Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.58, No.1(2018). p. 51-5 ; doi: http://dx.doi.org/10.14238/pi58.1.2018.51-5

Original Article

Prescribing antibiotics to pediatric dengue: increasing risk of bacterial resistance

Dhanunjaya Sandopa[1], Sree Keerthi Nethi[1], Sai Charitha Sreeram[1], Narasimha Kumar Godlaveti Vijay[2], Vyshnavi Biradavolu[1], Jagadeesh Vijay Kakimani[1]

Abstract

Background Use of antibiotics to treat self-limiting viral infections like dengue fever (DF) without any co-morbid conditions in pediatric patients is common practice in India, and a major contribution of the inappropriate use of antibiotics in the country.

Objective To provide an analysis of diagnosis, grading, and prescribing of antibiotics in pediatric inpatients with DF in a tertiary care teaching hospital in India.

Methods Data from case sheets of all pediatric inpatients (n=370) diagnosed with DF without co-morbid conditions were collected with regards to diagnosis, grading, presence, and appropriateness of antibiotic usage according to the *2009 WHO Guidelines*, the *National Vector Borne Disease Control Program (NVBDCP) of India Guidelines*, and the *Hospital Infection Society (HIS) Guidelines*.

Results Platelet count determination (50% of the cases) was the major diagnostic method for dengue. Inappropriate grading of DF was seen in 20% of patients. Almost 75% of the 370 dengue cases were prescribed antibiotics for the expressed purpose of avoiding hospital-acquired infections. A single antibiotic was given in 225 prescriptions (60.81%), 2 antibiotics in 33 (8.91 %) cases, and 3 antibiotics in 9 (2.43%) cases.

Conclusions Prescribing one or more antibiotics to treat self-limiting viral infections is considered as inappropriate and may lead to the development of multidrug resistance. Furthermore, excess use of antibiotics in infancy may induce imbalances in gut and microbiota, called dysbiosis, and increases the probability of occurrence of diseases such as obesity, diabetes, and asthma in later life. These findings can inform the development of antibiotic stewardship in the treatment of dengue. **[Paediatr Indones. 2018;58:53-7 ; doi: http://dx.doi.org/10.14238/pi58.1.2018.53-7]**.

Keywords: *antibiotics; bacterial resistance; dengue; inappropriate use*

In the field of medicine, the battle between bacteria and mankind can be explained in three phases: the pre-antibiotic era, the antibiotic era, and the post-antibiotic era. The period before the introduction of sulfa drugs and penicillin is considered to be the 'pre-antibiotic era.' Bacteria dominated mankind and bacterial infections were the leading cause of death.[1] Discovery of penicillin by Sir Alexander Fleming in 1928 laid the foundation and hope of controlling bacterial infections. Since that time, the 'antibiotic era' has seen the discovery of many antibiotics, which has transformed modern medicine and saved millions of lives.[2] These discoveries gave hope that mankind would rein over bacterial infections forever. However, the foremost driving force for discovering newer antibiotics was the development of resistance to the existing antibiotics. Eventually, the antibiotic pipeline began to dry up, because the pharmaceutical industry considers investment in antibiotic study to be unprofitable,

From the Department of Clinical Pharmacology, Sri Padmavathi School of Pharmacy, Tirupathi, Andhrapradesh[1], and the Department of Pharmacology, Siddha Central Research Institute, Chennai, Tamilnadu[2], India.

Reprint requests to: Mr. Dhanunjaya Sandopa, Assistant Professor, Department of Clinical Pharmacology, Sri Padmavathi School of Pharmacy, Tirupathi, Andhrapradesh, India 517503. Telp. +91-9177392747; Fax. 0877 – 2237732; Email: dhanuspsp@gmail.com.

fearing a possible lack of returns. This approach of the pharmaceutical industry is due to the short period of antibiotic usage compared to other drugs used to treat metabolic, cardiovascular, and central nervous system disorders. Hence, bacterial resistance to antibiotics is inevitable, as newer antibiotics may be outdated in a short span of time.[2]

In response to antibiotics, bacteria change in ways that reduce or eliminate drug effectiveness. These changes are due to the evolution of antibiotic resistance genes by spontaneous mutations and furthered by natural selection of resistant strains over sensitive ones.[3] Once a strain develops resistance, the once-effective antibiotic will no longer inhibit the bacteria. If this continues, mankind will eventually face a cataclysmic condition. In view of this, the US *Centers for Disease Control and Prevention* (CDC) declared in 2013 that the human race is now in the 'post-antibiotic era.' Moreover, the *World Health Organization* (WHO) warned of a dreadful antibiotic resistance crisis.[2] This situation is comparable to the pre-antibiotic era, in that irrational use of antibiotics has led to the emergence of resistant strains and infections which are not yet recognized and the re-emergence of virulent forms of previous infections.[1] Resistance development is an evolutionary process, with unpredictable times. Resistance requires constant exposure of bacteria to the antibiotic. Hence, the rational or irrational use of antibiotics drives the evolution of bacterial resistance. As such, the greater the exposure of bacteria to antibiotics, the faster the evolution of resistance.[3]

Dengue and chikungunya are the third and fourth most common monsoon diseases in India. They are mosquito-borne (*Aedes aegypti*) viral diseases associated with urban environments. Dengue manifests as sudden onset of fever and severe headache; it occasionally produces shock and hemorrhage leading to death. Chikungunya is characterized by pain usually lasting 3-7 days and, in some cases, results in persistent arthritis. These diseases share common symptoms of a typical bacterial infection, and mislead health workers to use antibiotics unnecessarily. In addition, illicit prescribing of antibiotics by medical practitioners is increasing the condition of resistance, due to improper diagnosis, lack of understanding of the potential dangers of inappropriate use, costs, and outcomes of therapy.[4] During our hospital visit as per the curriculum of Pharm. D. course in the pediatric ward, we observed the use of antibiotics to treat diseases which are generally self-limiting, to avoid hospital-acquired infections in Sri Venkateswara Ramnarayana Ruia Government General Hospital (SVRRGGH), Tirupathi. Hence, we aimed to evaluate the extent of inappropriate prescribing of antibiotics in treating dengue fever (DF) in pediatric patients.

Methods

This cross-sectional, observational study was carried out for 6 months (July to December 2016) in the inpatient Department of Pediatrics, SVRRGGH, Tirupathi, India. The minimum required sample size (n=370) used was based on the pilot study that was performed in the early weeks of July 2016 on 50 patients.

The study was approved by the Institutional Review Board, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupathi, India. All patients admitted to the pediatric inpatient ward of SVRRGGH with dengue fever during the study period were included in the study, except for those with other infections and co-morbid conditions.

A specially designed pro forma was used for collecting data, including patient demographics, past medical history, family and surgical history, traveling and transfusion history, signs and symptoms, diagnosis, and medications presently prescribed for each patient. The data were obtained from patient case profiles after obtaining parental informed consent. All prescriptions were analyzed for the appropriate diagnosis, grading, and presence of antibiotics, according to the *2009 WHO Guidelines*[5] and *NVBDCP Guidelines of India*.[6] In addition, the presence of appropriate antibiotics for hospital-acquired infection was also assessed based on *HIS Guidelines of India*.[7-9]

Results

In this study, we observed more DF cases (**Table 1**) in children between the age group 5-10 years (52.97%), followed by 0-4 years (37.29%) and 11-15 years (9.23%). This may be because of children playing in unsanitary places or field areas where there is risk

of being bitten by mosquitoes. There is no existing scientific reason for high prevalence of dengue in children, but the rate of mortality in pediatrics is high due to secondary infections, developing immunity, and exposure to virulent strains, while most children remain asymptomatic.[10]

Table 1. Age distribution of dengue fever patients

Age group	No. of cases (N=370)
0-4 years	138
5-10 years	196
11-15 years	36

Out of 370 cases, 181 (48.91%) cases were diagnosed based on platelet count, followed by NS1 antigen (36.75%), IgM (12.7%) and IgG (1.62%) antibodies, while only 4.4% of cases were diagnosed solely based on symptoms (**Table 2**).

Table 2. Diagnostic parameters used to diagnose dengue fever

Parameters	No. of cases (N=370)
PLT, n (%)	181 (48.91)
NS1AG, n (%)	136 (36.75)
IgM, n (%)	47 (12.7)
IgG, n (%)	6 (1.62)

In this study, 315 (85.13%) cases were appropriately graded and 72 cases (19.45%) were inappropriately graded (**Table 3**). Of the 315 appropriately-graded cases, mild dengue was observed in 132 cases (41.9%), moderate dengue in 176 cases (55.87%), and severe dengue in 7 cases (2.22%). Among the moderate and severe cases, DHF prevalence was 49.45% (183 subjects) in which DHF1 contributed to the highest percentage (48.63%; 89 cases), followed by DHF 2 (47.54%), and DHF 3 (3.82%).

Table 3. Appropriateness in grading dengue fever

Grading	No. of cases (N=370)
Inappropriate, n (%)	72 (19.45)
Appropriate, n (%)	315 (85.13)

Of 370 confirmed dengue cases, 267 (74.6%) cases were prescribed antibiotics. A single antibiotic was prescribed to 225 cases (60.81% of all cases), 2 antibiotics to 33 (8.91%) cases, and 3 antibiotics to 9 (2.43%) cases, at a time (**Figure 1**). Triple therapy antibiotics included cefotaxime in all prescriptions with cefixime, azithromycin, amoxyclav, doxycycline, and ceftriaxone in different combinations. Antibiotics given as dual therapy were ceftriaxone with doxycycline, cefotaxime, or amoxyclav, and cefotaxime with doxycycline, cefixime, or metronidazole.

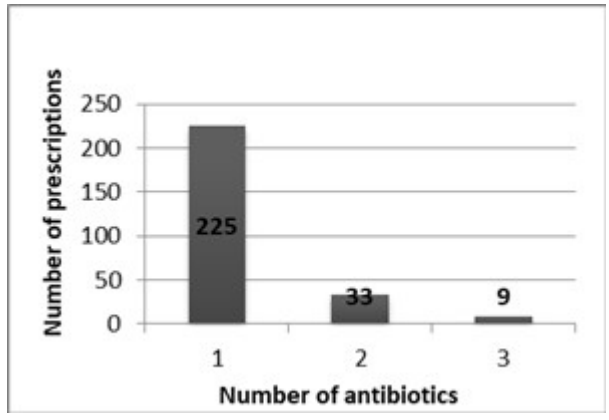

Figure 1. Distribution of antibiotics

Among the antibiotics prescribed, cefotaxime and ceftriaxone were most commonly used (96 cases; 35.90% for each drug), followed by doxycycline (13.8%), amoxyclav (8.6%), cefixime (2.6%), amikacin (1.5%), azithromycin (0.75%), as well as ciprofloxacin and metronidazole (0.38%) (**Table 4**).

Table 4. Antibiotic prescribing pattern

Antibiotic	No. of prescription (N=267)
Cefotaxime, n(%)	96 (35.9)
Ceftriaxone, n(%)	96 (35.9)
Doxycycline, n(%)	37 (13.8)
Amoxyclav, n(%)	23 (8.6)
Cefixime, n(%)	7 (2.6)
Amikacin, n(%)	4 (1.5)
Azithromycin, n(%)	2 (0.75)
Ciprofloxacin, n(%)	1 (0.38)
Metronidazole, n(%)	1 (0.38)

Discussion

The most common monsoon diseases in India are malaria, diarrhea, dengue, chikungunya, typhoid, viral fevers, and cholera. They all share some common symptoms and present challenges for the physician. Antibiotics are of no use in management of dengue and chikungunya, as they are viral, infections. According to the *WHO Clinical Guidelines*[5] and *the 2014 NVBDCP Guidelines*,[6] no drug of choice for dengue exists, as drugs that directly act against dengue virus are still in the pipeline.[11] Hence, therapy is solely based on the management of symptoms. Accurate diagnosis of dengue can be confirmed based on serum positivity for NS1 antigen, IgM, and IgG antibodies. The NS1 antigen can be determined by ELISA, which is highly sensitive, specific,[12] and helpful in the early diagnosis of acute infection. In our study, we observed that platelet count determination had been used in most (50%) of the cases to diagnose dengue infection. This approach is not appropriate because thrombocytopenia occurs due to destruction of platelets, mediated by antiplatelet-antibodies observed from the 3rd day to the 7th day of illness. Moreover, platelet count may also fall in other infections like HIV, HHV-6, ehrlichiosis, Rickettisia, malaria, hepatitis-C, cytomegalovirus, Epstein-Barr syndrome, *Helicobacter pylori*, and *E. coli.* Hence, platelet count is not an ideal diagnostic parameter to diagnose dengue fever. However, it can be considered for prognosis of the disease. These implementations can make the physician clear and confident regarding usage of antibiotics and further allows him to follow strict regimen recommended by *WHO* and *HIS of India* and thus reduce the need for antibiotic use and cost burden on the patient.

Once the dengue diagnosis has been confirmed, grading plays a major role in the success of the treatment. Inappropriate grading may result in failure of therapy, and the need for advanced assessment of complications. As manifestations of DF vary by grades, different treatment approaches are required, as mentioned in the *WHO Guidelines*. Mild dengue does not require therapy with IV fluids, while moderate and severe dengue requires IV fluid maintenance. Moderate dengue can be managed with IV fluids at a rate of 2 to 3 mL/kg/hr, with reassessment of complete blood count (CBC) to increase the rate up to 5 to 10 mL/kg/hr for 2 hours. In severe dengue, hemodynamic status of the patient requires assessment, for the basis of the physician to decide between a bolus of 20 mL/kg in 15 minutes or maintenance with IV fluids at a rate of 5 to 10 mL/kg/hr over 1 hour. Otherwise, DF may be fatal after entering into the phases like shock and coma.[5,6]

In our observation, 75% of the cases were prescribed with antibiotics, under the guise of avoiding hospital-acquired infections. However, antibiotics are not necessary to treat dengue, according to the guidelines. Empiric antibiotics are being prescribed for suspected infections to avoid hospital-acquired infections. However, this empiric use of antibiotics for treating nosocomial infections should be according to the HIS guidelines. In addition, antibiotics like amikacin, doxycycline, and amoxyclav should not be used without performing susceptibility tests, while ceftriaxone and cefixime cannot be used prior to performing hypersensitivity tests.[13-16] Azithromycin, ceftriaxone, and metronidazole can only be used for the prophylaxis of endocarditis and sexually transmitted diseases (STDs).[17,18] In addition, usage of amoxyclav in dengue can further increase the risk of bleeding.[14]

The prescribing of antibiotics is an art requiring skill in using the appropriate antibiotic for the particular infection. Inappropriate usage of more than one antibiotic increases the chances of developing multidrug resistance, which is a serious issue to be considered. Though there are many policies describing the appropriate indications for use of antibiotics, these drugs are often used inappropriately. Furthermore, if this scenario continues, the list of organisms developing resistance will increase. More powerful and costlier antibiotics must be prescribed for simple infections, which may have many adverse effects and can present an economic burden to patients.

In conclusion, prescribing one or more antibiotics to treat self-limiting viral infections is considered as inappropriate, and leads to the development of multidrug resistance. Furthermore, excess use of antibiotics in infancy may induce imbalances in gut and microbiota, called dysbiosis, and increase the probability of diseases such as obesity, diabetes, and asthma in later life.[19] These findings can be used to improve antibiotic stewardship in the treatment of dengue.

Acknowledgments

The authors are grateful to all who have contributed to the success of this study. We especially acknowledge the Department of Pediatrics, Sri Venkateswara Ramnarayana Ruia Government General Hospital (SVRRGGH), Tirupathi, India for assistance in procuring data. It has been a privilege and wonderful experience to be part of this esteemed institution and we owe our sincere thanks to our Principal, Dr. D. Ranganayakulu, Sri Padmavathi School of Pharmacy (SPSP), Tirupathi. We would also like to express our profound gratitude to Mrs. P. Sulochana, BA, LLB, Chairperson, SPSP, Tirupathi who provided the facilities to execute this work.

Conflict of Interest

None declared.

References

1. Yoneyama H, Katsumata R. Antibiotic resistance in bacteria and its future for novel antibiotic development. Biosci Biotechnol Biochem. 2006;70:1060-75.C.
2. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40:277-83.
3. Read AF, Woods RJ. Antibiotic resistance management. Evol Med Public Health. 2014;2014:147.
4. Eandi M, Zara GP, Della Pepa C. Application of pharmacoeconomics to the use of antibiotics. Clin Microbiol Infect. 2000;6:90-2.
5. World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization; 2009. p.1-147.
6. National vector borne disease control programme. National guidelines for clinical management of dengue fever. 2014 Dec; [cited 2016 March 17] Available from: https://www.scribd.com/document/347257604/Dengue-National-Guidelines-2014-Compressed.
7. Hospital Infection Society guidelines. Nosocomial Infection – Prevention and Management. 1-10; [cited 2016 March 15]. Available from: http://www.apiindia.org/pdf/pg_med_2008/Chapter-08.pdf.
8. World Health Organization. Prevention of hospital-acquired infections: a practical guide. Malta: WHO; 2002. p.1-64.
9. Mohammed M, Mohammed A, Mirza M, Ghori A. Nosocomial infections: an overview. Int Res J Pharm. 2014;5:7-12.
10. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol. 2013;5:299-309
11. Ghazala Z, Anuradha HV, Shivamurthy MC. Pattern of management and outcome of dengue fever in pediatric in-patients in a tertiary care hospital: a prospective observational study. International Journal of Basic & Clinical Pharmacology. 2014; 3:534-8. DOI: http://dx.doi.org/10.5455/2319-2003.ijbcp20140623.
12. Bisordi I, Rocco IM, Suzuki A, Katz G, Silveira VR, Maeda AY, *et al.* Evaluation of dengue NS1 antigen detection for diagnosis in public health laboratories, São Paulo State, 2009. Rev Inst Med Trop São Paulo. 2011;53:315-20.
13. HL Sharma, KK Sharma. Penicillins, cephalosporins and other β-lactam antibiotics. In: Kothari Divyesh A, editors. Principles of pharmacology. 2nd ed. New Delhi: Paras Medical Publisher; 2103. p. 722-8.
14. Sharma HL, Sharma KK. Aminoglycosides. In: Kothari Divyesh A, editor. Principles of pharmacology. 2nd ed. New Delhi: Paras medical publisher; 2103. p. 738.
15. Harvey RA. Protein synthesis inhibitors. In: Clark MA, editor. Pharmacology. 6th ed. New Delhi: Lippincott's Illustrated Reviews Series; 2012. p. 395-404.
16. Sharma HL, Sharma KK. Broad spectrum antibiotics: tetracyclines and chloramphenicol. In: Kothari Divyesh A, editor. Principles of pharmacology. 2nd ed. New Delhi: Paras medical publisher; 2103. p. 748-50.
17. Sharma HL, Sharma KK. Macrolides, ketolides, lincosamides, oxazolidones and other antibacterial drugs. In: Kothari Divyesh A, editor. Principles of pharmacology. 2nd edition. New Delhi: Paras medical publisher; 2103. p. 741-3.
18. Sharma HL, Sharma KK. Antiamoebic and other antiprotozoal drugs. In: Kothari Divyesh A, editor. Principles of pharmacology. 2nd ed. New Delhi: Paras Medical Publisher; 2103. p. 819-21.
19. Vangay P, Ward T, Gerber JS, Knights D. Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe. 2015;17:553-64.