Research Article

Prescribing Patterns in Dengue Fever in Paediatric Patients in A Tertiary Care Hospital: A Retrospective Cross Sectional Study

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ABSTRACT

Dengue fever (DF) is the most common arboviral infection of mankind gaining global attention. Prescribing patterns in DF helps to evaluate the present trends of drug usage, drug expenditures, appropriateness of prescriptions and adherence to evidence-based recommendations. The objective was to study the prescribing patterns, approval status, inclusion in World Health Organization essential medicines list (WHO-EML) and National List of Essential Medicines (NLEM), cost of drugs prescribed in the treatment of paediatric DF. Data was collected from medical records of DF paediatric in-patients of SSIMS & RC Hospital, Davangere. The prescribing patterns, approval of drugs by Drug Controller General of India (DCGI) and United States Food and Drug Administration (USFDA), cost of drugs and listing in WHO-EML and NLEM were analysed. The drugs were classified into different groups based on WHO-ATC (Anatomical Taxonomical Chemical) classification. Descriptive statistics was applied using MS Excel 2010. The commonly used treatment modalities in 136 DF cases were antipyretics (100%), intravenous fluids (IVFs) (97.1%), antiulcer agents (94.1%) and anti-emetics (79.4%). Of 512 drug prescriptions majority (93.6%) were single drug formulations. 99.2% of drug prescriptions were approved by DCGI and 97.3% by FDA. >87% of drugs were enlisted in NLEM and WHO-EML. Only 6.3% drugs were prescribed by generic names. The most commonly prescribed ATC class of drugs belonged to A02B, N02B and A04A. The costliest drug prescribed was Inj. Piperacillin+Tazobactam. The results showed that utmost priority was given to symptomatic management of dengue fever with antipyretics, intravenous fluids, antiulcer agents and anti-emetics.

Keywords: Approval status, Dengue fever, Essential medicines, Prescribing patterns.

INTRODUCTION

Dengue fever is a vector-borne viral infection of global importance.[1] In some parts of the world, it is mainly a paediatric public health problem.[2,3] In India, dengue infection has been known to be endemic for over two centuries as a benign and self-limited disease[4] and epidemics have been reported in many parts of the country. Karnataka had the second highest number of cases in the year 2010 in India up to August. According to the sources the numbers of dengue cases are increasing.[5]

There is no definitive antiviral treatment for dengue fever. The treatment is entirely symptomatic taking care of complications during the course of illness.[6] Intensive care is required for severely ill patients, including intravenous fluids, blood or plasma transfusion and medicines.[7]

It is essential to be cognizant with the current prescribing patterns of drugs to make basic comparisons between situations in different areas or at different times. Also, when an intervention is undertaken to improve the aspects of drug use, the drug indicators can be used to measure the impact.[8] Drug utilization research facilitates the rational use of drugs in populations[9] and hence it is important for clinical, educational and economic reasons.[10]

Classifying the drugs according to WHO-ATC system serves as a tool for the presentation and comparison of drug consumption statistics at international levels.[11-12] Adoption of essential medicines list for procurement and supply of medicines in the public healthcare system would result in improved availability of medicines, cost saving and more rational use of drugs.[13]

Data about drug usage patterns in DF in India are particularly lacking.

Keeping the above facts in consideration the objective of the present study was to study the prescribing patterns, approval status, inclusion in World Health Organization essential medicines list (WHO-EML) and National List of Essential Medicines (NLEM), cost of drugs prescribed in the treatment of paediatric DF.

MATERIALS AND METHODS

Study design, setting and study population

A cross sectional, retrospective study was carried out in in-patients admitted to paediatric department with a clinical diagnosis of dengue fever in SSIMS & RC hospital, Davangere, Karnataka, India. The study was carried out between June 2013 to August 2013. Relevant data was recorded in a self designed standardized pro forma.

Data Collection

The data collected in the proforma included details on patient demographics (IP number, age, sex and duration of hospital stay) and drugs prescribed [drug name, dose, route of administration, frequency, duration of therapy].

Analysis of data

- The prescription pattern was analyzed by using the prescribing indicators as mentioned in the World Health Organization (WHO) core drug use indicators. The total number of drugs prescribed, average number of drugs per prescription, number of drugs in generics, number of drugs used as monotherapy and in combinations was calculated.[8]
- Approval status of the drugs was checked in the official website for Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services (DCGI), India and Drugs @FDA: FDA Approved Drug Products.[14,15]
- Drugs were classified into different groups based on WHO-ATC classification.
- The adherence of drug prescription was checked with the WHO essential medicines list (EML) 2011 and National List of Essential Medicines (NLEM) 2011.[13,16]
- Cost of individual drugs for the prescribed dose was calculated taking into consideration the average cost of leading brands of drug prescribed.

For convenience of interpretation intravenous fluids (IVFs), blood and blood products used in the treatment were not included under drug prescriptions and were analyzed separately.

Ethical considerations

The study was done after obtaining approval from Institutional Research and Ethics Committee.

Statistical analysis

Descriptive statistics were applied to the collected data using Microsoft Excel 2010 software. Results are expressed in percentages, mean and standard deviation (SD).

RESULTS AND DISCUSSION

A total 136 paediatric dengue fever patients were included in the study. Majority (44.1%) of them were in the age group between 6-10 years. Females (51.5%) were most affected. The mean age was almost comparable in both genders (Table 1).

48 (35.3%) patients had positive dengue serology. Platelet count ≤ 50,000 was noted in 36 (26.5%) patients (Table 2).

The most commonly used treatment modalities in the management of DF were antipyretics (100%), IVFs (97.1%), antiulcer agents (94.1%) and anti-emetics (79.4%). Antimicrobial usage was seen in only 48.5% of cases. (Table 3, Figure 1).

The most commonly preferred IVF was ½ DNS [82 (60.3%)] (Table 4).

A total of 512 drug prescriptions were analysed of which majority [480 (93.6%)] were single drug formulations. More than 97% drugs were approved by DCGI and FDA and more than 87% were included in WHO-EML and NLEM. Parenteral formulations (64.1%) were most commonly prescribed. Only 32 (6.3%) drugs were prescribed by their generic names (Table 5).

Paracetamol (Tablet, Syrup and suppository) was the most commonly prescribed single drug [138(27%)]. Among antimicrobials Inj. Ceftriaxone [28/90(31.1%)] was the most preferred single formulation. The FDC most commonly prescribed was Amoxicillin + Clavulanic acid [10/32(31.3%)]. The drugs not approved by FDA were Inj. Ceftriaxone + sulbactam and Inj. Cefuroxime + Clavulanic acid. The only drug which was not approved by any of the drug regulatory bodies was Inj. Cefoperazone + Sulbactam. The drugs which were not included in both WHO-EML and NLEM were Syrup Sucralfate, Syrup Silymarin, Tab Mefenamic acid, Tab Naproxen, Inj. Cefuroxime, Inj. Levofloxacin, Inj. Piperacillin + Tazobactam, Inj. Ceftriaxone + sulbactam, Inj. Cefoperazone + Sulbactam and Inj. Cefuroxime + Clavulanic acid. The drug included in WHO-EML but not in NLEM was artemether+lumefantrine. The drugs included in NLEM but not in WHO-EML were alprazolam and pantoprazole (Table 6).

The cost per dose and the total cost spent during hospital stay was highest for Inj. Piperacillin + Tazobactam (297.4Rs and 4461 Rs respectively) and least for Syrup Silymarin (0.1 and 0.5Rs respectively) (Table 6).

The most commonly prescribed ATC class of drugs were A02B and N02B [138(27%) each], followed by A04A [108(21.1%)]. J01D class [46 (9%)] was the most prescribed antimicrobial class followed by class J01C and class P01B [12 (2.3%) each] (Figure 2).

Table 1: Patient demographic and other characteristics [n=136 patients]

Age (years)	
< 1	2 (1.5%)
1-5	34 (25%)
6-10	60 (44.1%)
11-15	30 (22.1%)
≥ 16	10 (7.4%)
Gender	
Males	66 (48.5%)
Females	70 (51.5%)
Other characteristics	
Mean age of males (Years)	8.3 ± 4.1 years
Mean age of females (Years)	8.3 ± 4.4 years
Mean duration of hospital stay (Days)	5.6± 2.1 days
Patients on ventilator support	2 (1.5%)
Number of deaths	Nil

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Table 2: Laboratory parameters of patients (n=136)

1. Blood counts	Number (%)	2. Dengue serology	Number (%)
Total leucocyte count elevation	70 (51.5)	NS1 positive	36 (26.5)
i) Neutrophils elevation	60 (44.1)	IgM positive	6 (4.4)
II) Lymphocytes elevation	10 (7.4)	IgG positive	2 (1.5)
Total leucocyte count decreased	60 (44.1)	NS1, IgM positive	4 (2.90)
Blood counts normal	6 (4.4)	Dengue negative	46 (33.8)
		Not available/ not done	42 (30.9)
3. Platelet count at admission (cells/Cumm)	**Number (%)**	**4. Haematocrit**	**Number (%)**
		< 30%	16 (11.8)
>1,00,000	50 (36.8)	30 – 34.9%	52 (38.2)
51,000 – 1,00,000	46 (33.8)	35 – 39.9%	42 (30.9)
21,000 – 50,000	30 (22.1)	40 – 44.9%	14 (10.3)
*≤ 20,000	6 (4.4)	45 – 49.9%	6 (4.4)
Not available/ not done	4 (2.9)	Not available/ not done	6 (4.4)
5. Liver Function Tests	**Number (%)**	**6. Renal function tests and Electrolytes**	**Number (%)**
Albumin decreased	6 (4.4)	Sodium abnormality	10 (7.4)
Prothrombin Time (PT) prolonged	6 (4.4)	Potassium abnormality	50 (36.8)
Activated Partial Thromboplastin Time (APTT) prolonged	12 (8.8)	Blood urea elevation	Nil
Enzymes elevation	20 (14.7)	Serum creatinine elevation	Nil

*Least platelet count noted during hospital stay was 7000 in 2 patients (1.5%)

Table 3: Treatment characteristics (n=136 patients)

Treatment Class	Number of patients prescribed (%)	% of patients prescribed	Prescribed Duration (Mean±SD) days
IVFs	132	97.1	-
Antiulcer agents	128	94.1	4.1 ± 2
Antipyretics	136	100	3.7 ± 1.8
Anti-emetics	108	79.4	3.8 ± 2.1
Antimicrobials	66	48.5	3.8 ±1.2
Vitamin K	10	7.4	1.4 ± 0.9
Liver protectants	6	4.4	3.7 ± 2.3
*Analgesics	4	2.9	4 ± 1.4
*Diuretics	6	4.4	2.3 ± 1.2
*Cardiac stimulants	2	1.5	2
*Corticosteroids	2	1.5	5
*Antispasmodics	2	1.5	6
*IV Solution Mannitol	2	1.5	2
*Skeletal muscle relaxants	2	1.5	4
*Anxiolytics	2	1.5	2
Platelets	26	19.1	-
FFP	12	8.8	-

*indicates the groups which are included under group "Others" in figure-1; Average number of platelets prescribed per patient: 4.1 ± 3.7; Average number of FFP prescribed per patient: 4

In the present study, of 136 patients diagnosed as DF, 35.3% showed positive dengue serology, 46% negative and for the remaining, serology was either not done or reports not available. As serological diagnosis demands a collection of samples five days post disease onset, the negative serology encountered may be attributed to serological testing in the early course of the disease.[17] Suharti et al., in his study evaluated patients who fulfilled

the clinical WHO criteria for dengue fever/dengue haemorrhagic fever and surprisingly found that 51% of the patients were negative for dengue infection serologically.[18] Majority of children affected by DF were between the age group of 6-10 years and this was similar to the incidence of DF reported during 1996 Delhi epidemic.[19] Slight female preponderance of dengue affection was seen in this study.
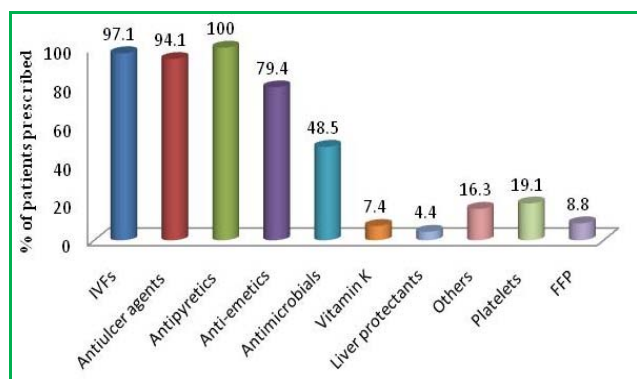

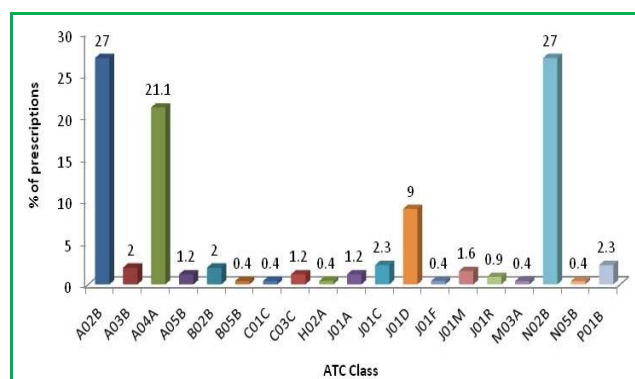**Figure 1:** Treatment characteristics

Figure 2: Prescription according to ATC class

Table 4: Intravenous fluids (IVFs) prescription characteristics [n=132 patients]

Type of IVF	Number of patients (%)
1/2 DNS (Dextrose Normal Saline)	82(60.3)
DNS	26(19.7)
Normal Saline (NS)	24(18.2)
Isolyte-P	8(6.1)
Ringer Lactate (RL)	2(1.5)

Average number of IVFs prescribed per patient: 1.1 ± 0.4

In the management of dengue fever, the priority treatment included antipyretics (100%), intravenous fluids (97.1%), antiulcer agents (94.1%) followed by anti-emetics (79.4%).Intravenous rehydration has been shown to reduce the case fatality rate to less than 1% of severe cases.[20]Prescription of antipyretics, anti-peptic ulcer agents and anti-emetics was mainly for symptomatic management of DF. Antimicrobials were administered in less than 50% of cases who had elevated neutrophil counts due to secondary bacterial infections and also in very sick looking patients. For some patients anti-

malarials were started empirically keeping malaria into account.

Although around 1/4th of patients had platelet count ≤ 50,000 at the time of admission (Table II), the requirement of platelet transfusion was seen in less than 20%. This is because prophylactic transfusion of platelets is indicated only in patients with platelet count <20,000/Cumm without bleeding manifestations and therapeutic transfusion, in bleeding patients with platelet count ≤ 50,000/Cumm and in those with proven disseminated intravascular coagulation.[21] Meanwhile, the patients who were transfused with platelets in the present study had a platelet dip below 20,000/Cumm during hospital stay. Fresh Frozen Plasma (8.8%), liver protectants like Silymarin (4.4%) and Vitamin K (7.4%) were preferred in patients who had liver function abnormalities and elevated International Normalized Ratio (INR>1.4). Diuretics and dopamine were administered to patients showing features of heart failure and skeletal muscle relaxants (vecuronium) to patients on ventilator.

In our study, 512 drug prescriptions were analyzed and majority of them were found to be single drug formulations (93.6%). All the FDCs prescribed were antimicrobials belonging to beta lactams and anti-malarials.

Table 5: Drug prescription characteristics [n=512 prescriptions]

Characteristics	Number of prescriptions (%)
Single drug formulations	480(93.6)
Fixed dose combinations	32(6.3)
Drugs approved by DCGI	508(99.2)
Drugs approved by FDA	498(97.3)
Drugs listed in WHO essential medicines list*	450(87.9)
Drugs listed in NLEM*	468(91.4)
Parenteral drug formulations prescribed*	328(64.1)
Drugs by intravenous (i.v.)route	318(62.1)
Drugs by intramuscular(i.m.) route	10(2)
Enteral drug formulations prescribed	184(35.9)
Tablets	112(21.9)
Syrups	70(13.7)
Suppositories	2(0.4)
Drugs prescribed by generic names*	32(6.3)
Average number of drugs prescribed per patient	3.8 ± 1.1

*WHO core drug use indicators

Table 6: Prescription characteristics, ATC code, approval status and enlistment in essential medicine list of drugs

Drug	Number of prescriptions	ATC code	Approval status		Listing in essential medicines		Average cost / dose (Rs.)	Average cost during hospital stay (Rs.)
			DCGI	FDA	WHO	NLEM		
ATC class: A02B Drugs used for peptic ulcer and GERD								
Inj. Ranitidine	114	A02BA02	Y	Y	Y	Y	2	17
Inj. Pantoprazole	20	A02BC02	Y	Y	N	Y	35.4	168.7
Tab. Pantoprazole	2	A02BC02	Y	Y	N	Y	6	6
Syp. Sucralfate	2	A02BX02	Y	Y	N	N	3.2	29.2
ATC class: A03B Belladona derivatives , Plain								
Inj. Hyoscyamine	2	A03BA03	Y	Y	Y	Y	12.3	73.8
ATC class: A04A Anti emetics and Anti nauseants								
Inj. Ondansetron	108	A04AA01	Y	Y	Y	Y	25	122.2
ATC class: A05B Liver therapy, Lipotropics								
Syp. Silymarin	6	A05BA03	Y	Y	N	N	0.1	0.5
ATC class: B02B Vitamin K and other Hemostatics								
Inj. Vitamin K	10	B02BA01	Y	Y	Y	Y	7.2	10.1
ATC class: B05B IV solutions								
Inj. Mannitol	2	B05BC01	Y	Y	Y	Y	55.5	111
ATC class: C01C Cardiac stimulants excluding cardiac glycosides								
Inj. Dopamine	2	C01CA04	Y	Y	Y	Y	232.2	464.4
ATC class: C03C High Ceiling Diuretics								
Inj. Frusemide	6	C03CA01	Y	Y	Y	Y	1.9	4.7
ATC class: H02A Corticosteroids for systemic use, Plain								
Inj. Dexamethasone	2	H02AB02	Y	Y	Y	Y	9.6	143.7
ATC class: M01A Non-steroids, anti-inflammatory and anti-rheumatic products								
Tab. Mefenamic acid	2	M01AG01	Y	Y	N	N	2.4	12
Tab. Naproxen	2	M01AE02	Y	Y	N	N	39	234
ATC class: M03A Muscle relaxants, peripherally acting								
Inj. Vecuronium	2	M03AC03	Y	Y	Y	Y	179.3	717.2
ATC class: N02B Other analgesics and antipyretics								
Syp. Paracetamol	60	N02BE01	Y	Y	Y	Y	2.1	24.5
Tab. Paracetamol	76	N02BE01	Y	Y	Y	Y	1.1	14.9
Supp. Paracetamol	2	N02BE01	Y	Y	Y	Y	8.2	24.6
ATC class: N05B Anxiolytics								
Tab. Alprazolam	2	N05BA12	Y	Y	N	Y	2.8	5.5
ANTIMICROBIALS								
ATC class: J01A Tetracyclines								
Tab. Doxycycline	6	J01AA02	Y	Y	Y	Y	22.7	173.4
ATC class: J01C Beta lactams anti bacterials, Penicillins								
Inj. Amoxicillin + Clavulanic acid	2	J01CR02	Y	Y	Y	Y	121.8	1218
Tab. Amoxicillin + Clavulanic acid	6	J01CR02	Y	Y	Y	Y	17.5	176.5

Table 6: Prescription characteristics, ATC code, approval status and enlistment in essential medicine list of drugs (Continued.....)

Drug	Number of prescriptions	ATC code	Approval status		Listing in essential medicines		Average cost / dose (Rs.)	Average cost during hospital stay (Rs.)
			DCGI	FDA	WHO	NLEM		
Syp. Amoxicillin + Clavulanic acid	2	J01CR02	Y	Y	Y	Y	10.6	42.4
Inj. Piperacillin + Tazobactam	2	J01CR05	Y	Y	N	N	297.4	4461
ATC class: J01D Other Beta lactam anti bacterials								
Inj. Ceftriaxone + Sulbactam	6	J01DD54	Y	N	N	N	145.3	892.7
Inj. Cefoperazone + Sulbactam	4	J01DD62	N	N	N	N	123.8	1138.5
Inj. Ceftriaxone	28	J01DD04	Y	Y	Y	Y	48.1	476.3
Inj. Cefuroxime	6	J01DC02	Y	Y	N	N	109.3	821.1
Inj. Cefotaxime	2	J01DD01	Y	Y	Y	Y	15.5	62
ATC class: J01F Macrolides, Lincosamides and Streptogramins								
Tab. Azithromycin	2	J01FA10	Y	Y	Y	Y	6.7	20.1
ATC class: J01M Quinolone anti bacterials								
Inj. Ofloxacin	4	J01MA01	Y	Y	Y	Y	94.5	837
Tab. Ofloxacin	2	J01MA01	Y	Y	Y	Y	8.8	70
Inj. Levofloxacin	2	J01MA12	Y	Y	N	N	31.7	126.8
ATC class: J01R Combination of anti bacterials								
Inj. Cefuroxime +Clavulanic acid	4	J01RA03	Y	N	N	N	167.2	621
ATC class: P01B Antimalarials								
Tab. Chloroquine	6	P01BA01	Y	Y	Y	Y	1	3.1
Tab. Artemether + Lumefantrine	6	P01BF01	Y	Y	Y	N	22.3	105.3

More than 97% of the drug prescriptions were approved by both DCGI and FDA and almost 88% of drug prescriptions were included in both WHO-EML and NLEM probably depicting rational use of drugs in this study. Anti malarial drug artemether + lumefantrine combination was the only drug included in WHO-EML but not in NLEM. In spite of this, the drug was preferred equally to chloroquine and this may be attributed to emerging of resistant malarial parasites in this area.

The most commonly preferred route of administration was parenteral and in particular intravenous route. Since majority of dengue patients will have gastrointestinal disturbances like nausea and vomiting the prescription preference to parenteral formulations was justified.[22] Very few drugs were prescribed by their generic names (used interchangeably with rINN-recommended International Non-proprietary Name). Prescription of drugs by their generic names helps in the identification of

the products, making it easier for the prescribers, dispensers and users to choose between other alternatives competing in terms of quality, price or convenience.[23,24] Hence the generic drug prescriptions should be increased over prescriptions with branded drugs.

The most commonly prescribed ATC class of drugs include A02B, N02B and A04A which mainly constituted drugs used in the supportive management of dengue fever.[22]

The drugs which constituted majority of prescriptions like antipyretics, antiulcer agents and anti emetics were of average cost which may be afforded by majority of people. The costliest drug prescribed during treatment was antibiotic Inj. Piperacillin + Tazobactam. Though constituted only 0.6% of the prescriptions, it shared the highest cost per dose (297.4 Rs) and overall highest cost spent during hospital stay (4461 Rs). There is a need for

using other cost effective antimicrobials. The least cost was spent on Syrup Silymarin (0.5 Rs).

In our study, an attempt has been made to assess approval status of drugs, listing in EML and categorising drugs according to WHO-ATC class. Analysing drugs on the above grounds would give a broader perspective of drug prescription patterns and may help in developing specific treatment guidelines in the management of DF.

Limitations of the study

The sample size was the major limitation of the study as only cases admitted between June 2013 and August 2013 were included for analysis. The culture and sensitivity reports of patients receiving antimicrobials were not noted. Indirect costs related to drugs and other treatment aspects of DF were not analysed. The adverse drug reaction profiles of drugs prescribed were not analysed.

CONCLUSION

The results showed that utmost priority was given to symptomatic management of dengue fever with antipyretics, IVFs, antiulcer agents and anti-emetics as DF has no known specific treatment till today. Majority of the drugs prescribed were approved by regulatory bodies and were included in essential medicines lists which can attribute to rationality of prescriptions. As the incidence of DF is increasing with epidemics the demand for specific treatment guidelines is in great need.

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