REVIEW ARTICLE

Off-label Use of Antibiotics in Pediatrics

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Abstract

Usage of antibiotics off-label, in neonates and children, is an important public health issue. An overwhelming number of antibiotics are marketed and prescribed without clear labeling for use in pediatrics. It presents an even larger and more complex issue in neonates, children younger than 2 years, and those with chronic and/or rare diseases due to a lack of good clinical trials in these pediatric subgroups. The purpose of off-label use is to benefit an individual patient. The article details the prevalence of off-label antibiotic use in pediatrics and the reasons for the same. An attempt is made to highlight the different recommendations for antibiotic use in two pediatric drug formularies, the non-availability of child-friendly formulations and the lack of studies on newer antibiotics in neonates and children that necessarily results in antibiotics being prescribed off-label in children.

Keywords: Antibiotics, Drug formulary, Neonate, Off-label antibiotics, Off-label medications, Pediatric.

Pediatric Infectious Disease (2022): 10.5005/jp-journals-10081-1315

Introduction

The objective of the drug regulatory authority is to ensure that medicinal products which are manufactured in India or imported, are of acceptable quality, safety, and efficacy. The Drug Controller General of India (DCGI) heads the Central Drug Standard Control Organization (CDSCO), which approves and regulates the devices and drugs marketed in India. The drug is finally, on approval, labeled with inserts (i.e., drug monograph), specifying the details for the drug use (i.e., target population, dose, indication, specific use).[1] "Off-label" use refers to[2] the use of a drug that is either not included in the package insert for that drug, not recommended for a particular age, route of administration or duration, and/or not detailed in the BNF for children (BNFc)[3] and/or IAP Drug Formulary (IAPDF).[4] Very recent changes in recommendations or guidelines may also amount to "off-label" use. However, the absence of labeling for a specific age group or a specific disorder, due to lack of pediatric data, does not necessarily mean that the drug's use is improper for that age or disorder.[5] Guidelines as in BNFc or IAPDF do not regulate the use of drugs. Therapeutic decision-making is guided by the best available evidence and the importance of the benefit for the individual patient. Many of the antibiotics currently used in the pediatric age group lack documentation regarding dosage, efficacy, and safety due to practical difficulties in performing gold standard clinical trials in this age group. It is bizarre logic, however, to argue that studies in neonates and children are deferred to protect them, only to increase the risks of medicating without proper evidence.[6] Off-label use of antibiotics, and publication of data of such use, in neonates, children, and adolescents, is acceptable if it is in the best interest of the child.

The article will try to advise involving the use of unlicensed antibiotics or licensed antibiotics for unlicensed uses ("off-label" use). Such advice reflects careful consideration of the options available to manage a given condition and the weight of evidence and experience of unlicensed intervention in treating bacterial infectious disease in neonates and children. However, limitations of the marketing authorization should not preclude unlicensed use where clinically appropriate.

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How to cite this article: Unni JC. Off-label Use of Antibiotics in Pediatrics. Pediatr Inf Dis 2022;4(2):43–46.

Source of support: Nil

Conflict of interest: None

Off-label Use of Antibiotics in Pediatrics

Antibiotics are the most commonly prescribed drugs in children and off-label prescription is very common due to various reasons like prescribing for a younger age, prescribing off-label doses, and prescribing at an off-label frequency of drug administration.[7] Though few antibiotics have been labeled for use in pediatric patients, many others such as fluoroquinolones, azithromycin, linezolid, or daptomycin are still being prescribed in an off-label manner.[8,9] This raises concern in the light of emerging multidrug-resistant pathogens.

In NICUs,[10–13] around 50% of antibiotic use is off-label, unlicensed use was 11.6 and 78% of off-label use are due to prescriptions outside recommended dose—usually at a higher than recommended dose to ensure efficacy regardless of safety concerns. Another off-label use is for off-label indications and dosing intervals. In the newborn, the most common off-label drugs prescribed were ampicillin and gentamicin. The other antibiotics implicated were cefotaxime, vancomycin, and amikacin.

In children,[10,14,15] off-label antibiotic use ranged from 20 to 70% in various studies; off-label dosing was around 20–25% for ceftriaxone and vancomycin in the treatment of LRTI, meningitis, and sepsis, 21–24% for off-label indication while prescribing cefotaxime and ceftriaxone for surgical prophylaxis and meningitis.[10] Highest off-label use of antibiotics was in children aged <2 years[14,15] and when a child needed in-patient treatment for 6–10 days.[15] Overuse of IV antibiotics, antibiotics for URTI, and

misuse of third-generation cephalosporins in management of LRTI in children are rampant even today.[16]

Differences in Recommendations for Antibiotics Therapy in the Two Pediatric Drug Formularies—BNFc and IAPDF

The variation in the reporting of off-label use of antibiotics in neonates, children, and adolescents in various studies depends on which pediatric drug formulary is used as a reference.

Aminoglycosides

Amikacin is mentioned as an IV treatment for a pseudomonal lung infection in cystic fibrosis in BNFc but therein states that the drug is not licensed for this indication. The IAPDF does not mention this as an indication for use of amikacin as penetration of bronchial secretions of parenteral aminoglycoside is poor. Nebulization with preferably tobramycin, colistin, or gentamicin is preferred because it allows direct delivery of the drug to the sites of infection within the airways while avoiding systemic exposure.[17]

Streptomycin: BNF for children, though it advises streptomycin in combination with other anti-tubercular drugs for tuberculosis resistance to other treatment, and brucellosis as an adjunct to doxycycline, lists it as not licensed for use in children in the UK. This is because half of MDRTB in the UK are resistant to streptomycin.[18] In IAPDF streptomycin, in addition to these indications, is also recommended for treating tularemia, plague, and bacterial endocarditis esp. enterococcal endocarditis along with penicillin G for synergistic effect when other anti-infectives are ineffective or contraindicated.

Carbapenems

Imipenem with cilastatin use in neonates from birth has been noted in both BNFc and IAPDF but BNFc mentions that it is not licensed for use in children under 1 year and children with renal impairment. The WHO report on the use of carbapenems states that imipenem with cilastatin could be administered to neonates,[19] and in that statement mentions that BNFc does not license it for infants <3 months age.

Meropenem is not licensed for use in children under 3 months.[19] Though BNFc also recommends the same, it and the IAPDF detail neonatal dosage in its meropenem monograph.

Cephalosporins

Cefixime: Uncomplicated gonorrhea is an indication for use of cefixime in a single 400 mg dose for adolescents as per bnfc (not in iapdf) but it states it is an unlicensed use. CDC update on treatment of uncomplicated gonorrhea no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea due to recognition of increasing resistance to the drug.[20]

Ceftriaxone: BNF for children categorizes ceftriaxone as not licensed for the treatment of *H. influenzae* Type b disease, congenital gonococcal conjunctivitis, pelvic inflammatory disease, and uncomplicated gonorrhea in children <12 years of age; and for prophylaxis of meningococcal meningitis.

The *H. influenzae* resistance is due to the emergence of beta-lactamase-negative, ampicillin-resistant (BLNAR) strains and beta-lactamase-positive, amoxicillin/clavulanate-resistant (BLPACR) in certain countries.[21] It is, as yet, not applicable in India.

Macrolides

Azithromycin: BNF for children, though it suggests azithromycin may be given for prophylaxis of group a streptococcal infection in patients who are allergic to penicillin and treatment of chronic *pseudomonas aeruginosa* infection in cystic fibrosis, mild to moderate multidrug resistant (MDR) typhoid; it cautions that the drug is not licensed for these indications. The IAPDF recommends its use for group a beta-hemolytic streptococcal pharyngitis and tonsillitis (primary prophylaxis of rheumatic fever; but not for secondary prophylaxis), treatment and postexposure pertussis prophylaxis, uncomplicated and MDR typhoid fever, atypical pneumonia, diphtheria as a second choice to penicillins, non-gonococcal urethritis, or cervicitis due to susceptible strains of *chlamydia trachomatis*, bacterial endocarditis prophylaxis, chancroid, and Legionella infections. Specific dosage recommendations are recommended for uncomplicated and MDR typhoid fever, primary prophylaxis of rheumatic fever, treatment, and postexposure pertussis prophylaxis, atypical pneumonia, and diphtheria.

Clarithromycin: BNF for children details clarithromycin for the prevention of pertussis but states that oral suspension is not licensed for use in infants under 6 months and an intravenous infusion is not licensed for use in children under 12 years. In IAPDF, clarithromycin finds a place in pediatric therapeutics for the treatment of atypical pneumonias and as part of the regimens for eradication of *H. pylori.* It does not recommend clarithromycin for neonates.

Sulfonamides

Cotrimoxazole–IAPDF recommends it as the drug of choice for blood and mucus diarrhea though there are increasing reports of cotrimoxazole-resistant shigellosis. It is also one of the drugs recommended in long-term prophylaxis for recurrent urinary tract infections in children. IMNCI recommends giving cotrimoxazole to children with confirmed or suspected HIV infection or children who are HIV exposed starting at 4–6 weeks of age;[22] and for community-acquired pneumonia and otitis media. BNF for children states that cotrimoxazole should be considered for use in acute exacerbations of chronic bronchitis, UTI, and otitis media in children only when the organism is sensitive and there is good reason to prefer it.

Quinolones

Ciprofloxacin is the only quinolone included in BNFc while IAPDF also includes an *ofloxacin* monograph. Levofloxacin has not yet been detailed in IAPDF. In addition to indications in BNFc, ciprofloxacin and ofloxacin are recommended for typhoid fever; and ofloxacin as an alternate therapy for invasive shigellosis and for anthrax, plague, tularemia, and Q fever in children who do not tolerate doxycycline.

Tetracyclines

Doxycycline: In addition to the indications prescribed in the BNFC, IAPDF adds cholera, amebiasis, actinomycosis, brucellosis, plague, multidrug-resistant *P. falciparum* (resistant to both chloroquine and sulfadoxine-pyrimethamine)–with quinine; and as an alternative therapy for yaws, listeriosis, Vincent's infection and *Clostridium* species infections. It is given empirically for children presenting in septic shock and acute encephalitis syndrome, considering scrub typhus as a possible etiology.[23] The use under 12 years of age is not recommended and doses for children 8 and above are detailed in

both BFNC and IAPDF but doxycycline is administered to young children with cholera, malaria, scrub typhus, and other rickettsial infections and CDC has considered the rehabilitation of doxycycline for use in children under 8 years of age.[24]

Oxazolidinone

Linazolid: The BNFC rightly does not license linezolid for use in children and cautions to reserve the drug for pneumonia (when other antibacterials, e.g., A glycopeptide, such as vancomycin, cannot be used) and complicated skin and soft-tissue infections caused by gram-positive bacteria, when other antibacterials cannot be used. The IAPDF does not enforce strong reservations for its use in treating resistant organisms but mentions vancomycin-resistant enterococcal infections as an indication. The drug is one of the only available options for treating MDR gram positives, MDR, and extensively drug-resistant tuberculosis and disseminated non-tuberculous mycobacterial infections in children.[25]

Antibiotics with No Child-friendly Formulations

Clindamycin, doxycycline—These two antibiotics are available as capsules in India. Capsules need to be opened and emptied to make a suspension in a medium acceptable to the neonate or child. However, this should only be advised when justified. The capsule contents may taste unpleasant and the bioavailability of the opened capsule may differ from that of the intact product.[26] It is definitely not advisable to open a capsule and administer the powder if the reason for having a capsule formulation is to avoid its degradation or neutralization by gastric juices.

Doxycycline, linezolid, cloxacillin, and levofloxacin, e.g., are available as tablets. Parents or caregivers are often required to manipulate an adult medicine to obtain an appropriate dose for a child, e.g., by splitting the tablet to provide a smaller dose or in more complex cases preparing a suspension from a crushed tablet. Such manipulations increase the variability in the product by inaccurate measurement, issues with stability, or errors in instruction for manipulation. Crushing certain tablets to mix them with food or water may change the rate or extent of drug absorption and its efficacy. Whatever method is used to cut or crush a tablet, it is near to impossible to provide an accurate dose where small doses are required as in the neonate, infant, or small-sized toddler. Dispersible tablets that dissolve in a small amount of liquid in a spoon, if acceptable taste-wise to the child, are easier to administer; but they too need to be titrated to provide the correct dose.

All these medications without proper child formulations are therefore included in the off-label use of antibiotics in children and are not supported by guidelines or evidence.[27]

Lack of Age-specific Parenteral Formulations

The main route of administration in sick neonates and children is the intravenous route. Ideally, most IV medications for neonates and children must be made available in a unit dose dispensation to afford accurate administration of the calculated dose, especially for concentration-dependent antibiotics like aminoglycosides; and to avoid wastage. Time-dependent drugs, like cephalosporins or imipenem, need to be given as infusions over 8–12 hours, 2–3 times a day. The drug drip has to be prepared each time immediately before administration to ensure efficacy and minimize the risk of contamination.

Calculating decimal fractions involving hundredths of a milliliter can be confusing and difficult, and therefore errors of dosing and, due to the hazards of mixing, infections are a distinct possibility. For injections, the volume presented in a container should not be >10 times the dose for the smallest child. All other formulations may be considered off-label. Studies have shown that measurement of volumes <0.1 mL, for IV dosing, accounts for 25% of medicine manipulations within pediatric hospitals.[28]

Child-friendly IV formulations should be such that the need for measuring small volumes is mitigated; enabling easy dosing to cover body weights from 0.5 to 5 kg (a 10-fold range).

Hospitals caring for neonates and children must be equipped with user-friendly devices, for accurately and reproducibly delivering small volumes IV and standard "vein viewer" gadgets.

Emerging MDR Bacterial Infections, Newer Antibiotics, and Off-label Use in Children

World over, only a few clinical trials are being conducted on newer antibiotics in the pediatric age group with 76 clinical trials investigating one or more antibiotics recruiting children between 0 years and 18 years of age in comparison to 4,078 trials in adults. Of these 76 trials, only 23 have recruited neonates and among them, only 8 clinical trials globally recruited preterm neonates. Respiratory and systemic infections, the most common clinical indications for antibiotics in pediatrics, are not currently being evaluated.[29,30]

Of the available antibiotics for MDR bacterial infections, tigecycline has got restricted approval for use in children;[31,32] daptomycin is not licensed for use in children;[33] piperacillin with tazobactam is not licensed for use in children under 12 years by BNFc (except for children 2–12 years with neutropenia and complicated intra-abdominal infections and its use for acute exacerbation of bronchiectasis is also not licensed) and further studies are suggested to determine its dose in critically ill children;[34,35] and cefepime, though licensed by FDA for use in children above 2 years of age, its efficacy and safety in pediatric patients remain unclear.[36] Cefepime and the 5th generation cephalosporins do not find a mention in BNFc. Most of these antibiotics are prescribed off-label for infections which could be treated with other first-line, narrower spectrum antibiotics.

Need of the Hour

All those caring for neonates and children have been crying hoarse regarding the urgent need for a plethora of studies on pharmacokinetics, pharmacodynamics, dosing and dosing intervals, child-friendly oral and parenteral formulations, medication delivery systems, and devices to make evidence-based decisions on antibiotic choice. This would enable appropriate "labeling" of antibiotics and reduce this notion that pediatricians use medicines off-label. The system of double-checking by making it mandatory that all antibiotic prescriptions be checked and endorsed by two physicians or a physician and a clinical pharmacist could make for better prescribing behavior.[37]

Conclusion

Rational use of off-label medications may be permitted as, in most instances, it is for the benefit of the child. Therapeutic

decision-making should always be guided by the best available evidence as much of the antibiotic decisions are today left to the physician's discretion.

References

1. Corny J, Lebel D, Bailey B, et al. Unlicensed and off-label drug use in children before and after pediatric governmental initiatives. J PediatrPharmacol Ther 2015;20(4):316–328. DOI: 10.5863/1551-6776-20.4.316.
2. Unni JC, Joseph RB. Off-label medications in pediatrics. Indian J Pediatr 2019;86(12):1149. DOI: 10.1007/s12098-019-03029-9.
3. Joint Formulary Committee. British National Formulary for Children. London: BMJ Group and Pharmaceutical Press; 2019–2020.
4. IAP Drug Formulary 2019. IAP drug formulary with IAP recommendations for drug therapy of pediatric illnesses Unni JC, Nair MKC, Menon PSN, ed. 5th ed., Cochin: Publication of Indian Academy of Pediatrics. Pixel Studio; 2019.
5. Frattarelli DA, Galinkin JL, Green TP, et al. American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. Pediatrics 2014;133(3):563–567. DOI: 10.1542/peds.2013-4060.
6. Yen E, Davis JM, Milne CP. Impact of regulatory incentive programs on the future of pediatric drug development. Ther Innov Regul Sci 2019;53(5):609–614. DOI: 10.1177/2168479019837522.
7. McLay JS, Tanaka M, Ekins-Daukes S, et al. A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians. Arch Dis Child 2006;91(7): 584–587. DOI: 10.1136/adc.2005.081828.
8. Porta A, Esposito S, Menson E, et al. Off-label antibiotic use in children in three European countries. Eur J Clin Pharmacol 2010;66(9):919–927. DOI: 10.1007/s00228-010-0842-1.
9. Zingg W, Posfay-Barbe KM. Antibiotic use in children- Off-label use. Curr Drug Targets 2012;13(7):885–892. DOI: 10.2174/138945012800675777.
10. Mukattash TL, Hayajneh WA, Ibrahim SM, et al. Prevalence and nature of off-label antibiotic prescribing for children in a tertiary setting: a descriptive study from Jordan. Pharm Pract (Granada) 2016;14(3):725. DOI: 11.18549/PharmPract.2016.03.725.
11. Laforgia N, Nuccio MM, Schettini F, et al. Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. Pediatr Int 2014;56(1):57–59. DOI: 10.1111/ped.12190.
12. Kouti L, Aletayeb M, Aletayeb SMH, et al. Pattern and extent of off-label and unlicensed drug use in neonatal intensive care units in Iran. BMC Pediatr 2019;19(1):3. DOI: 10.1186/s12887-018-1370-x.
13. Casañ VA, Escribano BC, Garrido-Corro B. Off-label and unlicensed drug use in a Spanish neonatal intensive care unit. Artículo de opinión 2017;41:371–381.
14. Puja, Dhasmana DC, Kohli S, et al. Off-label use of antibiotics in hospitalised children in a tertiary care teaching hospital. Int J Basic Clin Pharmacol 2018;7(10):1970–1973. DOI: 10.18203/2319-2003.ijbcp20183932.
15. Saiyed MM, Lalwan T, Rana D. Off-label medicine use in pediatric inpatients: a prospective observational study at a tertiary care hospital in India. Int J Pediatr 2014;2014:415815. DOI: 10.1155/2014/415815.
16. Miao R, Wan C, Wang Z, et al. Inappropriate antibiotic prescriptions among pediatric inpatients in different type hospitals. Medicine (Baltimore) 2020;99(2):e18714. DOI: 10.1097/MD.0000000000018714.
17. Ratjen F, Brockhaus F, Angyalosi G. Aminoglycoside therapy against Pseudomonas aeruginosa in cystic fibrosis: a review. J Cystic Fibro 2009;8(6):361–369. DOI: 10.1016/j.jcf.2009.08.004.
18. Streptomycin. TB drug monographs. http://www.tbdrugmonographs.co.uk/streptomycin.html. Accessed on 17/4/20.
19. Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. Use of carbapenems in children. http://origin.who.int/selection_medicines/committees/subcommittee/2/Carbapenems.pdf. Accessed on 17/4/20.
20. CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. MMWR Morbid Mortal Wkly Rep 2012;61:590–594.
21. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in haemophilus influenza. Clin Microbiol Rev 2007;20(2):368–389. DOI: 10.1128/CMR.00040-06.
22. Integrated Management of Childhood Illness for High HIV Geneva: World Health Organizationhttps://www.ncbi.nlm.nih.gov/books/NBK144140/.
23. Rathi N, Kulkarni A, Yewale V. IAP guidelines on rickettsial diseases in children; For Indian academy of pediatrics guidelines on rickettsial diseases in children committee. Ind Pediatr 2017;54(3):223–229. DOI: 10.1007/s13312-017-1035-0.
24. Gaillard T, Briolant S, Madamet M, et al. The end of a dogma: the safety of doxycycline use in young children for malaria treatment. Malar J 2017;16(1):148. DOI: 10.1186/s12936-017-1797-9.
25. Garazzino S, Tovo P. Clinical experience with linezolid in infants and children. J Antimicro Chemother 2011;66(Supplement 4):iv23–iv41. DOI: 10.1093/jac/dkr074.
26. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. Br J Clin Pharmacol 2015;79(3):405–418. DOI: 10.1111/bcp.12268.
27. Richey RH, Shah UU, Peak M, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatr 2013;13(1):81. DOI: 10.1186/1471-2431-13-81.
28. Ainscough LP, Ford JL, Morecroft CW, et al. Accuracy of intravenous and enteral preparations involving small volumes for paediatric use: a review. Eur J Hosp Pharm 2018;25(2):66–71. DOI: 10.1136/ejhpharm-2016-001117.
29. Thompson G, Barker CI, Folgori L, et al. Global shortage of neonatal and paediatric antibiotic trials: rapid review. BMJ Open 2017;7(10):e016293. DOI: 10.1136/bmjopen-2017-016293.
30. Unni JC. Newer antibiotics: need for more studies in neonates and children. Pediatr Inf Dis 2019;1(4):164–168. DOI: 10.5005/jp-journals-10081-1212.
31. Mastrolia MV, Galli L, De Martino M, et al. Use of tigecycline in pediatric clinical practice. Expert Rev Anti Infect Ther 2017;15(6):605–612. DOI: 10.1080/14787210.2017.1318064.
32. Iosifidis E, Violaki A, Michalopoulou E, et al. Use of tigecycline in pediatric patients with infections predominantly due to extensively drug-resistant gram-negative bacteria. J Pediatric Infect Dis Soc 2017;6(2):123–128. DOI: 10.1093/jpids/piw009.
33. Silvia G, Elio C, Maria DG, et al. Daptomycin for children in clinical practice experience. Pediat Infect Dis J 2016;35(6):639–641. DOI: 10.1097/INF.0000000000001121.
34. De Cock PAJG, van Dijkman SC, Jaeger AE, et al. Dose optimization of piperacillin/tazobactam in critically ill children. J Antimicrob Chemother 2017;72(7):2002–2011. DOI: 10.1093/jac/dkx093.
35. Knoderer CA, Karmire LC, Andricopulos KL, et al. Extended infusion of piperacillin/tazobactam in children. J Pediatr Pharmacol Ther 2017;22(3):212–217. DOI: 10.5863/1551-6776-22.3.212.
36. Jan S, Ragunanthan B, DiBrito SR, et al. Cefepime efficacy and safety in children: a systematic review and meta-analysis. Front Pediatr 2018;6:46. DOI: 10.3389/fped.2018.00046.
37. Dassner AM, Girotto JE. Evaluation of a second-sign process for antimicrobial prior authorization. J Pediat Infect Dis Soc 2018;7(2): 113–118. DOI: 10.1093/jpids/pix015.