Original Article

EPIDEMIOLOGY AND OUTCOME OF *SHIGELLA*, *SALMONELLA* AND *CAMPYLOBACTER* INFECTIONS IN TRAVELLERS RETURNING FROM THE TROPICS WITH FEVER AND DIARRHOEA

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ABSTRACT

Introduction: During a study on fever after a stay in the tropics, we aimed at investigating the epidemiology and outcome of invasive bacterial enteritis due to *Shigella*, *Salmonella* or *Campylobacter* spp. in patients diagnosed with febrile traveller's diarrhoea.

Methods: From April 2000 to September 2006, we evaluated prospectively 594 travellers presenting with fever and diarrhoea within a month after a stay in the tropics. Patients not found with a systemic infection were assumed to have febrile traveller's diarrhoea (TD). Invasive bacterial enteritis was confirmed by isolation of *Shigella*, *Campylobacter* or nontyphoidal *Salmonella* in stool cultures.

Results: Systemic infections (mainly malaria) were diagnosed in 259 (44%) evaluated travellers. Invasive bacterial enteritis, either alone or with another infection, was confirmed in 114 (34%) of the 335 remaining patients with febrile TD. Aetiologies were distributed between *Campylobacter jejuni* (47, 41%), *Shigella* spp. (43, 38%), *Salmonella* spp. (22, 19%) and mixed *Campylobacter-Salmonella* infection (2, 2%). Invasive bacterial enteritis accounted for about a third of febrile TD cases occurring after a stay in sub-Saharan Africa, North Africa/Middle East or Latin America, and for half of those occurring after a travel to southern Asia (including 33% only due to *C. jejuni*). Resistance to fluoroquinolones was exclusively observed in *C. jejuni* isolates, but at an overall rate of 53%. Clinical failure occurred in 33% of the patients with *C. jejuni* infection empirically treated with a fluoroquinolone.

Conclusion: Invasive bacterial enteritis was a frequent aetiology of febrile TD. *C. jejuni* was the leading pathogen after a travel to southern Asia, and was associated with high rate of resistance to fluoroquinolones and of clinical failure.

Key words: Fever, traveller, diarrhoea, tropics, enteritis

INTRODUCTION

Fever and intestinal symptoms (mostly diarrhoea) are two leading complaints in ill travellers returning from a journey to tropical or subtropical destinations (1-3). When an international traveller presents with both symptoms concomitantly, one should consider the diagnosis of febrile traveller's diarrhoea (TD), but also of a systemic infection associated with intestinal symptoms (e.g. malaria, typhoid fever or acute schistosomiasis), and even of a systemic infection concomitant with traveller's diarrhoea (dual infection). Therefore, the initial workup of such cases should look simultaneously for common systemic and enteric travel-related infections.

Traveller's diarrhoea may affect up to 50% of the persons travelling from industrialized to developing countries, and this attack rate has remained largely unchanged since more than 50 years (4). A high proportion of TD cases remain without aetiology after thorough microbiological evaluation (40-50%), but indirect evidence suggests that bacterial enteropathogens cause up to 80% of all TD cases (4,5). Globally, the most common bacterial enteropathogens are the

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diarrhoea-producing *E. coli* (DEC), including mainly enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC) and enteropathogenic *E. coli* (EPEC). These 3 pathogens are responsible for 20-30%, 15-20% and 10-15% of all TD cases respectively, but substantial differences in prevalence are found according to the continent of acquisition (4,6). The DEC isolates are not cultured in most routine laboratories of clinical settings (7). The other important bacterial enteropathogens are *Campylobacter*, *Shigella* and nontyphoidal *Salmonella* spp., the so-called invasive bacteria causing together about 20% of all TD cases (but up to 40% in some regions). The remaining aetiologies of TD are other bacterial enteropathogens (Vibrios, *Aeromonas*, *Plesiomonas*), viruses (mainly noroviruses and rotavirus) and parasites (*Giardia*, *Entamoeba histolytica*, *Cryptosporidium*,...).

About 20% of the patients diagnosed with TD present with fever, and some of them also have dysenteric symptoms (8,9). In such cases, an inflammatory colitis is present in addition to the usual secretory alterations. Febrile traveller's diarrhoea is mostly due to the invasive bacterial enteropathogens and to a lesser extent to some strains of DEC, non-choleraic vibrios and *Aeromonas* (5,7,10,11).

Invasive bacterial enteritis due to *Shigella*, nontyphoidal *Salmonella* or *Campylobacter* spp. was found as a frequent cause of fever in returning travellers attending our centre, ranking third after malaria and respiratory infections (12). The present study reviewed the epidemiology, clinical presentation, resistance pattern and outcome of invasive bacterial enteritis in the subset of patients diagnosed with febrile traveller's diarrhoea.

MATERIALS AND METHODS

Study setting and participants

The study was conducted at the Institute of Tropical Medicine (outpatient referral centre for travel/tropical pathology) and at the University Hospital of Antwerp, Belgium. From April 2000 to September 2006, we enrolled prospectively all travellers presenting with fever (temperature ≥ 38°C, or combination of fever sensation with sweats and chills) after a stay in the tropics or subtropics (defined as any non-industrialized country at least partly situated between the 35° northern and 35° southern latitude). Aetiology of all febrile episodes were determined according to a methodology extensively described (12). Final diagnosis could be aetiological, if a pathogenic micro-organism was demonstrated in a relevant specimen or if serology against an infectious agent was definitive or strongly suggestive, or clinical if fever was undisputedly due to a specific syndrome.

Febrile traveller's diarrhoea

For the present study, we reviewed all cases having developed fever and diarrhoea during or within one month after travel. Diarrhoea was defined by the patient reporting at least two unformed stools. Standard workup was performed to look for systemic infections, and patients' faeces were processed systematically through usual microscopy (wet mount examination), parasitic examination and routine stool cultures. Patients presenting with fever and diarrhoea but not found with a systemic infection were assumed to have febrile traveller's diarrhoea. Febrile TD could be bacterial in case of isolation of an invasive enteropathogen ("confirmed bacterial enteritis") or if faecal leukocytes were found at stool examination ("suspected bacterial enteritis"), "parasitic" in the presence of a protozoan or helminthic pathogen in the faeces, or "of unknown aetiology" if no bacterial or parasitic pathogen and no faecal leukocytes could be demonstrated. Selective isolation of *Campylobacter* species was performed on Campylosel Agar (bioMérieux, Marcy-L'étoile, France) and incubated in a microaerobic atmosphere (generated by Anaerocult C, Merck, Darmstadt, Germany); for isolation of *Yersinia* stool was incubated on Yersinia CIN agar (bioMérieux); SS Agar and MacConkey Agar (bioMérieux) were used for the detection of *Shigella* and *Salmonella* and in addition, the stool was enriched on selenite at 37°C for 24 hours. For detection of *Vibrio* sp., liquid stool samples were enriched in alcaline peptone water at 37°C for 24 hours followed by incubation on Thiosulfate Citrate Bile Sucrose Agar for 24 hours. The isolates were further identified by conventional microbiological methods. Drug susceptibility was tested by disk test diffusion. Inhibition diameters were measured and interpreted according to the instructions of the manufacturers, and susceptibility and resistance breakpoints were defined according to international recommendations. All *Shigella* and *Salmonella* isolates were tested for ampicillin, cotrimoxazole, nalidixic acid and ofloxacin (Sensidiscs, Becton Dickinson, Sparks, MD, USA); *Campylobacter* isolates were tested for erythromycin and norfloxacin (Neo-Sensitabs, Rosco, Taastrup, Denmark). Isolation of diarrhoea-producing *E. coli* and of other bacterial enteropathogens was not routinely performed in our laboratory during the study period.

Management and outcome

Ambulatory or inpatient treatment was offered at the clinician's discretion. After major systemic infection like malaria had been excluded, initial management of febrile TD could consist of symptomatic treatment (mainly antipyretics and loperamide) or empirical antibiotherapy, according to first-line laboratory results, clinician's decision and patient's convenience. Fluoroquinolones (for 3-5 days) were the empirical treatment of choice during the study period, except if another antibiotherapy had been already initiated, or in children and pregnant women, where a macrolide (most of the time azithromycin) was offered. Patients found with any of the invasive bacterial enteropathogens were systematically contacted by phone when the culture result and susceptibility testing were available (usually 3 to 5 days after initial consultation) in order to evaluate the clinical evolution and the eventual need for antibiotic initiation or modification. Clinical failure was defined as the persistence of fever and/or diarrhoea for more than 3 days after initiation of antibiotic treatment. Final outcome was then reassessed within the following weeks by a follow-up consultation or phone call according the standard study procedure (12).

Statistical analysis

Statistical analyses were performed with SPSS software, version 15 (SPSS Inc., USA). The chi-square test was used to compare categorical variables. All tests were two-tailed, and P values < 0.05 indicated statistical significance.

Ethical issue

All patients were informed about the objectives of this observational study. Patient data were rendered anonymous for further analyses. The study was designed, conducted and analyzed independently of any sponsoring. The protocol was approved by the ethical committee of both study sites.

RESULTS

Main diagnoses in travellers with fever and diarrhoea

A total of 1730 febrile episodes having developed during or within one month after a tropical stay were evaluated during the study period. At presentation, 594 patients (34%) complained of diarrhoea beside fever; 192 (32%) of them had seen another physician before consulting us. Stool examination and culture were performed in 512 patients (86%). Systemic infections were diagnosed in 259 travellers (44%) returning with fever and diarrhoea, and malaria was found in half of them (Table 1). According to the case definition, febrile traveller's diarrhoea was diagnosed in the remaining 335 (56%) patients. Diarrhoea had developed during travel in 184 of them (55%) or with a median delay of 6 days after return for the remaining patients. Invasive bacterial enteritis was confirmed in 114 travellers (87 as a single diagnosis and 27 concomitantly with another infection) and suspected in another 36 patients. Few cases were due to parasites. Aetiology often remained unknown (Table 1).

Table 1: Main diagnoses in travellers presenting with fever and diarrhoea within one month after return from the tropics (n = 594)

	n	%
Systemic infections	259	44
Malaria	124	21
Respiratory tract infection	39	7
Dengue	18	3
Mononucleosis-like syndrome	11	2
Enteric fever (due to S. typhi or S. paratyphi)	11	2
Hepatitis A or E	9	1.5
Rickettsial infection	8	1.5
Acute schistosomiasis	7	1
Miscellaneous	32	5
Febrile traveller's diarrhoea	335	56
Confirmed bacterial enteritis (single infection)	87	14.5
Confirmed bacterial enteritis (with another infection)	27*	4.5
Suspected bacterial enteritis (only faecal leukocytes)	36	6
Parasitic enteritis (protozoan or helminthic pathogen)	5**	1
Unknown aetiology	180	30

* Invasive bacterial enteritis (due to *Shigella*, *Campylobacter* or nontyphoidal *Salmonella*) was diagnosed concomitantly with giardiasis (n = 6), malaria (n = 5), mononucleosis-like syndrome (n = 3), dengue (n = 2), skin/soft tissue infection (n = 2), acute schistosomiasis (n = 2), *Cyclospora cayetanensis* enteritis (n = 2), *Cryptosporidium* spp. enteritis (n = 2), rickettsial infection (n = 1), infection due to *S. paratyphi* A (n = 1), and *Trichuris trichiura* enteritis (n = 1).

** Including amoebic colitis (n = 2); *Cyclospora cayetanensis* enteritis (n = 2), *Strongyloides stercoralis* enteritis (n = 1)

Invasive bacterial enteritis

The 114 cases with confirmed invasive bacterial enteritis accounted for 34% of all patients diagnosed with febrile TD. The mean age of this subgroup was 33 years (range: 11 months-73 years) and the median delay from onset of symptoms to consultation was 3 days (range: 1-30 days). Causative enteropathogens were distributed between *Campylobacter jejuni* alone (47, 41%), *Shigella* spp. alone (43, 38%; including 21 *S. sonnei*, 18 *S. flexneri* and 4 *S. dysenteriae*), *Salmonella* spp. alone (22, 19%) and dual infection *Campylobacter-Salmonella* (2, 2%). Faecal leukocytes were found at direct stool microscopy in 29 of the 114 patients (25%) with positive stool culture. They were observed more frequently in *Shigella* (19/43, 44%) than in *C. jejuni* (7/47, 15%) or *Salmonella* (3/22, 14%) infections ($P = 0.001$ for the comparison between the 3 pathogens).

Prevalence of invasive bacterial enteritis was 30% (56/183) in patients returning with febrile TD from sub-Saharan Africa, 31% (13/42) from North Africa/Middle East, 37% (11/30) from Latin America and 51% (36/70) from southern Asia (Indian subcontinent and Southeast Asia). Infection due to *C. jejuni* infection was most frequent after a travel to this latter destination, reaching 33% of all febrile TD cases (Table 2). In contrast, shigellosis tended to be more often diagnosed in febrile TD occurring after a travel to sub-Saharan Africa or Latin America.

Resistance pattern of bacterial enteropathogens

As shown in Table 2, overall resistance rates to ampicillin and cotrimoxazole were high for *Shigella* (50% or more) and moderate for *Salmonella* (about 25%). All *Shigella* and *Salmonella* isolates were however susceptible to ofloxacine in our travellers, even if 2 *Shigella* and 2 *Salmonella* isolates exhibited resistance to nalidixic acid. In contrast, most *C. jejuni* strains were resistant to norfloxacine (53%), but at a lower rate in strains originating from sub-Saharan Africa when compared to those from other regions (31% versus 64%, $P = 0.03$). No *C. jejuni* isolate was found resistant to macrolides.

Presentation and outcome of invasive bacterial enteritis

Of the 87 cases with invasive bacterial enteritis as sole diagnosis, 30 (34%) presented with high fever (≥39°C), 22 (25%) with vomiting and 12 (14%) with bloody diarrhoea. Leukocytosis (white blood cell count > 10,000/mm3) was observed in 27/83 (33%) cases and a high level of C-reactive protein (CRP > 5 mg/dL) in 35/78 (45%) cases. Both abnormalities were more frequently seen in invasive bacterial enteritis than in febrile TD of "unknown aetiology", where they were respectively found in 20% and in 21% of the cases ($P < 0.001$ for both comparisons). Of note, no clinical or laboratory characteristics were discriminative for a specific invasive bacterial enteropathogen.

Hospitalization was necessary for 18 patients (21%) finally diagnosed with invasive bacterial enteritis. Four had a severe dehydration at presentation, but no fatality occurred.

As shown in Table 3, symptomatic treatment was initially offered to 33 of the 87 patients (38%) with single bacterial enteritis, but 23 of them (70%) had an unsatisfactory evolution (meaning that they were still complaining of diarrhoea and/or fever when contacted 3 to 5 days after initial consultation); all were given antibiotics according to the pathogen susceptibility and symptoms abated rapidly. The remaining 54 patients were

Table 2: Prevalence and resistance pattern of bacterial enteropathogens found in patients with febrile traveller's diarrhoea (n = 325) per travel destination

	Sub-Saharan Africa (n = 183)	Southern Asia (n = 70)	North Africa-Middle East (n = 42)	Latin America (n = 30)	*P*
Campylobacter jejuni, n (%)	16 (9)	23 (33)	6 (14)	4 (13)	< 0.001
norfloxacine-R*, n/n (%)	5/16 (31)	14/23 (64)	5/6 (83)	2/4 (50)	
Shigella spp., n (%)	28 (15)	5 (7)	3 (7)	7 (23)	0.07
ampicillin-R, n/n (%)	14/28 (50)	2/5 (40)	1/3 (33)	3/7 (43)	
cotrimoxazole-R, n/n (%)	20/28 (71)	3/5 (60)	3/3 (100)	5/7 (71)	
Salmonella spp., n (%)	12 (6)	8 (11)	4 (9)	-	0.2
ampicillin-R, n/n (%)	2/12 (17)	3/8 (37)	2/4 (50)		
cotrimoxazole-R, n/n (%)	1/12 (8)	2/8 (25)	2/4 (50)		

* R denotes "resistant"

Table 3: Initial attitude and rate of clinical failure or unsatisfactory evolution per aetiology in cases with (single) invasive bacterial enteritis (n = 87)

	C.jejuni (n=31)	*Shigella* spp. (n=39)	*Salmonella* spp. (n=17)	Total (n=87)
Empirical antibiotherapy	21 (68)	24 (62)	9 (53)	54 (62)
Clinical failure	6*/21 (29)	1**/24 (4)	0/9 (0)	7/54 (13)
Symptomatic treatment	10 (32)	15 (38)	8 (47)	33 (38)
Unsatisfactory evolution	6/10 (60)	11/15 (73)	6/8 (75)	23/33 (70)

Note: all results are n (%) or n/n (%)
* All 6 cases failed under treatment with a fluoroquinolone
** This case failed under treatment with cotrimoxazole

empirically treated with antibiotics; clinical failure was observed in 6 of 18 (33%) patients with *C. jejuni* infection first treated with a fluoroquinolone and in one with *Shigella* enteritis first treated with cotrimoxazole. Of note, 9 patients infected with a norfloxacine-resistant *C. jejuni* strain and treated empirically with a fluoroquinolone cured "spontaneously".

Patients diagnosed with invasive bacterial enteritis and another infection recovered after appropriate combined therapy. All 36 patients with suspected bacterial enteritis (faecal leukocytes only) were immediately given a fluoroquinolone and cured uneventfully. Finally, of the 180 patients with febrile TD of "unknown aetiology", 86 (48%) were empirically treated with a fluoroquinolone and, except for 4 patients, all patients improved rapidly. Of the remaining 94 patients first treated symptomatically, 5 were given antibiotics later on because of unsatisfactory evolution and recovered.

DISCUSSION

In our referral travel clinic, diarrhoea was present in about a third of travellers returning from the tropics with fever. Systemic infections and in particular malaria were frequently diagnosed in this subset of ill travellers. Invasive bacterial enteropathogens were found in 30 to 50% of the patients diagnosed with febrile TD, depending on the continent of exposure, with *Campylobacter jejuni* as the major single aetiology (33%) after a stay in southern Asia. Resistance to and clinical failure with fluoroquinolones were only observed in travellers infected with this pathogen.

The major limitation of this study is that the actual prevalence of true bacterial enteritis was largely underestimated since the stool workup was not always performed, has a non-optimal sensitivity and in particular did not include isolation of diarrhoea-producing *E. coli* and other less common bacterial enteropathogens. Many cases of febrile TD without aetiological confirmation were probably due to pathogenic *E. coli*, repeatedly identified as major enteropathogens worldwide (4-6,13-15) Also, this study explored the aetiology of febrile TD at return, and does not provide any data on diarrhoea resolved during travel. The other study limitations are inherent to its observational single-centre design. In addition, the unavoidable selection bias does not allow the generalization of our findings as such to any other clinical setting. However, we think that our observations may provide several useful messages for first-line and hospital physicians increasingly confronted with sick returning travellers.

First of all, diarrhoea and other abdominal manifestations may be present in various systemic infections, including serious tropical conditions like malaria (16,17). In addition, dual infections are not uncommon in travel medicine. Consequently, in a traveller returning with fever and diarrhoea, a diagnosis of traveller's diarrhoea should only be made when potentially severe tropical or cosmopolitan infections have been reasonably excluded. Several clinical and first-line laboratory predictors of common tropical conditions have been well identified to assist the initial judgement (18).

Invasive bacterial enteritis was finally confirmed in about a third of all patients diagnosed with febrile TD. This high prevalence is mainly explained by the entry criterion of our study

(fever), which skewed the aetiological results to the more severe forms of TD. In symptomatic travellers returning from southern Asia, we isolated invasive pathogens in up to 50% of the cases, particularly *C. jejuni*. This confirms previous observations on the disproportionate contribution of *C. jejuni* as a cause of traveller's diarrhoea in this part of the world (4, 19).

Empirical antibiotherapy is recommended for traveller's diarrhoea, in particular if fever or dysenteric symptoms are present. This strategy appears clinically justified if one considers the high prevalence of invasive bacterial pathogens, the substantial associated morbidity and the high rate of unsatisfactory evolution with a symptomatic treatment only. It is also true that a substantial number of bacterial TD cases cure without any antibiotic, as illustrated by the high percentage of spontaneous recovery among patients with febrile TD of unknown aetiology or by the good evolution of several cases infected with quinolone-resistant *Campylobacter* and empirically treated with a fluoroquinolone. Unfortunately, at initial assessment, no clear-cut predictor could discriminate patients for whom antibiotics would be most beneficial. The presence of leukocytosis and higher CRP levels might however help clinicians in favouring empirical antibiotics.

The choice of empirical antibiotics for TD has evolved according to their known activity against prevalent enteropathogens in the regions visited (20). Not surprisingly, the susceptibility of *Shigella* and *Salmonella* was very low for "outdated" drugs like ampicillin or cotrimoxazole (21-23). However, both bacteria were found universally sensitive to the fluoroquinolones in our study. In our experience, a stay in sub-Saharan Africa was rather predictive for shigellosis in patients returning with febrile TD, as recently confirmed (4). The presence of the faecal leukocytes may also suggest this diagnosis, but this finding was somehow limited by the substantial number of febrile TD cases with faecal leukocytes but no identified pathogen as well as by the low sensitivity of faecal leukocytes to identify culture-positive TD.

On the other side, the rate of *C. jejuni* resistance to the fluoroquinolones exceeded 50% in strains originating from any region (24-27), except sub-Saharan Africa. Therefore, when invasive bacterial enteritis is suspected, a macrolide should be preferred when *C. jejuni* is the most likely pathogen (depending on the geographical risk), because of the high risk of clinical failure with fluoroquinolones.

Our data provide therefore some reinsurance about the use of a fluoroquinolone as empirical treatment for most patients with febrile TD, but since this study has been conducted, emergence of quinolono-resistance among *Salmonella* and *Shigella* isolates has been demonstrated in several locations (22, 23), underlining the continuous need of monitoring the resistance patterns of TD including in travel clinics. Our findings also support the recommendation of most experts to use azithromycin as first-line treatment in traveller's diarrhoea acquired in southern Asia. This recommendation has also been endorsed since 2008 by the Belgian scientific group of travel medicine (consensus reports of the "Wetenschappelijke Studiegroep Reisgeneeskunde/Groupe d'Etude Scientifique de la Médecine du Voyage" available at http: //www.itg.be). Of note, oral rifaximin, which is a promising option for most patients with traveller's diarrhoea, is not yet available in Belgium and seems anyway less effective when it is used against invasive bacterial enteropathogens (8).

In conclusion, in travellers returning from the tropics with fever and diarrhoea, serious tropical conditions should be first excluded. Febrile traveller's diarrhoea is often due to common invasive bacterial pathogens and particularly to *C. jejuni* after a travel to southern Asia. Since resistance rates of *C. jejuni* to fluoroquinolones are high nowadays in most regions of the world, macrolides should be preferred as empirical treatment of febrile TD acquired in Asia.

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