Abstract

Objectives

Enteric fever is predominantly managed as an outpatient condition in endemic settings but there is little evidence to support this approach in non-endemic settings. This study aims to review the outcomes of outpatients treated for enteric fever at the Hospital of Tropical Diseases in London, UK.

Methods

We conducted a retrospective analysis of all patients with confirmed enteric fever between August 2009 and September 2020. Demographic, clinical, laboratory and microbiological data were collected and compared between the inpatient and outpatient populations. Outcomes investigated were complicated enteric fever, treatment failure and relapse.

Results

Overall, 93 patients (59% male, median age 31) were identified with blood and/or stool culture confirmed enteric fever and 49 (53%) of these were managed as outpatients. The commonest empirical treatment for outpatients was azithromycin (70%) and for inpatients was ceftriaxone (84%). Outpatients were more likely than inpatients to receive only one antibiotic (57% vs 19%, $p < 0.01$) and receive a shorter duration of antibiotics (median 7 vs 11 days, $p < 0.01$). There were no cases of complicated disease or relapse in either the inpatient or outpatient groups. There was one treatment failure in the outpatient group. Azithromycin was well-tolerated with no reported side effects.

Conclusions

Our findings suggest that outpatient management of uncomplicated imported enteric fever is safe and effective with the use of oral azithromycin. Careful monitoring of patients is recommended as treatment failure can occur.

Keywords

Salmonella Typhi
Salmonella Paratyphi
Enteric fever
Returning travellers
Antimicrobial resistance
Treatment

Introduction

Enteric fever is a febrile illness caused by gram-negative bacteria *Salmonella enterica* serovar Typhi or *Salmonella enterica* serovars Paratyphi A, B or C. Globally there are approximately 14 million cases of enteric fever every year and approximately 135,000 deaths (1). Highest incidence rates occur in South Asia, and in localised epidemics in sub-Saharan Africa, where it remains a significant public health problem (2). In the UK between 2014 and 2019, 2089 cases of enteric fever were notified to UK Health Security Agency (previously Public Health England, PHE) from England, Wales and Northern Ireland, of which 93-99% were travel-related, the majority returning from South Asia (3).

Patients with enteric fever usually present after a 7-14 day incubation period, with systemic symptoms such as fevers, chills, headache, malaise, myalgia and a dry cough (4). A minority of patients will later develop complications including gastrointestinal haemorrhage, intestinal perforation, encephalopathy, sepsis and shock (4,5). Risk factors for complicated disease include older age and longer time to antimicrobial treatment (4). Complication and case fatality rates vary by population studied and are reported as high as 27% and 2% respectively in certain endemic settings in the absence of effective therapy (5,6). In non-endemic settings such as the UK they are considerably lower than this at 2-8% and <1% respectively (7–9).

Outpatient management of uncomplicated enteric fever is common in endemic settings, with up to 90% of cases managed at home (4,10). However, there is minimal existing data or guidance on outpatient management of enteric fever in non-endemic settings. Previously published case series from the UK report over 80% of enteric fever patients managed as inpatients, despite the low rates of complicated disease (7–9).

This study aimed to identify whether outpatient management of enteric fever patients in a non-endemic setting is safe and associated with comparable outcomes to inpatient management at a large tertiary referral hospital in London, UK.

Materials and methods

Study design

We conducted a retrospective descriptive study of all microbiologically confirmed cases of enteric fever presenting to University College London Hospital (UCLH), from 20th August 2009 to 20th September 2020. UCLH is a large tertiary referral hospital in central London

covering both paediatrics and adult patients and comprising of multiple hospitals including The Hospital of Tropical Diseases (HTD), a specialist infectious diseases and tropical medicine hospital.

Cases of confirmed enteric fever were defined as those with a positive blood culture or a positive stool culture with a compatible clinical illness within the last 28 days. Cases from August 2009-November 2011 were identified from a prospective GDPR-compliant UCLH enteric fever database. Cases from November 2011- September 2020 were identified by searching the UCLH electronic laboratory information management system for all microbiological specimens that isolates *S*. Typhi or *S.* Paratyphi A, B or C during that period.

For each case of confirmed enteric fever, epidemiological, demographic, clinical, laboratory and microbiological criteria were gathered retrospectively from the electronic health records and the laboratory information management system WinPath. Inpatients were defined as those admitted beyond an emergency attendance. Visits to accident and emergency or the walk-in service at HTD were defined as outpatient visits. Missing data are noted in the analysis.

Complicated enteric fever was defined as enteric fever associated with severe sepsis or shock, gastrointestinal bleeding, intestinal perforation, encephalopathy or metastatic infection, consistent with other guidance (11,12). Treatment failure was defined as a positive blood culture or fever persistence > 7 days of treatment with an appropriate antibiotic. Relapse was defined as re-occurrence of symptoms confirmed with positive blood culture within 1 month of initial presentation. An appropriate antimicrobial was defined as an antimicrobial to which the isolate was susceptible by EUCAST/ BSAC criteria at the time of testing.

Microbiology

Blood culture isolates from positive BD BACTEC ™ bottles were cultured at 37°C in 5% CO_2 for 18-24 hours on blood agar and cystine lactose electrolyte-deficient agar plates. Faecal specimens were cultured under similar conditions using mannitol selenite enrichment broth and xylose lysine deoxycholate agar plates. Organisms isolated were identified as *Salmonella* enterica by API20E (bioMérieux, Marcy l'Etoile, France) until 2012 and MALDI-TOF thereafter; serovar identification was performed by serological agglutination and confirmed by Gastrointestinal Bacterial Reference Unit (GBRU), UK Health Security Agency.

Antimicrobial susceptibility was confirmed as per national guidance for Salmonella infections (BSAC from 2009-2015 and EUCAST 2016 onwards (13). Ciprofloxacin susceptibility testing was performed using ciprofloxacin disc testing and E-test MIC evaluation (Biomerieux until 2017, Liofilchem thereafter). Additional disc diffusion tests were used according to existing recommendations (nalidixic acid changed to pefloxacin disc testing from 2016). Isolates were reported as Ciprofloxacin resistant if the MIC was greater than 0.064 microgram/mL.

Azithromycin sensitivity was determined using E test strips (Biomerieux until 2016, Liofilchem 2017 onwards) with an epidemiological cut-off MIC of $\leq$ 16 mg/L used to define susceptible as per EUCAST guidelines. Other antimicrobial susceptibilities, including ceftriaxone, amoxicillin and co-trimoxazole, were determined using standard disc diffusion methods.

All isolates were sent to the GBRU for confirmation, phage typing and confirmatory susceptibility testing if required.

Statistical analysis

All data were recorded on a password protected standardised data collection spreadsheet on Microsoft Excel version 16.58. All data were analysed using Microsoft Excel and Rstudio version 1.4.1103.

Non-normally distributed continuous variables were expressed as median and interquartile range and compared using the Wilcoxon rank sum test. Categorical variables were compared using Fishers exact test. A *p* value of < 0.05 was considered significant.

Results

Demographics and epidemiology

Between August 2009 and September 2020, a total of 93 patients were identified with culture-confirmed enteric fever of which 49 (53%) were managed as outpatients (Table 1). Fifty-five patients (59%) were male and the median age was 31 years with an interquartile range of 26 – 39 years. Four children (<18 years) were included in this study, the youngest aged 4 years old.

Table 1 – Demographics and Travel

Expressed as n (%) or median [IQR]

	Inpatients	Outpatients	Total
Gender	44 (100)	49 (100)	n=93
Female	19 (43)	19 (39)	38 (41)
Male	25 (57)	30 (61)	55 (59)
Age (n= 93)	32 [22-42]	31 [27-36]	31 [26-39]
Ethnic origin	37 (100)	37 (100)	74 (100)
White	14 (38)	21 (57)	35 (47)
Asian	19 (51)	11 (30)	30 (41)
Black	1 (3)	3 (8)	4 (5)
Mixed	0 (0)	1 (3)	1 (1)
Other ethnic group	3 (8)	1 (3)	4 (5)
Place of residence	42 (100)	49 (100)	91 (100)
UK	36 (86)	47 (96)	83 (91)
Asia	6 (14)	1 (2)	7 (8)
Africa	0	1 (2)	1 (1)
Region visited	41 (100)	49 (100)	90 (100)
South Asia	30 (73)	35 (71)	65 (72)
Southeast Asia	1 (2)	2 (4)	3 (3)
West Asia	2 (5)	0	2 (6)
West Africa	0	4 (8)	4 (4)
South America	1 (2)	3 (6)	4 (4)
Multiple regions	7 (17)	5 (10)	12 (13)

Microbiology

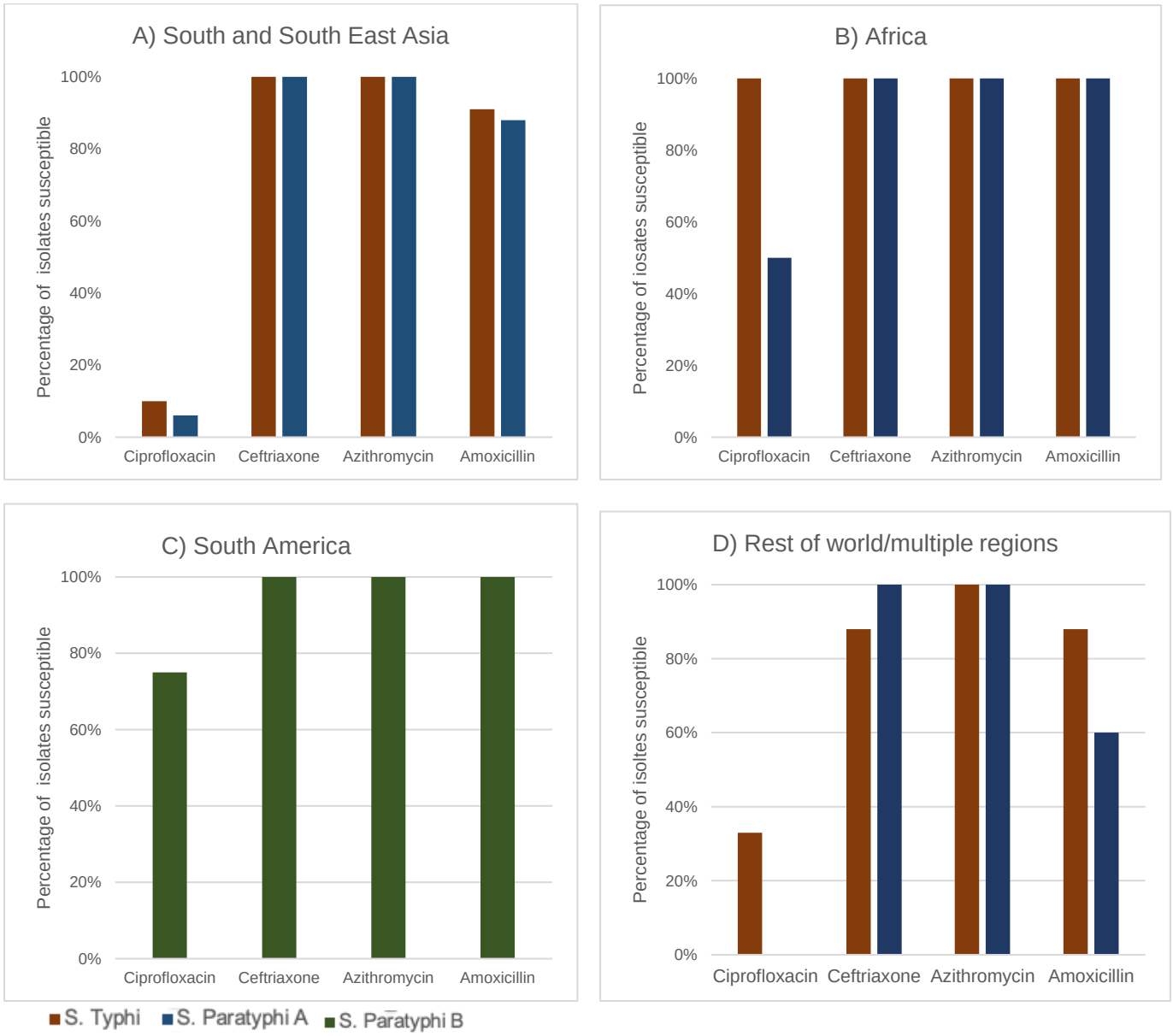
Of the 93 patients, 45 (48%) had infection with *S.* Paratyphi A, 43 (46%) with *S.* Typhi and 5 (5%) with *S.* Paratyphi B (Table 2). Patients infected with *S.* Typhi were more likely to be admitted than those with *S.* Paratyphi A (58% vs 38%, p = 0.06).

Table 2 – Microbiological features of cases of enteric fever diagnosed

	Inpatients	Outpatients	Total
Organism	44 (100)	49 (100)	93 (100)
S. Typhi	25 (57)	18 (37)	43 (46)
S. Paratyphi A	17 (39)	28 (57)	45 (48)
S. Paratyphi B	2 (5)	3 (6)	5 (5)
Positive culture	44 (100)	49 (100)	93 (100)
Blood culture (+/- stool)	40 (91)	43 (88)	83 (89)
Stool culture only	4 (9)	6 (12)	10 (11)

Antimicrobial susceptibilities are summarised in Figure 1. One isolate, in which the patient had travelled to Iraq, had a ceftriaxone minimum inhibitory concentration (MIC) of > 256 ug/L which was confirmed to be an extended-spectrum beta-lactamase (ESBL) *S.* Typhi (14). Confirmed azithromycin susceptibility was available for 75 samples. Thirteen of these isolates (17%) were initially reported as azithromycin resistant via in-house MIC gradient strip testing but were later confirmed by the reference laboratory as fully susceptible.

Figure 1: Confirmed antimicrobial susceptibilities to enteric fever pathogens in a cohort of patients with confirmed enteric fever from HTD, by region



Clinical features and laboratory parameters on presentation

Symptoms and laboratory findings are summarised in tables 3 and 4. Common laboratory abnormalities at presentation included a raised CRP (100%), raised alanine transferase (ALT) (64%), lymphopenia (59%) and thrombocytopaenia (27%). Inpatients had a higher CRP (median 97 mg/dL vs 49 mg/dL, p <0.01) and higher ALT (median 82 U/L vs 47 U/L, p <0.01) than outpatients.

Table 3: Symptoms on first presentation

Expressed as n(%)

	Inpatient	Outpatient	Total
	n=42	n=47	n=89
Fever*	42 (100)	47 (100)	89 (100)
Diarrhoea	30 (71)	25 (53)	55 (62)
Any GI upset**	34 (81)	29 (62)	63 (71)
Headache	15 (36)	30 (64)	45 (51)
Cough	14 (33)	10 (21)	24 (27)

*defined as self-reported fever or documented fever in clinical notes

**diarrhoea, constipation, nausea or vomiting

Table 4: Laboratory results on first presentation

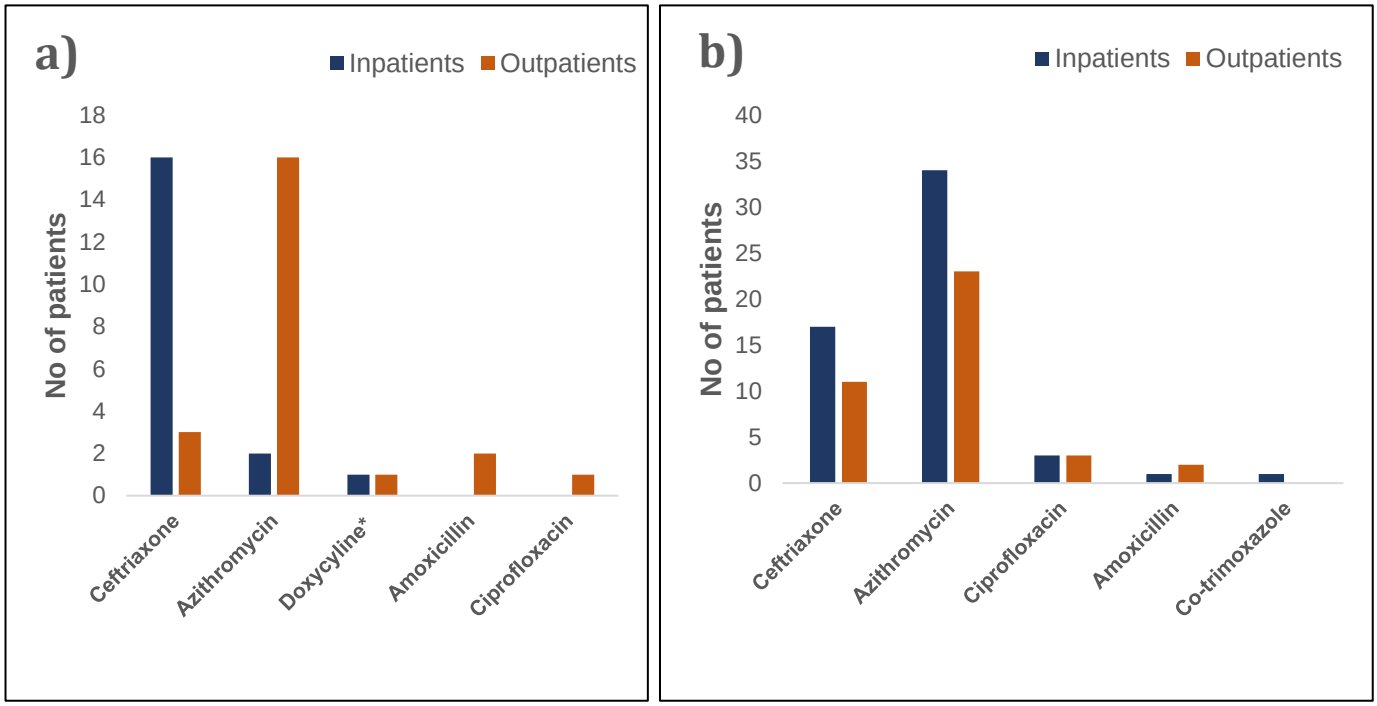
Expressed as median [IQR]

	Total	Inpatient	Outpatient	Normal ranges	p value (IP vs OP)
	n=73	n = 31	n = 42		
Haemoglobin (g/L)	138 [127-146]	133 [124-143]	138 [130-149]	M: 130-180 F: 115-165	0.06
WCC (10^9/L)	5.64 [4.67-7.12]	6.18 [4.75-7.68]	5.31 [4.63-6.73]	4.0-11	0.25
Neutrophil count (10^9/L)	3.66 [2.86 – 4.89]	3.90 [3.23-5.31]	3.28 [2.80-4.03]	1.8-7.5	0.04
Lymphocyte count (10^9/L)	1.36 [0.94 – 1.87]	1.36 [0.87-2.00]	1.35 [1.03-1.86]	1.0-4.0	0.9
Eosinophil count (10^9/L)	0.000 [0.000-0.010	0.000 [0.000-0.000]	0.000 [0.000-0.018]	0.1-0.4	0.02
Platelets (10^9/L)	192 [145 – 245]	202 [135-266]	187.5 [158-232]	140-400	0.8
C-reactive protein (mg/L)	74 [42-119]]*	97 [69-134]	49 [32-89]	< 5	<0.01
Sodium (mmol/L)	137 [134-139]*	135 [132-137]	138 [136-139]	133-136	<0.01
Creatinine (µmol/L)	73 [62-88]	73 [62-84]	74 [63-88]	M: 59-104 F: 45-84	0.6
Alanine transferase (ALT) (U/L)	55 [42-103]	82 [56-186]	47 [37-77]	M: <50 F: <35	<0.01
Maximum ALT during illness	95 [52-200]	149 [80-303]	60.5 [41-122]		<0.01
Bilirubin (µmol/L)	9 [6-12]	10 [6.5-13.5]	8 [6-10]	< 21	0.13
Albumin (g/L)	43 [39-45]	41 [37-45]	43 [41-45]	35-50	0.07
Alkaline phosphatase (IU/L)	82 [63-115]	92 [83-141]	70 [57-80]	30-130	<0.01

Treatment

Of the 93 patients, treatment details were available for 87 (94%); 43 inpatients and 44 outpatients. Commonest overall antibiotics used were oral azithromycin (756 total antibiotic days prescribed) and intravenous ceftriaxone (514 antibiotic days prescribed). Inpatients were more likely than outpatients to receive empirical ceftriaxone (84% vs 13%, p <0.01) whereas outpatients were more likely to receive empirical azithromycin than inpatients (70% vs 11%, p <0.01)

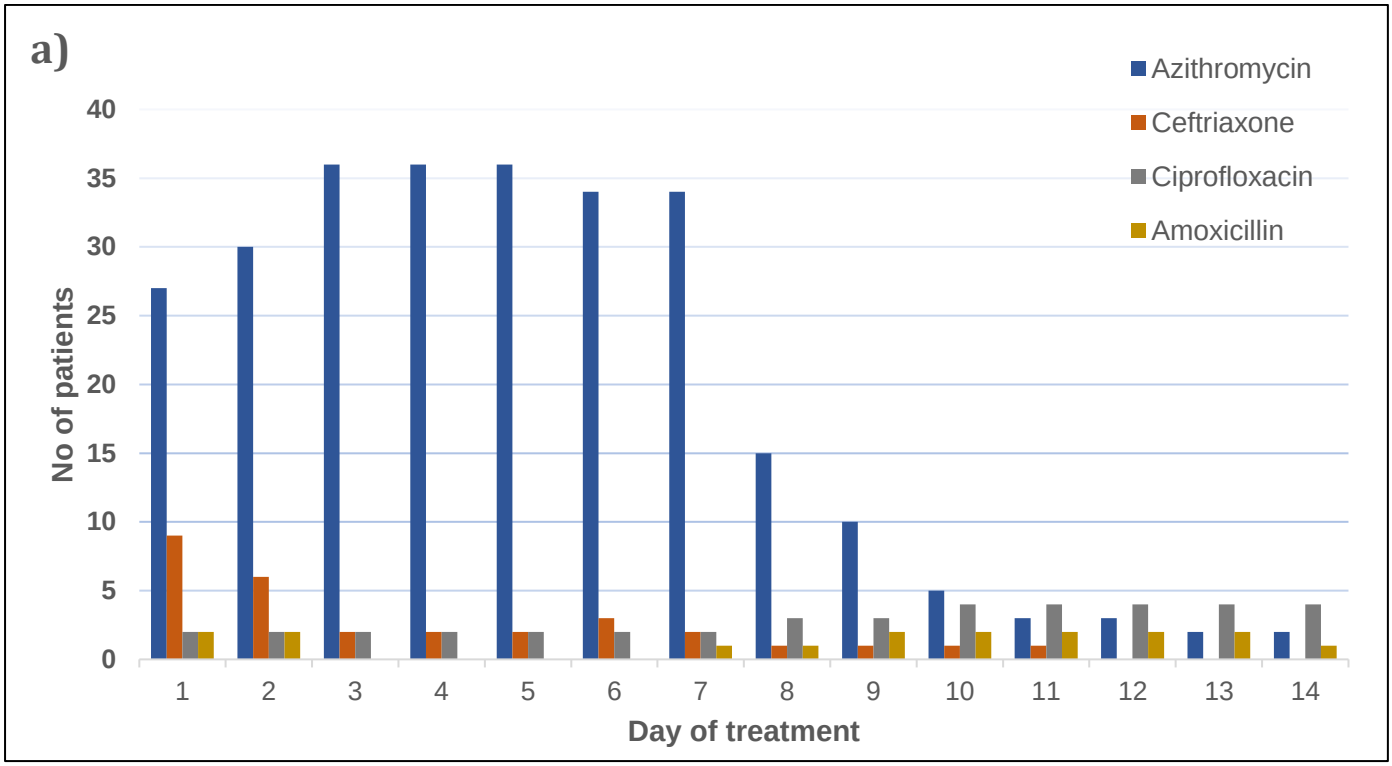
Figure 2: Empirical (a) and targeted (b) antibiotic choices in a cohort of patients with confirmed enteric fever at HTD

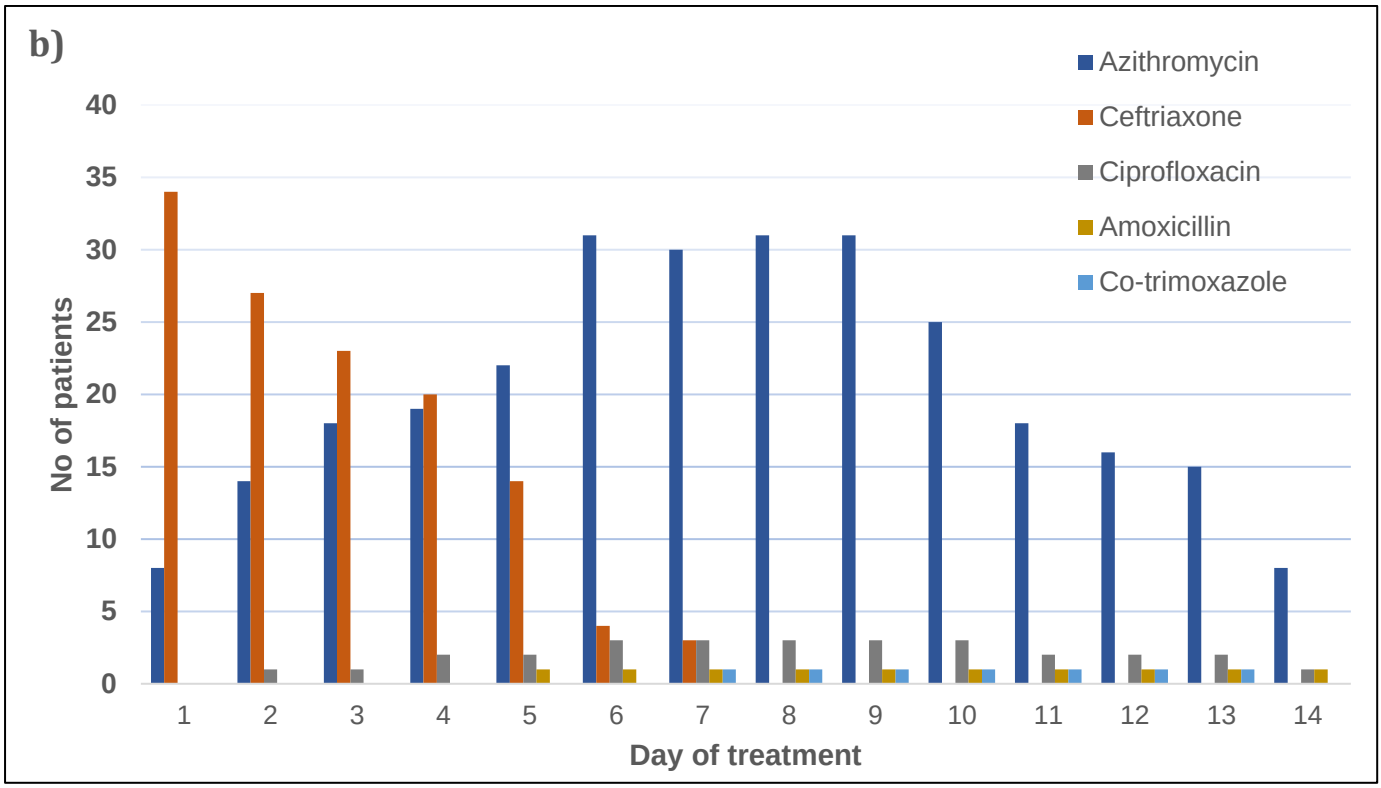


**Doxycycline was used in combination with rifampicin in one patient*

Antibiotics used in outpatients and inpatients over the first two weeks of treatment is shown in figure 3. Fourteen outpatients (32%) received ceftriaxone during their treatment course, compared to 34 inpatients (77%). One inpatient received no treatment for enteric fever whilst admitted but was treated empirically for brucellosis with doxycycline and rifampicin and stool cultures were positive for *S.* Paratyphi B post discharge.

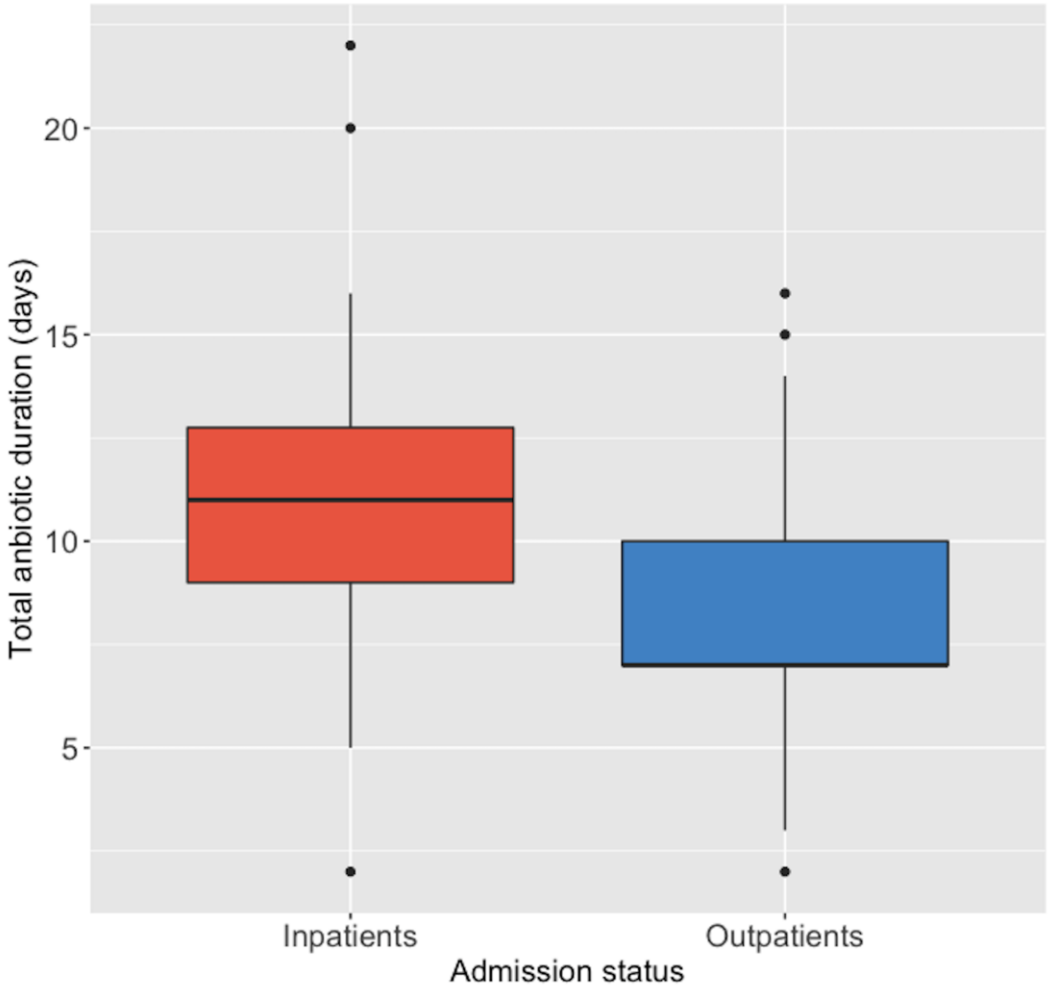
Figure 3: Timeline of antibiotics used for outpatients (a) vs inpatients (b) in a cohort of patients with confirmed enteric fever at HTD





Outpatients were more likely than inpatients to only have one antibiotic prescribed (57% vs 19%, $p < 0.01$). In addition, overall antibiotic duration was shorter in outpatients compared to inpatients (7 and 11 days, $p < 0.01$, Figure 4).

Figure 4: Total antibiotic duration by admissions status in cohort of patients with confirmed enteric fever at HTD



Outcomes

Of the 44 patients admitted to hospital, 29 were admitted on first presentation to our service (66%), and all but one patient was admitted within 3 days of first presentation (98%). Median admission was 4 days with almost a quarter of the inpatients (23%) admitted for one day or less. Two patients had short re-admissions (1 or 2 days) 1 day post initial discharge for ongoing symptoms. Of note, two patients were diagnosed with relapses having been seen and recently treated for enteric fever at other hospitals.

In this cohort 58 patients (62%) initially presented to the HTD, whereas 35 (38%) presented to the emergency department (ED). Patients were more likely to be admitted and treated as inpatients if they presented to the ED than if they presented to HTD (70% admission rate vs 33% admission rate respectively, $p < 0.01$).

There was one treatment failure in the outpatient population; a patient who was given 8 days of oral azithromycin for an azithromycin-susceptible organism but continued to have low-grade fevers at the end of the course. This patient was switched to 7 days of amoxicillin, did not require admission and made a good recovery with resolution of symptoms following the course of amoxicillin. A further two outpatients were given extended courses of azithromycin (14 days); one for ongoing fevers at day 6 of treatment and one for persistent bacteraemia at day 6 of treatment. Both made a good recovery after 14 days treatment. Two further outpatients were admitted to different hospitals for short admissions following starting oral treatment where they both received IV ceftriaxone. Both returned to our clinic two weeks later and had recovered well with no complications.

Three outpatients were switched from oral azithromycin to IV ceftriaxone due to reported azithromycin resistance. These three patients then completed courses of ciprofloxacin, amoxicillin and ceftriaxone as outpatients. A further patient was switched from azithromycin to oral ciprofloxacin for the same reason. All four of these isolates were later confirmed by the reference laboratory as azithromycin sensitive. No patients were switched from azithromycin due to side effects or intolerance.

Discussion

We conducted an 11-year retrospective review of all laboratory confirmed enteric fever cases at a large central London teaching hospital. We show that in this cohort of uncomplicated, adult patients with imported enteric fever, the majority of patients were treated as outpatients, predominantly with oral azithromycin. Those selected for outpatient management had comparable outcomes to inpatients with no recurrences or complications

and only one patient had treatment failure. To the best of our knowledge, this is the first large dataset from a non-endemic country to support outpatient management with oral antimicrobial therapy in patients with uncomplicated disease.

The demographics, epidemiology and microbiology of enteric fever in this cohort is consistent with previously reported case series and national data from the UK (3,7,8). Rates of S. Paratyphi A infection are higher than in endemic countries which may reflect increased rates typhoid vaccination amongst the traveller cohort or a large proportion of returnees from South Asia where *S*. Paratyphi A rates are highest (1,7). One case of ESBL *S*. Typhi was reported in this cohort but no XDR cases, despite some reported cases on return from Pakistan to the UK (15). As rates of ESBL and XDR enteric fever continue to rise we can expect to see this reflected in imported cases, highlighting the need for empiric XDR treatment in those returning from XDR endemic areas (11).

The cohort of patients presenting to our centre is primarily that of young adults with uncomplicated disease. Although admitted patients were more symptomatic on presentation and had higher CRP, ALT and ALP values there were no differences in outcomes between the inpatient and outpatient population. These presenting symptoms are likely to influence clinician decisions to admit patients but may not be predictive of severe or complicated disease in this population.

In this study over 50% of patients were treated as outpatients which is far higher than any other case series reported from the UK and an increase from 3% in the prior cohort from our centre (7). Potential reasons for such an increase include an expansion in outpatient infectious diseases services and staffing at our centre and increased experience and confidence in using oral azithromycin to treat drug-resistant enteric fever. In addition, this cohort included very few elderly or very young patients who are more at risk of complicated disease, perhaps contributing to the high levels of outpatient management in this setting (6).

Place of initial presentation affected admission rates in this cohort, with patients presenting to the ED more likely to be admitted than those presenting directly to the HTD infection service. This is unsurprising as patients with an undifferentiated fever, or gram-negative rods in their blood culture, presenting to the ED are likely to be managed under a ‘sepsis’ pathway and admitted through the medical take. The high rates of outpatient management in this cohort are therefore likely secondary to the significant numbers of patients directly presenting to the HTD. This highlights the importance of returning travellers, where possible,

being directed to specialist infection services early in their management, either by GPs or local hospital services, to avoid potential unnecessary admission.

In organisations without local specialist infection services, returning travellers with a fever should ideally be discussed with the regional specialist infection service to aid appropriate management. If enteric fever is confirmed or highly suspected then clinicians should be directed to the British Infection Association guidelines for diagnosis and management of enteric fever. These guidelines suggest patients with mild and uncomplicated disease and that can tolerate oral medication, can be considered for outpatient management (11). However, hospital outpatient systems are required to detect and respond to patients who might be failing treatment, which may not be feasible in all units.

Treatment strategies in this cohort were variable despite a relatively homogenous cohort of uncomplicated patients. This highlights the need for standardised antimicrobial treatment of such patients which is now available in the form of the BIA enteric fever guidance (11). Oral azithromycin was the predominant medication used to treat outpatients in this cohort and was well-tolerated. A small minority had prolonged fevers, a finding that has been confirmed in previous studies and may be due to reduced extracellular concentrations of azithromycin causing prolonged bacteraemia (16).

Prolonged fever despite appropriate antibiotics is commonly seen in enteric fever and not necessarily associated with treatment failure. Although we had one treatment failure in this cohort, azithromycin use does not appear associated with increased treatment failure rates or recurrence in comparison to other antimicrobials when compared in randomised-controlled studies (17–20). The definition of treatment failure also varies greatly between studies, and the BIA enteric fever guidelines suggest that treatment failure is considered in patients with a persistent fever AND other symptoms after seven days of effective antimicrobial therapy, persistent bacteraemia at 7 days or in those that develop complications or deteriorate at 5 days. Only at this point should an antimicrobial switch (from an antimicrobial that the isolate is known to be sensitive to) be considered. Furthermore, given that azithromycin is currently the only appropriate empiric oral treatment for enteric fever, the benefit of avoiding intravenous treatment with ceftriaxone likely outweighs the small possibility of extended fever times without associated clinical failure.

In this cohort a small number of cases were initially reported as azithromycin resistant leading to changes in antimicrobial agents. It is now well-understood that azithromycin E-tests are difficult to read due to the trailing edge of the E-test and use of a second-reader is

suggested (21). Of note, there were no azithromycin-resistant isolates reported by UKHSA in this time period (15).

Approximately a third of outpatients in this cohort received ceftriaxone at some point during their treatment course. Good outcomes have previously been seen by treating uncomplicated enteric fever patients using a course of IV ceftriaxone through Outpatient Parenteral Antibiotic Therapy (OPAT) (22). However, oral azithromycin is equally efficacious to ceftriaxone in the treatment of uncomplicated enteric fever and may reduce the risk of intravenous cannula associated complications and relapse (17,23,24). Given this, and the excellent outcomes with oral azithromycin in this population, we suggest there is minimal need for the use of outpatient ceftriaxone therapy in treating uncomplicated enteric fever. Patients with antimicrobial allergies, poor compliance or vomiting may still require intravenous therapy and patients should be individually assessed for outpatient treatment suitability.

Worldwide antimicrobial resistance to *S*. Typhi and *S*. Paratyphi A is increasing (25). Rising resistance to fluoroquinolones and now ceftriaxone has led to increasing use of azithromycin as first-line therapy for enteric fever (25–27). Concerningly, sporadic cases of azithromycin resistance have now been reported globally (28,29). Antimicrobial stewardship is therefore of vital importance in conserving remaining antimicrobial treatments against enteric fever. Outpatients in this study were treated with fewer antimicrobials and shorter durations of antimicrobials than their inpatient counterparts, despite having relatively similar characteristics and outcomes, highlighting the antimicrobial stewardship advantages of outpatient management.

This is a retrospective observational review and therefore is limited by the reliance on data documentation, potential selection bias and variability in treatment regimens used. Nonetheless this large case series does highlight important information regarding outpatient treatment of enteric fever that may help guide clinicians working in non-endemic areas.

Conclusion

In summary, patients selected for outpatient treatment of uncomplicated enteric fever at our centre had good outcomes which were comparable to those of the inpatient population. Oral azithromycin appears safe and well-tolerated and associated with low risk of treatment failure or relapse when used in the outpatient setting. Close monitoring of outpatients is advised to investigate for possible treatment failure and complications.

Authorship contributions

NM: Conceptualisation, Data curation, Methodology, Investigation, Formal Analysis, Writing – original draft, Visualisation. LN: Conceptualisation, Methodology, Data curation, Writing – reviewing and editing, Visualisation. SMJ: Methodology, Data curation, Investigation, Writing – reviewing and editing. TP: Conceptualisation, Methodology, Writing – reviewing and editing. GG: Conceptualisation, Methodology, Writing – Reviewing and editing. RH: Methodology, Writing – reviewing and editing, Visualisation. MB: Conceptualisation, Methodology, Writing – reviewing and editing, Visualisation, Supervision

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data sharing statement

All data generated or analysed during this study are published in this article

Patient consent for publication

Not required.

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