

Effectiveness of Presumptive Treatment of Acute Febrile Illness with Doxycycline or Azithromycin in Preventing Acute Encephalitis Syndrome in Gorakhpur, India: A Cohort Study

JEROMIE WESLEY VIVIAN THANGARAJ¹, KAMRAN ZAMAN², VISHAL SHETE¹, ASHOK KUMAR PANDEY², SARAVANAKUMAR VELUSAMY¹, AVINASH DEOSHATWAR³, MAHIMA MITTAL⁴, NIVEDITA GUPTA⁵ AND MANOJ MURHEKAR¹
 From ¹ICMR-National Institute of Epidemiology, Chennai; ²ICMR- Regional Medical Research Centre, Gorakhpur; ³ICMR- National Institute of Virology, Pune; ⁴Baba Raghav Das Medical College, Gorakhpur; and ⁵India and ⁵Indian Council of Medical Research, (ICMR), New Delhi; India.

Correspondence to: Dr Manoj Murhekar, ICMR- National Institute of Epidemiology, Chennai, India. mmurhekar@nieicmr.org.in.

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Objective: To estimate effectiveness of presumptive doxycycline or Azithromycin treatment in preventing progression of Acute Febrile Illness to Acute Encephalitis Syndrome in Gorakhpur.

Study Design: Prospective Cohort study.

Study Setting: Primary Healthcare Centers and Community Healthcare Centers of Gorakhpur district, Uttar Pradesh.

Participants: Children aged 1 year to less than 15 years with fever of 3 days to less than 15 days duration attending three selected peripheral health facilities in Gorakhpur during August to October, 2018.

Procedure: 35 medical officers in three selected Primary healthcare centers/Community healthcare centers were sensitized on the treatment strategy. After sensitization, study participants were enrolled and information about prescription of doxycycline or azithromycin was collected. Participants were telephonically followed-up to know their progression status from acute febrile illness to acute encephalitis syndrome.

Main outcome measure: Incidence of acute encephalitis syndrome among acute febrile illness patients who received

presumptive doxycycline or azithromycin treatment and those who did not receive this treatment.

Results: Of the enrolled 930 acute febrile illness patients, 801 (86%) were prescribed doxycycline or azithromycin and 725 (78%) could be telephonically followed-up. Progression to acute encephalitis syndrome was seen in 6 of the 621 patients who received presumptive treatment, and 5 of the 124 who did not receive the treatment. The relative risk of developing acute encephalitis syndrome among acute febrile illness patients who were prescribed presumptive treatment with doxycycline or azithromycin was 0.20 (95% CI: 0.06-0.65). The effectiveness of presumptive treatment with doxycycline or azithromycin strategy was 79.9% (95% CI: 35.4-94).

Conclusion: Presumptive doxycycline or azithromycin treatment to children presenting with fever in peripheral health facilities of the study blocks in Gorakhpur during August-November, 2018 was effective in preventing progression of acute febrile illness to acute encephalitis syndrome.

Keywords: Acute undifferentiated febrile illness, Japanese encephalitis, Management, Scrub typhus.

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Seasonal outbreaks of acute encephalitis syndrome (AES) have been occurring in four districts of Gorakhpur and three districts of Basti division of Uttar Pradesh, India since last four decades [1-3]. These outbreaks occur during monsoon and post-monsoon season every year, with cases peaking during August and September, before declining in late November. Outbreaks predominantly affect children aged less than 15 years and are associated with high case fatality ratios, ranging between 15 to 25% [3,4]. Japanese encephalitis accounts for less than 10% of AES cases, while the etiology of remaining AES cases remained largely unknown [5]. Studies conducted during

2014 – 2017 outbreaks revealed presence of IgM antibodies against *Orientia tsutsugamushi* in about two thirds of AES cases, suggesting scrub typhus as the major etiology of AES outbreaks [6-9]. Entomological studies have also confirmed transmission of scrub typhus pathogen in this region [10].

Accompanying Editorial in print issue.

Most scrub typhus infections are subclinical, only a few children develop febrile illness and a small proportion of these patients develop neurological manifestations [9,11]. Hence, early administration of appropriate antibiotics is crucial in preventing progression of acute

febrile illness (AFI) due to scrub typhus to AES. Based on the epidemiological, serological and entomological findings, the Indian Council of Medical Research (ICMR) in consultation with various stakeholders developed strategies for prevention and control of AES for each tier of health care system in Eastern Uttar Pradesh, focusing on early diagnosis based on clinical as well laboratory investigations and appropriate treatment with doxycycline or azithromycin (ICMR, Unpublished document). For peripheral health facilities, the recommended strategy is to investigate AFI patient for various etiologies including Japanese encephalitis virus, dengue, scrub typhus, leptospirosis and malaria as per feasibility, and treat appropriately. In case facilities for laboratory investigations are not available, which is the case in most peripheral facilities in Gorakhpur division, it was recommended that patient presenting with fever of three or more days duration during August-November (when AES cases peak) be presumptively treated with either doxycycline or azithromycin, based on clinical suspicion. In 2016, Government of Uttar Pradesh issued guidelines to the health facilities of districts in Gorakhpur division for this presumptive treatment [12]. We conducted this study in selected peripheral health facilities in Gorakhpur district during an outbreak season in 2018 to estimate the effectiveness of presumptive doxycycline or azithromycin (PDA) treatment strategy in preventing progression of acute febrile illness to AES.

We conducted the study in three blocks (administrative subunit) (Bhathat, Campierganj and Jangal Kaudia) in Gorakhpur district. As per the AES surveillance data from BRD Medical College, Gorakhpur, these blocks, together accounted for 17% of the AES patients reported from Gorakhpur division during 2016-2017. The primary health care in these blocks is delivered through three community health centers (CHCs), 9 primary health centers (PHCs) and 82 health sub-centers (HSCs), whereas the district hospital, Gorakhpur and BRD Medical College, Gorakhpur, respectively are the secondary-care and tertiary-care hospitals in the public sector in the district.

We sensitized 35 medical officers (including three pediatricians) and seven pharmacists from all the primary/community health centers in the three blocks about etiology of AES in the region. We planned the sensitization meetings separately in each of the three study sites. We sensitized the medical officers in a face-to-face two hour training session, explaining the AES scenario in Gorakhpur division, findings of investigations conducted to know the etiology of AES in Gorakhpur, and the rationale for the presumptive treatment along with treatment algorithm for

management of acute febrile illness (AFI) including dosage of doxycycline or azithromycin by weight as well as age. The recommended dosage was 4.5 mg/kg/day in two divided doses for five days for doxycycline and 10 mg/kg/day in single dose for five days for azithromycin [13]. Other than sensitization of Medical Officers about the PDA treatment strategy, the study team did not influence the prescription pattern.

This cohort study was conducted in three health facilities during August to October, 2018. The Institutional ethics committee of the ICMR-National Institute of Epidemiology, Chennai approved the study protocol. We enrolled all patients aged between 1 to less than 15 years with fever of three or more days to less than 15 days (Acute febrile illness, AFI) duration presenting to the outpatient departments of the selected health facilities. All AFI patients were referred to the study team stationed at the PHCs/CHCs, after they had completed the consultation with medical officers and had received the prescribed medicine at the pharmacy. We enrolled AFI patients after taking informed written consent from their accompanying caregivers. We collected their demographic information and clinical details. We extracted information about prescription of doxycycline or azithromycin from the medical prescription, and whether the drug was dispensed. We telephonically followed-up AFI patients three days and five days after attending the health facility to collect information about consumption of doxycycline or azithromycin, and their clinical status including recovery, and improvement or worsening of clinical condition. For children who did not improve or recover, we continued the follow-up beyond day 5.

AFI patient with change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) new onset of seizures (excluding simple febrile seizures) were considered as a patients of AES [14]. For children who progressed to AES, we collected information about the new symptoms and treatment sought, including hospitalization. We visited all patients who were hospitalized, collected information about their clinical and laboratory investigations. These patients' sera were tested for presence of immuno-globulin-M antibodies against *O. tsutsugamushi* using commercial ELISA (Scrub Typhus Detect, Inbios International Inc, Seattle, USA).

Statistical analyses: We compared the incidence of AES among AFI patients who received PDA treatment with that of AFI patients who did not receive PDA, by calculating the relative risk (RR) and its 95% confidence interval (CI). The effectiveness of PDA treatment

strategy was calculated by 1-RR formula [15]. We also calculated relative risk of developing AES among Acute undifferentiated febrile illness (AUI) patients who were prescribed PDA. We conducted sensitivity analysis to account for uncertainty of the outcomes among AUI patients who could not be followed up. We considered three assumptions: incidence of AES among patients who received and who did not receive PDA treatment was same, as found in our study; none of the patients lost to follow-up progressed to AES; and all patients lost to follow-up progressed to AES.

RESULTS

During August to October, 2018, we enrolled 930 AUI patients from three health facilities in the study. Of these, 560 (60%) had consulted a private practitioner before attending the public health facility. Majority (83%) of them had visited traditional healers in their nearby villages for the initial febrile illness episode. At public health facilities, 801 (86%) were prescribed doxycycline or azithromycin.

The mean age of AUI patients who received doxycycline or azithromycin was higher than those who did not receive doxycycline or azithromycin (7.5 vs 6.2 years, $P=0.001$). The median (IQR) duration of fever in both the groups was 5 days (range 4-7 days). The proportion of AUI patients who were prescribed PDA ranged between 76.4% (Campierganj) to 92.7% (Jangal Kaudiya).

We could telephonically follow-up 725 (78%) AUI patients. Of these, 621 (85.6%) had received doxycycline

or azithromycin treatment – 489 (78.7%) received azithromycin and 132 (21.3%) received doxycycline (**Fig. 1**). The remaining 97 (13.4%) received other antibiotics (Fluoroquinolones, 41; penicillin derivatives 31; cephalosporin, 13; and sulfonamide, 12) while 7 (1%) did not receive any antibiotics.

Six of the 621 AUI patients who received PDA treatment and five of the 104 who did not receive PDA treatment progressed to AES (cumulative incidence 0.96% and 4.8%, respectively). The relative risk (95% CI) of developing AES among AUI patients who were prescribed PDA treatment was 0.20 (0.06-0.65). The age adjusted relative risk (95% CI) was 0.19 (0.06-0.62). The effectiveness of PDA treatment strategy was 79.9% (95% CI: 35.4-94). Two of the six AES patients who received PDA treatment and three of the five AES patients who did not receive PDA treatment had IgM antibodies against *O. tsutsugamushi*.

Of the 725 AUI patients, 454 had focal symptoms such as cough, abdominal pain, loose stools, burning micturition. The remaining 271 were considered as acute undifferentiated febrile illness (AUI). Among the 271 AUI patients, 236 (87.1%) were prescribed PDA. Three of the 236 AUI patients who received PDA treatment and three of the 35 who did not receive PDA treatment progressed to AES. The relative risk (95% CI) of developing AES among AUI patients who were prescribed PDA treatment was 0.14 (0.03-0.70).

The results of sensitivity analysis as per assumptions regarding AUI patients lost to follow-up is shown in **Table I**.

DISCUSSION

The findings of our study indicate that PDA treatment to children with AUI attending peripheral health facilities was effective in preventing progression of AUI to AES. Several studies recommend presumptive/empiric treatment with either doxycycline or azithromycin, in areas where scrub typhus is endemic to minimize risk of death and severity of the disease [16-19]. Untreated AUI due to scrub typhus progress to AES by vascular injury to meninges [20]. *O. tsutsugamushi* multiplies at the site of infected chiggers bite leading to local and systemic reactions. Dissemination is primarily by hematogenous route, the principal targets being vascular endothelial cells and circulating phagocytes leading to widespread vasculitis. Central nervous system involvement occurs as a part of systemic infection. Pathogen factors like strain type and evolution of the organism to escape host immune systems might also contribute towards progression of illness [21-24]. There were several

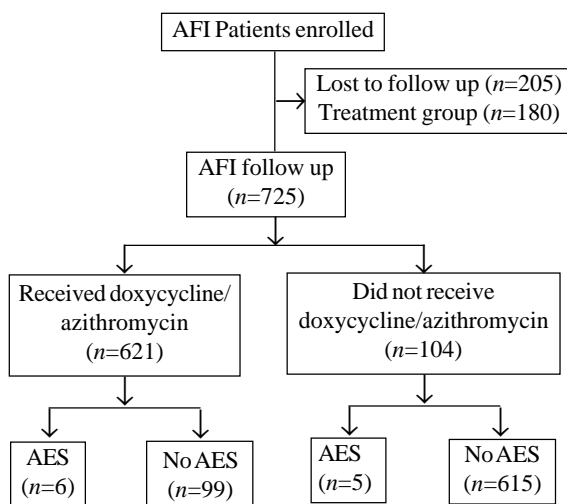


Fig. 1 Flowchart showing acute febrile illness (AFI) patients enrolled and those developing acute encephalitis syndrome (AES)

Table I Relative Risk of Progression to Acute Encephalitis Syndrome Among Acute Febrile Illness Patients Receiving Presumptive Doxycycline/Azithromycin Treatment, Gorakhpur, India, 2018

Assumption: AES incidence among patients who received and who did not receive PDA treatment was same, as found in the study

PDA	AES	No AES
Yes	8	793
No	6	123
Relative risk (95% /CI)		0.21 (0.08-0.60)

Assumption: None who was lost to follow-up progressed to AES

PDA	AES	No AES
Yes	6	795
No	5	124
Relative risk (95% /CI)		0.19 (0.06-0.62)

Assumption: All patients lost to follow-up progressed to AES

PDA	AES	No AES
Yes	186	615
No	30	99
Relative risk (95% /CI)		0.99 (0.71-1.4)

AES: Acute encephalitis syndrome; PDA: Presumptive; Doxycycline/azithromycin treatment.

reasons for considering presumptive treatment of AFI patients with doxycycline or azithromycin in Gorakhpur division. This includes lack of laboratory facilities for diagnosis of scrub typhus infection at primary care facilities. Moreover, serological tests for diagnosis becomes positive only around 5-7 days [25-27]. Other reasons include significant proportion of scrub typhus among the AFI patients, distinct seasonality of the disease during post-monsoon months, risk of progression of AFI patients to AES which is associated with high case fatality and over-burdened public health facilities. Over-reliance on traditional healers in rural areas might result in delay in reporting to public health facilities. There are very few studies which have attempted to estimate the effectiveness of the presumptive treatment with either Doxycycline or Azithromycin among AFI patients. In a study by Phimda, *et al.* [28], both doxycycline and azithromycin given empirically among adult patients with AUFI, were found to be highly effective with success rates of 96.5% and 97.4% respectively.

In our study, azithromycin was prescribed more frequently than doxycycline by medical officers. This could be due to hesitancy among medical officers to prescribe doxycycline among young children as well as lack of drug supply. DHR-ICMR guidelines recommend

doxycycline as one of the most effective antibiotics for the treatment of suspected rickettsial infections in India [13]. Also short course (<10 days) of doxycycline treatment is not associated with any increased risk of dental staining, enamel hypoplasia, or tooth color differences [29].

Our study has certain limitations. First, we followed up AFI patients telephonically and not by house to house visits. We therefore had to rely on parents' responses about treatment. Parents of all the 725 children informed that their children had consumed doxycycline or azithromycin in the prescribed doses. Second, we did not test AFI patients for scrub typhus etiology. This would have provided accurate information about incidence of AES among scrub typhus positive patients. Third, we could not follow-up 23% AFI patients who received PDA treatment and 19% patients who did not receive PDA treatment. Patients were considered lost to follow up only when we were not able to contact patients either at day 3 or day 5 or beyond. We conducted a sensitivity analysis to account for uncertainty of the outcomes among patients who were lost to follow-up. of the three assumptions, two assumptions indicated a protective effect for PDA treatment strategy, while the third assumption was remotely possible. Fourth, since the PDA has been recommended for AFI patients in public health facilities and already been rolled out, it was not possible to evaluate its efficacy using a clinical trial design.

Prescribing doxycycline or azithromycin presumptively, to children presenting with fever in peripheral health facilities between July and November could reduce AES burden by preventing progression of AFI to AES. The Government of Uttar Pradesh has already issued guidelines to district and block medical officers to prescribe doxycycline or azithromycin to AFI patients attending peripheral health facilities of Gorakhpur and Basti divisions. However, the strategy needs to be strengthened at the block level. The medical officers have to be repeatedly sensitized on rationale for PDA treatment among suspected scrub typhus patients. Further a close monitoring of implementation of this strategy, monitoring resistance to these antimicrobials, and ensuring adequate supply of doxycycline and azithromycin would yield higher compliance on PDA treatment strategy by the medical officers. Further, significant reduction in the disease burden due to AES in the region would require sensitizing doctors in private sector as well.

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WHAT IS ALREADY KNOWN?

- Treatment with doxycycline or azithromycin is effective in the treatment of rickettsial infections.

WHAT THIS STUDY ADDS?

- Presumptive doxycycline or azithromycin was effective in preventing progression of patients with acute febrile illness as well as acute undifferentiated febrile illness to acute encephalitis syndrome in Gorakhpur.

Ethical clearance: The study protocol was approved by the Institutional Ethics Committee of ICMR- National Institute of Epidemiology, Chennai (NIE/IHEC/201507-01, dated 18 July 2018).

Contributors: JWVT,NG,MM,MVM: conceived and designed the study; VS,AP,AD: collected data; KZ,AP: conducted laboratory investigations; SV,JWVT: analyzed the data; JWVT,MVM: prepared the first draft of the manuscript; KZ,VS,AP,SV,AD, MM,NG: provided critical inputs to revise the manuscript. All authors have seen and approved the final version of the manuscript.

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Competing interest: None stated.

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