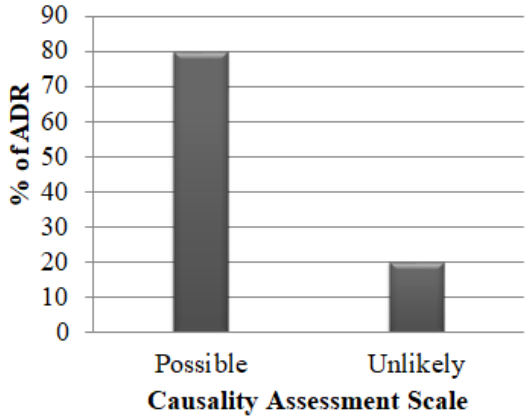

Figure 4. WHO-UMC Causality Assessment Scale.

The regular assessment of ADRs in pediatric patients is crucial. The current study is the first effort to analyze the adverse drug reactions (ADRs) caused by amikacin in pediatric patients in our healthcare environment [25]. This study was carried out in a tertiary care hospital in north India, and variations between

hospitals are likely due to variations in the local population's characteristics and the specialties offered by the hospitals, such as varying prescribing strategies, disease epidemiology, and ethnicities. In this hospital, the ADRs, which were reported from the pediatric surgery ward, were collected.

Our study reported five pediatric patients with ADRs after receiving the amikacin. The skin was the only system in the body affected by ADRs that manifested symptoms like redness, rashes, and tenderness. According to the study's demographic profile, more female than male patients reported ADRs. This might be because males and females react to medications pharmacokinetically and pharmacodynamically differently [22]. The suspected drug was given 0.1 ml intradermally, which was withdrawn for the management of ADR, and a rechallenge was performed in just one patient, and it turned out to be negative. Causality analysis is required to comprehend the elements that lead to the incidence of ADRs, and it was assessed. Most of the adverse drug reactions (ADRs) in the current investigation fell into the possible category according to the WHO UMC causality assessment scale, while one was classified as unlikely. The unlikely scale was because of the negative rechallenge [28]. Moreover, concomitant medications were also administered when a reaction appeared and while performing a rechallenge.

The nursing officers detected and reported all the ADRs [29]. ADR underreporting is a worldwide concern. Amidst the implementation of pharmacovigilance and the possible consequences of ADRs, the underreporting of ADRs is still a significant problem. Underreporting of ADRs is also a result of patients' parents' ignorance of pediatric children's adverse drug responses to prescription medications [30,31]. Establishing an obligatory, unified, periodic education intervention on adverse medication reactions is essential to provide better care for pediatric patients. To encourage and promote ongoing integrated training programs for all HCPs to improve ADR awareness and reporting, health officials should also stress the significance of proper cooperation between national, local, and international health authorities and manufacturers. Both strengths and shortcomings can be found in our investigation. The results of this study cannot be extrapolated to other healthcare facilities across the nation because it was conducted at a single center with just pediatric patients and for a specific drug. Due to the low reporting rate of the newly established ADR monitoring center and the short research duration, only a small number of discovered ADRs (n=5) were assessed.

HCPs may underreport for various reasons, including lack of interest, time restraints, and incentives [32,33]. Due to the hospital's voluntary reporting approach, which may result in certain ADRs being underreported, there is also a possibility that mild ADRs will go unreported [34]. Therefore, to further validate the results of the current study, a multicenter study and active surveillance of ADRs with a sizable sample size are needed. Due to the nature of the investigation, data and information may be scarce. However, the hospital pharmacovigilance center's registered ADR reports, available in hard copy, were the source of practically all the information.

There is a need for ongoing, periodic training on adverse drug reaction surveillance to monitor medication in children to prevent health risks. Furthermore, other populations with various treatment regimens, disease epidemiologies, and ethnicities may differ from our findings regarding the reported medication and clinical symptoms. Additionally, this is the first research on ADRs among pediatric patients in our institution. It could, therefore, serve as a foundation for further investigation and provide crucial proof for healthcare stakeholders and government decision-makers to take the necessary steps to minimize the burden of ADRs in pediatric patients [25].

4. Conclusion

This small-scale investigation revealed the current ADR pattern in pediatric patients using particular aminoglycosides. All of the adverse drug reactions (ADRs), according to data analysis, were skin-related, non-serious type, and recovered in nature. This study implies that controlling preventable ADRs in hospitals is essential nationally. Moreover, every healthcare facility needs to set up a pediatric pharmacovigilance system to closely track ADRs among pediatric patients to minimize them and reduce their morbidity rate. For better patient care and safety, tracking the incidence and prevalence rates of the ADRs and their management and performing upcoming investigations would be beneficial.

Acknowledgments

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Conflict of interest

The authors declare to have no conflict of interest.

References

[1] Siddiqi A, Khan DA, Khan FA, Razzaq A. Therapeutic drug monitoring of amikacin in preterm and term infants. Singapore Med J. 2009 May;50(5):486–9.

[2] Priyadharsini R, Surendiran A, Adithan C, Sreenivasan S, Sahoo FK. A study of adverse drug reactions in pediatric patients. J Pharmacol Pharmacother. 2011 Oct;2(4):277–80.

[3] D'Errico S, Zanon M, Radaelli D, Padovano M, Santurro A, Scopetti M, et al. Medication Errors in Pediatrics: Proposals to Improve the Quality and Safety of Care Through Clinical Risk Management. Front Med. 2021;8:814100.

[4] Galande AD, Khurana NA, Mutalik S. Pediatric dosage forms-challenges and recent developments: A critical review. J Appl Pharm Sci. 2020 July 1;10(7):155–66.

[5] Caceres Guido P, Perez M, Halac A, Ferrari M, Ibarra M, Licciardone N, et al. Population pharmacokinetics of amikacin in patients with pediatric cystic fibrosis. Pediatr Pulmonol. 2019;54(11):1801–10.

[6] Pacifici GM, Marchini G. Clinical Pharmacology of amikacin in infants and children. Clin Med Investig [Internet]. 2019 [cited 2024 January 6];5(1). Available from: https://www.oatext.com/clinical-pharmacology-of-amikacin-in-infants-and-children.php

[7] Illamola SM, Sherwin CM, van Hasselt JGC. Clinical Pharmacokinetics of Amikacin in Pediatric Patients: A Comprehensive Review of Population Pharmacokinetic Analyses. Clin Pharmacokinet. 2018 Oct;57(10):1217–28.

[8] Jenkins A, Thomson AH, Brown NM, Semple Y, Sluman C, MacGowan A, et al. Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affect either outcome or adverse events? A systematic review. J Antimicrob Chemother. 2016 Oct;71(10):2754–9.

[9] Pacifici and Marchini - 2019 - Clinical Pharmacology of amikacin in infants and c.pdf [Internet]. https://www.oatext.com/pdf/CMI-5-199.pdf

[10] Kato H, Hamada Y. Amikacin Therapy in Japanese Pediatric Patients: Narrative Review. Int J Environ Res Public Health. 2022 Feb 10;19(4):1972.

[11] Oliveira JS de, Rodrigues LB, Aurélio FS, Silva VB da. Risk factors and prevalence of newborn hearing loss in a private health care system of Porto Velho, Northern Brazil. Rev Paul Pediatr Orgao Of Soc Pediatr Sao Paulo. 2013 Sep;31(3):299–305.

[12] Dilley M, Geng B. Immediate and Delayed Hypersensitivity Reactions to Antibiotics: Aminoglycosides, Clindamycin, Linezolid, and Metronidazole. Clin Rev Allergy Immunol. 2022 Jun;62(3):463–75.

[13] Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. J Pharm Pract. 2014 Dec;27(6):573–7.

[14] Downes KJ, Hayes M, Fitzgerald JC, Pais GM, Liu J, Zane NR, et al. Mechanisms of antimicrobial-induced nephrotoxicity in children. J Antimicrob Chemother. 2020 Jan;75(1):1–13.

[15] Bock BV, Edelstein PH, Meyer RD. Prospective comparative study of efficacy and toxicity of netilmicin and amikacin. Antimicrob Agents Chemother. 1980 Feb;17(2):217–25.

[16] Kovačević T, Avram S, Milaković D, Špirić N, Kovačević P. Therapeutic monitoring of amikacin and gentamicin in critically and noncritically ill patients. J Basic Clin Pharm. 2016 Jun;7(3):65–9.

[17] Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007;13(1):119–26.

[18] Gambôa I, Sousa PD, Duarte D, Oliveira N. Amikacin Ototoxicity: Case Report and Literature Review. Otolaryngol Online J. 2018 https://www.semanticscholar.org/paper/Amikacin-Ototoxicity%3A-Case-Report-and-Literature-Gamb%C3%B4a-Sousa/d3cea16c7c714d03690bf3fd1265955c93e2134a

[19] Arulappen AL, Danial M, Sulaiman SAS. Evaluation of Reported Adverse Drug Reactions in Antibiotic Usage: A Retrospective Study From a Tertiary Care Hospital, Malaysia. Front Pharmacol. 2018;9:809.

[20] SK A, Y H. Drug utilization study on pediatric pneumonia patients in a tertiary care teaching hospital. Int J Health Care Biol Sci. 2021 October 28;70–4.

[21] Romano S, Fdez de Gatta MM, Calvo MV, Caballero D, Dominguez-Gil A, Lanao JM. Population pharmacokinetics of amikacin in patients with haematological malignancies. J Antimicrob Chemother. 1999 Aug;44(2):235–42.

[22] Chopra D, Rehan HS, Sharma V, Mishra R. Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. Indian J Med Paediatr Oncol Off J Indian Soc Med Paediatr Oncol. 2016;37(1):42–6.

[23] Bailey C, Peddie D, Wickham ME, Badke K, Small SS, Doyle-Waters MM, et al. Adverse drug event reporting systems: a systematic review. Br J Clin Pharmacol. 2016;82(1):17–29.

[24] Hs R, D C, Rk S, R M. Adverse drug reactions: trends in a tertiary care hospital. Curr Drug Saf [Internet]. 2012 November 1 [cited 2023 October 25];7(5). https://pubmed.ncbi.nlm.nih.gov/23150923/

[25] Z K, Y K, O K. Evaluation of Adverse Drug Reactions in Paediatric Patients: A Retrospective Study in Turkish Hospital. Front Pharmacol [Internet]. 2021 November 12 [cited 2023 October 25];12. Available from: https://pubmed.ncbi.nlm.nih.gov/34867419/

[26] Keche Y, Gaikwad N, Dhaneria S. Preventability, predictability, severity and causality assessment of adverse drug reactions reported from a teaching hospital in chhattisgarh: A retrospective analysis. J Fam Med Prim Care. 2021 Jul;10(7):2541–5.

[27] Geer MI, Koul PA, Tanki SA, Shah MY. Frequency, types, severity, preventability and costs of Adverse Drug Reactions at a tertiary care hospital. J Pharmacol Toxicol Methods. 2016 Sep 1;81:323–34.

[28] Lihite R, Lahkar M, Das S, Hazarika D, Kotni M, Maqbool M, et al. A study on adverse drug reactions in a tertiary care hospital of Northeast India. Alex J Med. 2016 Jun 1;53.

[29] Adverse drug reactions (ADRS) reporting: awareness and reasons of under-reporting among health care professionals, a challenge for pharmacists. https://springerplus.springeropen.com/articles/10.1186/s40064-016-3337-4

[30] Dittrich ATM, Smeets NJL, de Jong EFM, Kämink JL, Kroeze Y, Draaisma JMT, et al. Quality of Active versus Spontaneous Reporting of Adverse Drug Reactions in Pediatric Patients: Relevance for Pharmacovigilance and Knowledge in Pediatric Medical Care. Pharmaceuticals. 2022 Sep;15(9):1148.

[31] Joshi D, Gupta S, Singh TG, Parashar A, Singh SK. A Qualitative Evaluation of ADR Reporting in India: Non-Regulatory Confronts and Their Possible Solutions. ECS Trans. 2022 Apr 24;107(1):6763.

[32] Alsaleh FM, Alzaid SW, Abahussain EA, Bayoud T, Lemay J. Knowledge, attitude and practices of pharmacovigilance and adverse drug reaction reporting among pharmacists working in secondary and tertiary governmental hospitals in Kuwait. Saudi Pharm J. 2017 September 1;25(6):830–7.

[33] Lack of Awareness of Pharmacovigilance among Young Healthcare Professionals in India: An Issue Requiring Urgent Intervention - PMC https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6082015.

[34] Jose J, Rao PGM. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res. 2006 September 1;54(3):226–33.