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TREATMENT OF ENTERIC FEVER AND UNDIFFERENTIATED FEBRILE ILLNESS IN NEPAL: A REVIEW

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ABSTRACT: Typhoid fever and paratyphoid fever (also known as enteric fever, but collectively referred here as typhoid Fevers) are severe systemic illnesses characterized by sustained fever and abdominal symptoms. Treatment of typhoid fever becomes difficult by the development of multi-drug resistant of typhoid organisms especially to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol. In recent years, gradual development of resistance to fluoroquinolones has resulted in more challenges. Cefotaxime, ceftriaxone, Ciprofloxacin, Ofloxacin, Gatifloxacin, Co-trimoxazole, Ampicillin, Chloramphenicol, Azithromycin can be used for the treatment with the antibiotic susceptibility test. But difficulties arise with the culture negative (*i.e.* unidentified febrile illness). A larger study enrolling 10153 patients in Bheri Zonal Hospital and Nepalgunj Medical College in western Nepal reported that 23.45% and 31.77% cases respectively were most prevalent during June-August season. An antibiotic susceptibility was also carried out in B P Koirala Institute of Health Sciences, Dharan eastern Nepal, reported that none of the isolates were resistant to ciprofloxacin. Researchers reported that in Patan hospital no characteristics clearly distinguished typhus patients from those with blood culture-positive enteric fever. Across different region of the country there are different treatment patterns.

INTRODUCTION: Lack of access to these essential basic services like safe drinking water contributes substantially to high burden of disease like typhoid fever. Moreover, municipal water supply was found to be contaminated with sewage. Nepal is the low income (GDP per capita 689.81 USD in 2015) and earthquake of May 2015 increased the incidence of typhoid fever especially in those communities who have a temporary shelter in tent¹⁻³.

Post earth quake conditions, increases the risk of an enteric fever, especially school age children are more affected. Fortunately proper treatment had reduced the fatality from 20% to 1-4%⁴. Clean drinking water, proper hygiene and sanitation, antimicrobial therapy and vaccination program would control the enteric fever.

Chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole were traditional first-line drugs where as Azithromycin and Ceftriaxone are the most commonly used drugs in these days⁵. There are controversial reports that third-generation cephalosporins are inferior to gatifloxacin having slow clinical improvement and high relapse burden in treating enteric fever⁶. But that new Fluoroquinolones - gatifloxacin was found to be resistant against *S. typhi* (subclade of H 58)^{7,8}.

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As a challenge, chromosomal mutations, acquisition IncHI1 plasmids are responsible to become the drug resistant especially against fluoroquinolones^{5, 7}. There are 27 millions new infections of enteric fever each year in Asia and Africa. Chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin are already resistant to microorganisms and fluoroquinolones such as ciprofloxacin and ofloxacin are now widespread in Asia and Africa and found to be resistance. Enteric fever was treated effectively with Azithromycin is 5-7 days course⁹.

A RCT was conducted comparing gatifloxacin (10 mg/kg/day) and Ofloxacin (20 mg/kg/day) of 7 days course for treating enteric fever in Patan Hospital, a 450-bed teaching hospital within the Kathmandu Valley, Nepal. The researchers reported the evidence of acute murine typhus in 21 of 125 (17%) patients, with 12 of 21 (57%) patient's polymerase chain reaction (PCR)-positive for *Rickettsia typhi* and one each of the unidentified febrile case was due to seropositive for Hantavirus and seropositive for Q fever respectively. Doxycycline was effective in case of murine typhus¹⁰. A genome-wide association study of 432 individuals confirms enteric fever with positive blood culture. They found a strong association at rs 7765379 (odds ratio (OR) for the minor allele = 0.18, P = 4.5 × 10(-10), a marker mapping to the HLA class II region, in proximity to HLA-DQB1 from the samples of Nepal and Vietnam.

They concluded that HLA-DRB1- a major contributor to resistance against enteric fever, presumably through antigen presentation¹¹. Researcher concluded that Gatifloxacin was not superior to Ofloxacin in preventing failure of treatment, but use of gatifloxacin did result in more prompt fever clearance time compared to Ofloxacin^{12,13}. Chloramphenicol is a gold standard as a cheap and effective drug for enteric fever but is limited by the need for four-times a day frequency and duration of at least 14 days to prevent relapse. Availability of low quality and substandard drugs in the endemic area of enteric fever and availability of antibiotics without prescription are the main determinant of resistance development. Easy availability and affordability of fluoroquinolones is another problem. Azithromycin is a good alternative in chloramphenicol resistant stamps¹⁴.

MATERIALS AND METHODS: We searched using the following terms: typhoid fever in Nepal or Typhoid treatment in Nepal, MDR Typhoid in Nepal and Journal Article English (lang) in NepJOL (Nepal Journal Online), PubMed. We also searched Goggle Chrome, HINARI. Reports were obtained from the references of the articles used for analysis. Inclusion criteria for published studies were subjects who were assessed for the study of Typhoid causing organisms' serotype as well as the antibiotic susceptibility and medication treatment. Articles were reviewed if they were original research and the review articles or case report from any part of Nepal. The review was limited to English language articles published in scientific literature from any part of the world. We used articles published up to September 2016. Exclusion criteria were studies that reported the cases outside Nepal and containing only genomic studies. The articles identified were reviewed. Data obtained included location in Nepal, serotype of the organism, antibiotic susceptibility and medication used for the treatment of typhoid fever as well as unidentified febrile illness.

RESULTS AND DISCUSSION: The searches were carried out on different times starting from First June 2016 to Oct 3rd 2016 (PubMed Goggle Chrome, HINARI). 46 studies were retrieved initially. After removing duplicate studies, 34 remained, of which 9 were removed after reading their titles and/or abstracts. The entire texts of the 25 remaining studies were reviewed, of which 23 passed all exclusion criteria and met all inclusion criteria. All studies were from Nepal and cover one or other aspects of the management and treatment of typhoid fever and undifferentiated febrile illness in Nepal.

Due to the whispered multidrug resistance, physicians are much more dependent on fluoroquinolones for the management of enteric fever. But researchers reported the resistant isolate of *Salmonella enterica* serovar *typhi* that has serious implications for long term efficacy of this group of medication for the management of enteric fever^{15, 16}. One of the studies done in Chitwan Nepal demonstrated 100% susceptibility against *Salmonella paratyphi* A to Amikacin, Chloramphenicol and Ofloxacin while it was least susceptible to Ampicillin whereas *Salmonella typhi*

was highly susceptible to Ceftriaxone (94.1%) followed by Ofloxacin (90.9%) and Cefotaxime (90%). It was also least susceptible to Ampicillin (29.4%). The same study demonstrates the multidrug resistance was found to be 16.66% among the *Salmonella typhi* isolates¹⁷. A study from Dhulikhel Hospital, Nepal reported that Widal test and blood culture for *Salmonella typhi* were positive in 59% and 49% cases respectively. The fever clearance time was significantly better with ofloxacin compared to ciprofloxacin ($p < 0.05$) and ceftriaxone compared to chloramphenicol ($p < 0.05$). The release from treatment was significantly shorter with ceftriaxone compared to ofloxacin, ciprofloxacin and chloramphenicol ($p < 0.01$). Ceftriaxone was found to be 100% sensitive to *salmonella typhi*. Amoxicillin was only 52.1% sensitive to *Salmonella typhi*¹⁸. Another study of the same hospital reported that all of the *S. typhi* isolates were sensitive to amoxicillin-clavulanic acid. More than 95% of the isolates were sensitive to chloramphenicol, ceftazidime, ceftriaxone, and cotrimoxazole. In addition, 1.7% of the studied isolates showed multiple drug resistance patterns¹⁹.

A study with 4657 patient's blood samples in Bheri Zonal Hospital and 5496 patient's blood samples in Nepalgunj Medical College at western Nepal²⁰ found that 23.45% and 31.77% cases respectively were most prevalent during June-August season. An antibiotic susceptibility was also carried out in B P Koirala Institute of Health Sciences, Dharan eastern Nepal²¹, reported with special reference to multidrug resistance, susceptibility to ciprofloxacin and bacteriophage typing of *Salmonella enterica* serotype *typhi* isolated from blood sent for culture. Out of 132 strains of *S. enterica typhi*, isolated from 2,568 blood culture samples collected from the suspected enteric fever, were tested for susceptibility and 35 were multidrug-resistant strains. None of the isolates were resistant to ciprofloxacin.

Another study done in Patan Hospital reported that no characteristics clearly distinguished typhus patients from those with blood culture-positive enteric fever²². A study done in Birendra hospital Kathmandu reported that Ofloxacin was most sensitive antibiotic in 95.23 % cases followed by third generation cephalosporins (Ceftriaxone and Cefixime) in 90.47 % cases. Researchers concluded

that third generation cephalosporins may be the alternative for the treatment of fluoroquinolone resistant typhoid fever²³. On the reference to these facts we reviewed current treatment pattern of typhoid fever in Nepal.

CONCLUSION: Treatment paradigm has shifted to use of quinolones and third generation cephalosporins in occasion of multidrug resistant typhoid fever. There are scattered reports of resistance, treatment pattern and outcomes by these alternative agents. Within fluoroquinolones ofloxacin seems to be more susceptible compared to ciprofloxacin. Researcher from Nepal also founded Gatifloxacin was not superior to ofloxacin in preventing failure of treatment, but use of gatifloxacin did result in more prompt fever clearance time compared to ofloxacin. In some cases cephalosporins are highly susceptible comparing to ofloxacin. Amoxicillin and clavulanate in some areas are still 100% susceptible. We want to mark the fact that ofloxacin and in alternative ceftriaxone has been tried for such illness with success. More research has to be needed to make definitive conclusion and to add value for evidence based medicine practice.

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REFERENCES:

1. Karkey A, Jombart T, Walker AW, Thompson CN, Torres A, Dongol S, Thieu NT, Thanh DP, Ngoc DT, Vinh PV, Singer AC, Parkhill J, Thwaites G, Basnyat B, Ferguson N and Bake S: The Ecological Dynamics of Fecal Contamination and *Salmonella typhi* and *Salmonella paratyphi A* in Municipal Kathmandu Drinking Water, PLoS Neglected tropical disease 2016;10(1): 1-18.
2. Karkey A, Thompson CN, Thieu NT, Dongol S, Phuong TL and Vinh PV: Differential Epidemiology of *Salmonella typhi* and *paratyphi A* in Kathmandu, Nepal: A Matched Case Control Investigation in a Highly Endemic Enteric Fever Setting, PLoS Neglected tropical disease 2013; 7(8): e2391.
3. World Bank report - data.worldbank.org/country/Nepal.
4. Basnet B: Tackle Nepal's typhoid problem now, Nature. 2015; 524: 267.

5. Wong VK, Baker S, Pickard DJ, Parkhill J, Page AJ, Feasey NA, Kingsley RA, Thomson NR, *et al.*: Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella typhi* identifies inter- and intracontinental transmission events. HHS public Access 2015; 47(6): 632-9.
6. Arjyal A, Basnyat B, Nhan HT, Koirala S, Giri A, Joshi N, *et al.*: Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. Lancet Infect Dis. 2016; 16(5): 535-45.
7. Thanh DP, Karkey A, Dongol S, Ho Thi N, Thompson CN and Rabaa MA: A novel ciprofloxacin-resistant subclade of H58 *Salmonella typhi* is associated with fluoroquinolone treatment failure. E Life 2016; 5: 1-13.
8. Arjyal A, Basnyat B, Koirala S, Karkey A, Dongol S, Agrawaal KK, Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial. The Lancet Infectious diseases 2011; 11(6): 445-54.
9. Parry CM, Thieu NT, Dolecek C, Karkey A and Gupta R: Clinically and Microbiologically Derived Azithromycin Susceptibility Breakpoints for *Salmonella enterica* Serovars *typhi* and *Paratyphi* A, Antimicrob. Agents Chemother. 2015; 59(5): 2756-64.
10. Thompson CN, Blacksell SD, Paris DH, Arjyal A, Karkey A and Dongol S: Undifferentiated Febrile Illness in Kathmandu, Nepal, The American journal of tropical medicine and Hygiene. 2015; 92(4): 875-8.
11. Dunstan SJ, Hue NT, Han B, Li Z, Tram TT, Sim KS and Parry CM: Variation at HLA-DRB1 is associated with resistance to enteric fever. Nat Genet 2014; 46(12): 1333-6.
12. Koirala S, Basnyat B, Arjyal A, Shilpakar O, Shrestha K and Shrestha R: Gatifloxacin Versus Ofloxacin for the Treatment of Uncomplicated Enteric Fever in Nepal: An Open-Label, Randomized, Controlled Trial. PLoS Negl Trop Dis 2013; 7(10): e2523.
13. Prajapati B, Rai GK, Rai SK, Upreti HC, Thapa M and Singh G: Prevalence of *Salmonella typhi* and *paratyphi* infection in children: a hospital based study. Nepal Med Coll J. 2008; 10(4): 238-41.
14. Parry CM, Basnyat B and Crump JA: The management of antimicrobial resistant enteric fever. Expert Review of Anti-infective Therapy 2013; 11(12): 1259-61.
15. Koiralaa KD, Thanhb DP, Thapaa SD, Arjyala A, Karkeya A and Dongola S: Highly Resistant *Salmonella enterica* Serovar *typhi* with a Novel gyr-A Mutation Raises Questions about the Long-Term Efficacy of Older Fluoroquinolones for Treating Typhoid Fever, Antimicrob Agents Chemother. 2012; 56(5): 2761-2.
16. Global Antibiotic Resistance Partnership- Nepal Situation Analysis and Recommendations, Nepal Public Health Foundation (NPHF) and the Center for Disease Dynamics, Economics & Policy (CDDEP) 2015; 61-62.
17. Acharya A, Nepal HP, Gautam R and Shrestha S: Enteric Fever Pathogens and Their antibiotic Susceptibility Patterns in Chitwan, Nepal, Journal of Chitwan Medical College 2012; 1(2): 26-30.
18. Sharma NP, Koju R, Karmacharya BM and Adhikari D: Typhoid fever in Dhulikhel hospital, Nepal, Kathmandu University Medical Journal. 2004; 2(3): 188-92
19. Acharya D, Trakulsomboon S, Madhup SK and Korbsrisate S: Antibiotic susceptibility pattern and the indicator of decreased ciprofloxacin susceptibility of *Salmonella enterica* serovar *typhi* isolated from Dhulikhel Hospital, Nepal. Jpn J Infect Dis. 2012; 65(3): 264-7.
20. Shah GJ and Poudel TP: A Study of Typhoid Fever in Bheri Zonal Hospital and Nepalgunj Medical College Teaching Hospital, Banke, Nepal. JHAS 2013; 3(1): 31-34.
21. Khanal B, Sharma SK, Bhattacharya SK, Bhattarai NR and Kanungo DB: Antimicrobial Susceptibility Patterns of *Salmonella enterica* Serotype *typhi* in Eastern Nepal, J Health Popul Nutr. 2007; 25(1): 82-7.
22. Zimmerman MD, Murdoch, Rozmajzl PJ, Basnyat B, Woods CW and Richards AL: *Murine typhus* and Febrile Illness, Nepal. Emerg Infect Dis 2008; 14(10): 1656-9.
23. Singh UK, Neopane AK, Thapa M, Aryal N and Agrawal K: *Salmonella typhi* Infections and Effect of Fluoroquinolones and Third Generation Cephalosporin in Clinical Outcome. Journal of Nepal Paediatric Society 2011; 31(3): 216-21.

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