**Abstract**

**Background:**
Enteric fever, also known as typhoid fever, is a commonly diagnosed disease in Nepal. Globally, enteric fever affects 21.6 million people and causes 216500 deaths annually. Appropriate use of antibiotics is a key element in the successful treatment of enteric fever.

**Objective:**
The study was aimed to study antibiotic use and their appropriateness in the patient with Enteric Fever.

**Methods:**
A cross-sectional study was carried out in two tertiary-care hospitals viz. Manipal Teaching Hospital (MTH) and Western Regional Hospital (WRH) in western Nepal between Aug-September 2010. Appropriateness in this study was assessed using Medication Appropriateness Index (MAI) criteria which include indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and expense.

**Results:**
Mean use of antibiotics in WRH (2.18±0.87) was not significantly different (P = 0.015) from MTH (2.13±1.11). The Cephalosporin group of antibiotics was used widely to treat enteric fever in both hospitals. On average 1.12 Cephalosporin per patient in MTH and 0.93 Cephalosporin per patient in WRH were used.

On average, we found that 31.7% in MTH and 39.5% in WRH of patient’s treatments with antibiotics were inappropriate. Other common types of inappropriateness are expensive drugs [90% (MTH), 92% (WRH)], duplication of antibiotics [53% (MTH), 822% (WRH)], prescribing high generation antibiotics [80% (MTH), 89% (WRH)], and practical direction [17% (MTH), 33% (WRH)].

**Conclusion:**
Conclusively, more than thirty percent of patients in both of hospitals treated for enteric fever received inappropriate antibiotics. Hence we recommend future education or managerial intervention to improve appropriateness.

**Keywords:** Appropriateness, Antibiotic Use, Enteric Fever, Nepal.
Background

Enteric fever, commonly known as typhoid fever, is a severe systemic illness characterized by sustained fever and abdominal symptoms. Globally, enteric fever causes illnesses to 21.6 million and death to 216500 people every year. The disease is highly epidemic in Asian countries, especially in Nepal, India, Vietnam and Indonesia. Among Asian countries, Kathmandu, the capital city of Nepal is regarded as enteric fever capital of the world. Salmonella typhi and Salmonella paratyphi are regarded as the major causes of the disease in Nepal. Studies from Nepal suggests the emergence of multi-drug resistant isolates and resistance to first line drugs like co-timoxazole, amoxicillin, chloramphenicol and partial resistance to ciprofloxacin and ofloxacin. Reasons behind the emergence of antibacterial resistance are unknown. However, it is a well-known fact that antibiotic resistance is an inevitable consequence of irrational use of antibiotics. The availability of antibiotics on an over-the-counter basis in Nepal may play a role in the rise of antibiotic resistance. Although there are some studies detailing the emergence of a typhoid epidemic and antibiotic resistance in enteric fever, the number of studies on rational use of antibiotics is deficient.

The Medication Appropriateness Index (MAI) was originally developed by Hanlon et al. in 1992 to assist physicians and pharmacists in assessing the appropriateness of a medication for given patients. It consists of ten purviews: indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and expense. The present study was conducted to know the appropriateness of antibiotic therapy in the patients with Enteric Fever using Medication Appropriateness Index criteria.

Material and Methods

Study design: Cross-Sectional

Study duration: Two months (August 2010 to September 2010)

Study site: The study was conducted at Manipal Teaching Hospital (A private tertiary care center) and Western Regional Teaching Hospital (A public tertiary care hospital), which are two tertiary care hospitals in Western Nepal.

Materials: Data collection form and Medication Appropriateness Index (MAI).

Methodology: All data of patients suffering from enteric fever was collected from in-patient file using a data collection form. It included patient demography, history, clinical sign and symptoms, laboratory findings (biochemistry, microbiology, pathology and others), diagnosis, antibiotic therapy along with other concurrent medication (Medicine name, dosage, duration, quantity, direction) etc. Cost of medications was obtained from Hospital Pharmacy Unit.

Assessment of Appropriateness: In this study, we used the MAI criteria to assess the appropriateness of antibiotics therapy. MAI is a validated and reliability tested instrument and was used in several studies evaluating appropriateness. It has 10 domains which include indication, effectiveness, dosage, duration, direction, drug-drug interactions, drug-disease interactions, practicality, cost and duplication of therapy. Each domain has its own specific definition. In this study, we have used modified MAI criterion which was devised for evaluating antibiotic prescribing in inpatients by Tayler et al.

Study Definition: The study definition of each domain for this study is given below.

1. Indication: Indication in this study was defined based on the sign, symptom, disease, Lab result or condition for which antibiotics were prescribed.

   - Appropriate
   - Inappropriate
   - Marginal

2. Effectiveness: It was defined based on their sensitivity towards isolated organism and clinical outcome produced.

   - Appropriate
   - Inappropriate
   - Marginal

3. Dosage: It was defined as the total amount of medication administered during period for therapy as per WHO recommended guideline.

   - Appropriate
   - Inappropriate
   - Marginal

4. Direction: Directions in this study was defined as the instructions given for the use of a medication where we assessed the route of administration, relationship to food and liquid, the schedule, and time of the day.

   - Appropriate
   - Inappropriate
   - Marginal

5. Practical: It was defined as capable of being used or being put into practice where we assessed whether the directions for use were practical for the patient adherence.

   - Practical
   - Marginal
   - Impractical

6. Drug–drug interactions: It was defined as the effect one medication has on another medicine when administered concomitantly. To assess this we used Micromedex 2 healthcare series.

   - No Interaction
   - Interaction
   - Marginal

7. Drug–disease interaction: It was defined as the effect that the medicine has on a preexisting disease or condition and here we assesses whether the medicine worsened the patient’s disease or condition.

   - No Interaction
   - Interaction
   - Marginal
8. Duplication: Unnecessary duplication was defined as use of 2 medicines from the same chemical or pharmacologic class simultaneously in a manner that is no beneficial effects.

A _____ B _____ C _____

Necessary Unnecessary Marginal

9. Duration: It was defined as the length of therapy. In this study, we assessed the length of therapy that the patient has received according to WHO guidelines.

A _____ B _____ C _____

Appropriate Inappropriate Marginal

10. Expensiveness: In this we assessed the cost of the drug compares to other agents of equal efficacy and tolerability.

A _____ B _____ C _____

Least Expensive Marginal Most Expensive

Sample Size Calculation: Although, the prevalence of enteric fever is higher in Asian countries, it lies between 0.3-1%1-4. The required sample size was then calculated from formula n = Z^2α/2 P (1-P) / M^2 Where, M = margin of error, P = Prevalence of the characteristic. Thus, the sample size (n) at 95% confidence interval and 5% margin of error will be n = 1.962 x 0.01 x 0.99 / (0.05)^2 = 15.21 ~ 16 which is very less. Hence, we increased the required sample size up to 100 in each hospital so that we can apply descriptive statistics. So, all patients with enteric Fever treated with antibiotics during the study period were included.

Statistics: Descriptive statistics were used to analyse the data using Statistical Package for the Social Sciences (SPSS) for Windows Version 17.0 (SPSS Inc; Chicago, IL, USA).

Ethics: Ethical approval was obtained from the Nepal Health Research Council (NHRC), a national research authority under ministry of health and also permission for research were obtained from institutional research committee of the two study hospitals.

Results

1. Demography of Patients suffering from Enteric Fever:
The mean age of the patients was 22.81 ± 20.52 and 29.13 ± 17.84 in WRH and MTH respectively (Table 1).

Table 1. Demography of Patients suffering from Enteric Fever

<table>
<thead>
<tr>
<th>Demography</th>
<th>Parameter</th>
<th>WRH</th>
<th>MTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean</td>
<td>22.81 ± 20.52</td>
<td>29.13 ± 17.84</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Races</td>
<td>Brahman</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Chhetri</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Mangolian</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Newar</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Duration of stay</td>
<td>Mean</td>
<td>3.74±1.58</td>
<td>5.64±2.34</td>
</tr>
<tr>
<td>Departments</td>
<td>Medicine</td>
<td>63</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

2. Medicine used in the treatments:
Altogether, 565 and 796 drugs were used for the treatment of 100 patients from WRH and MTH respectively. Mean number of medicines used in the treatments of WRH (5.80±2.37) was not statistically different (P = 0.154) from MTH (7.91±2.85). Anatomical therapeutic classification (ATC) of prescribed medicine (Fig. 1) suggests antimicrobial class of drugs were highly prescribed in both hospitals.

Figure 1. Anatomical therapeutic classification (ATC) of drug prescribed in Enteric Fever

3. Antibiotic used in the treatment of enteric fever:
A total of 218 and 213 antibiotics were prescribed in WRH and MTH respectively for the treatment of 100 patients from each hospital (Total 200 Patients). Mean use of antibiotics in WRH (2.18±0.87) was not significantly different (P =0.015) from MTH (2.13±1.11). Further, study found that more than 20% of cases was treated with 3 antibiotics in the both hospitals (Fig. 2).
4. **Antibiotics Category:**

This study showed that the Cephalosporin group of antibiotic was used widely to treat enteric fever in both hospitals. On average 1.12 Cephalosporin in MTH and 0.93 Cephalosporin in WRH were used per treatment. The uses of Cephalosporin in two hospitals were not significantly different. Whereas, use of Macrolides in WRH was significantly higher than MTH (Table 2).

**Table 2 Category of antibiotics used per treatment**

<table>
<thead>
<tr>
<th>Group of Antibiotics</th>
<th>WRH</th>
<th>MTH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>0.33±.47</td>
<td>0.24±.45</td>
<td>0.018</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>0.93±.38</td>
<td>1.12±.50</td>
<td>0.052</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.02±.14</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>Co-amoxyclav</td>
<td>0.02±.14</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>Macrolide</td>
<td>0.54±.50</td>
<td>0.12±.33</td>
<td>0.000</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.05±.22</td>
<td>0.04±.20</td>
<td>0.497</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>0.07±.26</td>
<td>0.27±.57</td>
<td>0.000</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.01±.10</td>
<td>0.13±.34</td>
<td>0.000</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0.21±.41</td>
<td>0.18±.44</td>
<td>0.418</td>
</tr>
</tbody>
</table>

5. **Resistant pattern of Salmonella:**

Very few samples were taken from patients for doing cultures and sensitivity tests.

**Figure 3 Resistance patterns of Salmonella species.**

Among the tested sample only 12 sample in MTH and 4 samples in WRH had growths. The resistant pattern showed that Nalidixic Acid and Co-timoxazole were more than 80% resistance in both hospitals whereas Ciprofloxacin were more than 50% resistant in both the hospitals. (Fig.3).

6. **Cost of treatment of enteric fever:**

The mean cost of medication in enteric fever treatment in MTH and WRH was not significantly different. Similarly the mean costs of antibiotics in enteric fever treatment in both the hospitals were not statistically significant. The detail of cost is given in Table 3.

**Table 3 Mean cost of per treatment of enteric fever in two hospitals**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WRH</th>
<th>MTH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cost of prescribed Medication</td>
<td>1428.98±1178.35</td>
<td>2279.07±1533.49</td>
<td>0.029</td>
</tr>
<tr>
<td>Mean cost of Antibiotics</td>
<td>1228.49±840.28</td>
<td>1523.86±1054.19</td>
<td>0.422</td>
</tr>
<tr>
<td>Percentage of Antibiotic Cost</td>
<td>86</td>
<td>67</td>
<td>-</td>
</tr>
</tbody>
</table>

8. **Possible drug-drug interaction:**

The drug-drug interactions among the prescribed medicine were evaluated using Micromedex. There were drug-drug interactions in around 11% of patients prescribed medication. Some common drug-drug interactions are given in Table 4.

9. **Appropriateness of treatments:**

The appropriateness analysis of the treatment of enteric fever patients was done using Medication Appropriateness Index (MAI) 10 points indicators (Table 5) and each indicator was evaluated by researcher using WHO guidelines as illustrated in methodology. While assessing we found that majority of indications were inappropriate based on WHO guidelines.

**Table 4. Common drug-drug interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Interaction</th>
<th>Severity</th>
<th>Docum-entation</th>
<th>WRH</th>
<th>MTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Furosemide</td>
<td>Concurrent use may result in increased amikacin plasma &amp; tissue concentrations &amp; additive ototoxicity and/or nephrotoxicity</td>
<td>Major</td>
<td>Fair</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Norfloxacin</td>
<td>Concurrent use may result in an increased risk of seizures</td>
<td>Moderate</td>
<td>Fair</td>
<td>√</td>
<td>-</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Pantoprazole</td>
<td>Concurrent use may result in loss of ampicillin efficacy</td>
<td>Moderate</td>
<td>Fair</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Antacid</td>
<td>Ciprofloxacin</td>
<td>Concurrent use may result in decreased ciprofloxacin effectiveness</td>
<td>Moderate</td>
<td>Good</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Diclofenac</td>
<td>Concurrent use may result in increased ciprofloxacin plasma concentrations</td>
<td>Moderate</td>
<td>Excellent</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Ferrous sulphate</td>
<td>Concurrent use may result in decreased tetracycline and iron effectiveness.</td>
<td>Moderate</td>
<td>Good</td>
<td>-</td>
<td>√</td>
</tr>
</tbody>
</table>
Enteric fever is highly prevalent in Asian Sub-continent. In this study, the mean age of the patients suffering from enteric fever in two hospitals were 22.81±20.52 and 29.13 ±17.84 in WRH and MTH respectively which is similar to studies conducted by Karkey et al. (higher in age group between 15-30 years) in Kathmandu and Sharma et al. (28.33±15.2 )in Dhulikhel, Nepal4,15. However, another study conducted by Malla et al. in Kathmandu. Another study from Nigeria conducted by Farmakiotis D et al. in travelers found that the median duration of hospital stay was 7 days21, 22.

### Discussion:

**Demography patients with enteric fever:**

Enteric fever is highly prevalent in Asian Sub-continent. In this study, the mean age of the patients suffering from enteric fever in two hospitals were 22.81±20.52 and 29.13 ±17.84 in WRH and MTH respectively which is similar to studies conducted by Karkey et al. (higher in age group between 15-30 years) in Kathmandu and Sharma et al. (28.33±15.2 )in Dhulikhel, Nepal4,15. However, another study conducted by Malla et al. in Kathmandu found higher prevalence in children (35% in age group 0-9 and 31.8% in 10-19 years)16.

We found enteric fever was more prevalent in males (54% in MTH and 55% in WRH) in data from both hospitals, which is similar to studies conducted by Karkey et al. (higher in age group between 15-30 years) in Kathmandu and Sharma et al. (28.33±15.2 )in Dhulikhel, Nepal4,15. However, another study conducted by Malla et al. in Kathmandu found higher prevalence in children (35% in age group 0-9 and 31.8% in 10-19 years)16.

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### Duration of Hospital Stay:

Outcomes in the treatment of enteric fever were described as excellent in a European study20. The duration of the given treatment varied from person to person, and was based on the type of antibiotic therapy. In our present study, the mean duration of hospital stay was 3.74 ±1.58 in WRH and 5.64 ±2.34 in MTH. However, in a study conducted by Walia et al. in India found the duration of stay in the hospital to be around 8.2-12.1 with different treatment regimens and another study conducted by Farmakiotis D et al. in travelers found that the median duration of hospital stay was 7 days21, 22.

### Medicines Used in the Treatment:

Antibiotics remain the mainstay of treatment of enteric fever. Other medicines are merely symptomatic treatment. In our study, other concurrent medicines used were drugs used in GIT, drugs used in skeleton-muscular system, drug used on nervous system etc. Although we did not find a similar study on concurrent medication in enteric fever, a study conducted by Sharma et al. in Dhulikhel found common symptoms like fever, headache, chills, vomiting, cough, pain abdomen, diarrhea, constipation and disorientation which suggests the use of above mentioned class of drugs15. A review article on management of typhoid fever advocates use of tepid baths and sponging rather than use of NSAID23.

### Appropriateness of Antibiotics

**Discussion:**

**Demography patients with enteric fever:**

Enteric fever is highly prevalent in Asian Sub-continent. In this study, the mean age of the patients suffering from enteric fever in two hospitals were 22.81±20.52 and 29.13 ±17.84 in WRH and MTH respectively which is similar to studies conducted by Karkey et al. (higher in age group between 15-30 years) in Kathmandu and Sharma et al. (28.33±15.2 )in Dhulikhel, Nepal4,15. However, another study conducted by Malla et al. in Kathmandu found higher prevalence in children (35% in age group 0-9 and 31.8% in 10-19 years)16.

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in WRH and 2.13±1.11 in MTH which was not significantly different (P = 0.015). These suggest the overuse of antibiotics in the treatment of enteric fever in both of the hospitals. WHO guidelines for the treatment of enteric fever advocates the use of fluoroquinolone as first line therapy even in severe enteric fever 14. In contrast, majority of patients from either hospital received Ceftriaxone as first line therapy in the present study indicating indiscriminate use of newer generation antibiotics.

**Conclusion**

Our founding suggests that more than thirty percent of patients in both hospitals treated for enteric fever received inappropriate antibiotics. Expensiveness, prescribing higher generation antibiotics and duplication with antibiotics were common types of inappropriateness. It is well known fact that inappropriate use of antibiotic leads to antibiotic resistance, so such practice needs to be discouraged. Hence, we believe that this study will help in planning and determining types of intervention and we recommend future educational and managerial interventions to improve appropriateness.

**Limitation of the study**

Due to unavailability of established hospital guidelines, we have used WHO guidelines to assess the appropriateness, and is the main limitation of this study.

**Future scope of study**

An interventional study using local established guideline will be helpful in increasing appropriateness of drug therapy.

**Acknowledgment**

The authors acknowledge Mr. Anil Kumar Sah, Lecturer, CCT College, Butwal, Nepal for his whole hearted support and help in this study.

**Authors’ contributions**

All the authors in this contributed equally in designing this study to preparing the manuscript. All authors have gone through the manuscript and approved the same for publication.

**Conflict of Interests:**

The authors do not have any conflict of interest arising from the study.

**What this study adds:**

This study will provide an idea of determining appropriateness. Further it will help in planning and determining type of intervention to increase appropriateness of drug therapy.

**References**


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