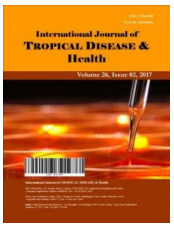

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Changing Patterns and Outcomes of Typhoid Fever in Egypt

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MS and AH designed the study, wrote the protocol, wrote the first draft of the manuscript. Authors MM and AF performed the statistical analysis, managed the analyses of the study, and managed the literature searches authors SA and DG approved and made the lab work. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Typhoid fever is an endemic disease in our country; however, the changing presentation may alter our diagnosis and management.
The Aim of the Work: To improve the management of typhoid fever in Egypt through studying the changes in the clinical picture, laboratory findings, response to antimicrobial treatment & outcomes.
Subjects and Methods: 590 patients were involved in the study, presenting symptoms, laboratory results, responses to medications and the outcomes were registered.
Results: fever was the most prevalent symptom (98.6%) followed by a headache (82.9%) and abdominal pain (71.5%); eating outdoor is the most prevalent risk factor (80.8%); Thirty patients who used quinolone were relapsed (14.4% of cases who used quinolone), while fifty-five patients who used 3rd generation cephalosporin were relapsed (21.1% of cases who used cephalosporins).

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Conclusion: Food handlers constitute the major risk factors, while the classical form of the disease is not the common presentation, with a low yield of blood culture and increasingly resistant to fluroquinolone and ceftriaxone.

Keywords: Drugs resistance; Egypt; enteric fever; salmonella; typhoid.

1. INTRODUCTION

Typhoid fever is a systemic infectious disease, typically presented with fever, headache, abdominal pain, relative bradycardia, splenomegaly, and leucopenia [1,2]. It is caused by Salmonella enterica sub-species which threaten public health, with particular concern over the widespread and fast emergence of resistance antibiotics [3,4]. It commonly occurs in regions with increased urbanisation with limited resources as safe water, health system and infrastructures as in India, South and Central America, and Africa; nevertheless cases have reported from some areas in Eastern Europe [5]. Egypt considered one of the endemic countries for the disease as reported by David et al. in 2012 [6], in the year 2000, the estimated incidence of typhoid fever in Egypt was 15 cases per 100,000 persons per year (Egyptian national syndrome-based surveillance, unpublished data). Contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilised with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior Helicobacter Pylori infection, were the most commonly reported risk factors [1,2,5,6]. However reliable data to estimate the burden of the disease in these areas are difficult to obtain and constitute true and great obstacles since many hospital lack facilities for blood culture, and up to 90% of patient with typhoid are treated as an outpatient. Many searches also reported the widespread prevalence of multidrug-resistant strains, where *Salmonella typhi* increasing and most of the antibiotics such as fluoroquinolones and azithromycin have become ineffective [7-9]. Looking for the modified clinical picture due to poor compliance of some patients in addition to the widespread of multi-drug resistant strains of *Salmonella Typhi* this makes great changes in treatment response & outcome of the disease.

2. THE AIM OF THE WORK

To improve management of typhoid fever in Egypt through studying the changes in the clinical picture, laboratory findings, response to antimicrobial treatment& outcomes.

2.1 Subjects and Methods

This study is a descriptive prospective one which was carried out in 2 different hospitals in 2 governorates (Suez Fever Hospital and Ismailia Fever Hospital) where they serve for more than 4 million people in Egypt. The study included 590 patients of typhoid fever above two years of both sexes, consecutively included during one year.

2.2 Inclusion Criteria

Patients above 2 years of both sex clinically suspected cases of typhoid (patients have a fever, headache, abdominal pain included in the study [1,2] with their Widal O agglutinin titer 1/320 [10], with the exclusion of those who have a history of antibiotic intake 2 days before blood culture.

2.3 Study Design

Each patient in the study was subjected to the following: 1- Full history taking: including sociodemographic, symptoms, previous exposure to risk activities; 2- Full Clinical examination including signs of complicated typhoid fever; 3- Investigations: Patients with suspected enteric fever investigated with blood culture (was done twice to increase the chance of isolation of the organism) , Widal test , serum bilirubin, liver enzymes (ALT, AST) & complete blood count after taking the information concerning the duration of illness before admission & the history of prior antibiotic therapy.

2.4 Blood Culture

Each sample was collected under complete aseptic condition via venipuncture, 10-20 ml from adults and 5-10 ml from paediatrics, where each sample divided between aerobic bottle and anaerobic bottle. The positive cultures were subjected to microscopic studies, and biochemical tests including catalase test, oxidase test, Indole test, urea hydrolysis, and citrate utilisation test.

Widal test was done for each patient as the following : 10 test tubes Prepared on a rack; In tube 1, 950ul of NaCl 0.85% solution was added; In tubes 2-10, 500ul of NaCl 0.85% solution was added; then 50ul of the serum sample was placed in tube 1 and mixed well; Starting from tube 1, twofold serial dilutions were prepared by transferring 500ul from one tube to the next tube, Mixed well after each transfer and Discarded 500ul from the last tube; the same steps were repeated for the positive and negative controls; In a new test tube labeled 'Saline Control', 500ul of 0.85% NaCl solution was placed; The antigens were mixed well, and one drop of antigen was added to each test tubes, and the rack was shaked well. Final serum dilution is 1:20,…, 1:10240. After that, the samples were Incubated in a water bath for 24 hours with temperature 37°C; 10. At the end of the incubation period, gently the rack was removed from the water bath to avoid disturbing the suspensions, and each tube was examined in turn and the agglutination was observed. Finally, the response to treatment (3rd generation cephalosporin, 2nd generation quinolone & azithromycin) were studied as regarding improvement of general conditions & drop of fever with follow-up the patients for 2 weeks for recurrence of symptoms.

2.5 Data analysis

Our sample size was calculated according to the known prevalence in Egypt and using the suitable equation [10,11]. Data collected then analysed and presented in the form of tables, as appropriate, by using the Statistical Package for Social Science (SPSS) software program version 20. Data presented as frequency (%) for qualitative variables.

3. RESULTS

This study included 590 patients, Table 1 shows that (54%) males and (46%) females, most of the cases clustered around the age 13 -18 years (42.4%); Most of the cases were from urban areas (80.2%), and (30.5%) of the cases were food handlers, while (49.5%)belonged to localized instantiation (nursery or school). Table 2 shows that eating outdoor is the most prevalent risk factor among the studied population (80.8%), followed by using of drugs decreasing gastric hyperacidity (37.1%) while the presence of chronic diseases was (16.6%), and absence of safe water supply was reported in (4.9%). Table 3 showing that the disease was more prevalent in summer & autumn (75.1%) than winter & spring (24.9%). Regarding the clinical symptoms as shown in Table 4 among our studied sample, fever was the most prevalent symptom (98.6%) followed by a headache (82.9%) and abdominal pain (71.5%). GIT symptoms were largely reported among the patients: nausea found in (78.5%), constipation in (36.6%), diarrhoea were in (37.3%) most of them were children, while anorexia was in (81.5%). a cough was reported in (31.5%). Table 5 shows the signs distribution among the sample, the most prevalent sign was abdominal tenderness (71.5%) followed by the coated tongue (57.9%), splenomegaly (39%), and hepatomegaly (29%). Regarding laboratory findings among the studied population, Table 6 shows that anaemia was the most prevalent finding (56.1%), followed by lymphocytosis (32.2%) and leucopenia (24.9%); it also shows leukocytosis in (22.5%), neutropenia in (18.6%) and thrombocytopenia in (10.2%). Hyperbilirubinemia was reported in (10.3%). In Table 7 we can see that blood culture was

Table 1. Frequency distribution of the studied population according to sociodemographic characteristics

Variable		No.	%
Age (years)	2-12years	211	35.6
	13-18y.	249	42.4
	19- 59y	120	20.3
	60-above	10	1.7
Gender	Male	319	54
	Female	271	46
Residence	Urban	473	80.2
	Rural	117	19.8
Occupation	Food handlers	180	30.5
	others	410	69.5
Localized instantiation	Nursery or school	292	49.5
	others	298	50.5

Table 2. Prevalence of different risk factors among studied sample

Variable		No.	%	p-value
Eating outdoor	present	477	80.8	<0.001
	absent	113	19.2	
Using of safe water	Present	561	95.1	<0.001
	Absent	29	4.9	
Using of drugs decreasing gastric hyperacidity	present	219	37.1	<0.001
	absent	381	62.9	
Presence of chronic disease	present	98	16.6	<0.001
	absent	492	83.4	
Presence of calcular cholecystitis	present	69	11.7	<0.001
	absent	521	88.3	
History of schistosomal infection	present	10	1.7	
	absent	580	98.3	<0.001
Antibiotic intake	present	210	36	<0.001
	absent	379	64	
Duration of antibiotic intake	One day	182	30.8	<0.001
	Two days	18	3.1	

**p value is significant <0.05*

positive (true positive cases) in 51% while negative (true negative cases) 49 %, and 56.7% who had negative culture used antibiotics before culture. By using a cutoff, ≥ 1/320 of O antigen sensitivity of Widal test was 88.43% while specificity was 60.28%. Finally, in Table 8 regarding treatment, 47.5% of our patients were on 3rd generation cephalosporin therapy, 35.4% on quinolone therapy, while 17.1% were on azithromycin therapy (all of them were children). Thirty patients who used quinolone were relapsed (14.4% of cases who used quinolone), while fifty-five patients who used 3rd generation cephalosporin were relapsed (21.1% of cases who used cephalosporins).

Table 3. Seasonal variations among studied sample

Onset of the disease	No.	%	p-value
Summer & autumn	443	75.1	<0.001
Winter & spring	147	24.9	

**p value is significant <0.05*

Table 4. Distribution of the symptoms among studied sample.

Variable		No.	%	p-value
Constipation	Present	216	36.6	<0.001
	Absent	374	63.4	
Diarrhea	Present	173	29.3	<0.001
	Absent	317	70.7	
Vomiting	Present	220	37.3	<0.001
	Absent	370	62.7	
Nausea	Present	463	78.5	<0.001
	Absent	127	21.5	
Abdominal Pain	Present	422	71.5	<0.001
	Absent	168	28.5	
Anorexia	Present	481	81.5	<0.001
	Absent	109	18.5	
Arthralgia	Present	199	33.7	<0.001
	Absent	391	66.3	
Malaise	Present	170	28.8	<0.001
	Absent	420	71.2	
Myalgia	Present	170	28.8	<0.001
	Absent	420	71.2	
Cough	Present	186	31.5	<0.001
	Absent	404	68.5	

Variable		No.	%	p-value
Chills	Present	109	18.5	<0.001
	Absent	481	81.5	
Headache	Present	489	82.9	<0.001
	Absent	101	17.1	
Fever	Present	582	98.6	<0.001
	Absent	8	1.4	

**p value is significant <0.05*

Table 5. Frequency distribution of the signs among studied population

Variable		No.	%	
Toxic face	Present	127	21.5	<0.001
	Absent	463	78.5	
Coated tongue	Present	342	57.9	<0.001
	Absent	248	42.1	
Rose spot	Present	40	6.8	<0.001
	Absent	550	93.2	
Epistaxis	Present	0	0	----
	Absent	590	100	
Relative bradycardia	Present	91	15.4	<0.001
	Absent	499	84.6	
Abdominal Tenderness	Present	422	71.5	<0.001
	Absent	168	28.5	
Hepatomegaly	Present	171	29.0	<0.001
	Absent	419	71.0	
Splenomegaly	Present	230	39.0	<0.001
	absent	360	61.0	

**p value is significant <0.05*

Table 6. Frequency distribution of presence of abnormal blood indices, and liver function among studied sample

Lab results	No.	%
Anaemia	331	56.1
Leucopenia	147	24.9
Leucocytosis	133	22.5
Lymphopenia	13	2.2
Lymphocytosis	196	33.2
Neutropenia	110	18.6
Thrombocytopenia	60	10.2
Thrombocytosis	47	8.0
Hyperbilirubinemia	61	10.3
Elevated ALT	403	68.3
Elevated AST	373	63.2

Table 7. Blood culture and Widal test among the studied population

Blood culture	Positive	301	51.0 %
	negative	289	49.0 %

Parameter for Widal test	Percent	95 % CI
Sensitivity	100	88.43 to 100
Specificity	79.31	60.28 to 92.01
Positive Likelihood Ratio	4.83	2.37 to 9.86
Negative Likelihood Ratio	0	
Positive Predictive Value	83.33	71.03 to 91.07
Negative Predictive Value	100	

Table 8. Frequency distribution of medications (antibiotics) used in treatment of typhoid and number of relapses among studied sample.

Variable		No.	%	No of relapse	%
drug used in treatment	3rd generation cephalosporin	280	47.5	59	21.1
	2nd generation quinolone	209	35.4	30	14.4
	azitrhromycin	101	17.1	0	0

4. DISCUSSION

Typhoid fever remains a serious problem in developing countries including Egypt. In this search we included 590 patients with typhoid fever to discover if there are any changing pattern regarding the clinical picture, laboratory findings, response to antimicrobial treatment and outcomes. It is well documented that typhoid fever has no racial predilection; but regarding gender, in our study showed that males are more commonly affected than females (54.2% versus 45.8%), which is less than what was reported before in Egypt [13], that males were 60.6%; even in the united states between 1999 and 2006, 54% of the reported cases were males [8]; these males predilection can be understood as they are more exposed to risk factors as eating outdoors, or living in group households with poor hygiene [14] . regarding age in our study 42.4% were between the age of (13 -18) years, while 35.6% were between the age of (2- 12), which reflect that children are commonly affected and this was comparable to what reported by Mahmoud SZ [13], and go internationally with most reported cases which affected school-aged children and young adult, but although we did not include infants in our study, their affection with typhoid cannot be ignored, but the clinical picture reported to be variable ranging from a mild febrile illness to severe convulsions [12,14,15]; older persons are not affected in endemic areas as they mostly became immunized due to clinical or subclinical exposure. There is no nonhuman vector in the transmission of the disease, as it is transmitted from asymptomatic carrier who shed the bacteria from his stool via contaminated food or beverages, hand to mouth transmission, or oral transmission via unsafe water supply; In our study using of safe water was in 94.9% which is different than old studies where unsafe water was a major risk factor; this high percent due to increased urbanization in the area of the study while eating outside was in 79.7% this due to staying outside for long periods in school, university & job; but interestingly About 30.5% of our cases worked as food handlers thus making eating outdoors a very important risk factor of typhoid fever in our locality. Regarding the clinical presentation of our cases mainly presented by fever, headache, and anorexia; other symptoms as cough, arthralgia and bowel disturbance were the less common; these presentations are nearly the same as reported in our area before and other researches in endemic areas [16,17]. The presenting signs also as coated tongue, hepatomegaly and splenomegaly, were not different from that reported by others. However relative bradycardia was less common from that reported by Mathura et al. [17] and this may reflect the differences in strains; and rose spots were less common in our study compared to what was mentioned by WHO, 2003 [18], which also can be explained by the differences in Typhoid strains or due to the commonly dark skin in our patients. It is very important here to mention that the classical forms of typhoid are not always there, for example the fever mostly has a steady insidious onset in our study and others [19-23] instead of the stepladder fever (the historical hallmark of typhoid). Although it is reported that patients with typhoid fevers are moderately anemic, this cannot explain that anemia was 55.9% in our study but it may be due to bad feeding habits among children and increased iron requirement in adolescent who were the majority of our patients; however, the other laboratory test in our study were not far different from others [19-23]. the most annoying thing in our study was the yield of the blood cultures, as only about half the cases was positive which is nearly the same in the study made 30 years ago; although the blood culture has to be positive in 85%-90% in patients with typhoid presented in the first week of illness [24]; these unfortunately can be explained that we still using old methods for cultures, and so we have to revise this seriously with our colleagues in microbiology, and as clinician we have to revise our protocols in general and fever hospitals to repeat the cultures 3 times, use large volume (10-30ml) blood and better to implement bone marrow culture to increase the yield and better diagnosis [24]. Moreover, the low yields of the cultures in our area and the developing countries obligate us to use the Widal test in high titer (which is no longer acceptable clinical method in the developed countries) beside the clinical

picture. Finally regarding treatment In our study 21.1% of patients used ceftriaxone and, 14.4% of patients used fluoroquinolone were relapsed, compared to 17% and 12% respectively in previous prospective trials [25-28], however in the study done by Mahmoud SZ [13], none among the patients who used fluoroquinolone had relapsed; while no relapses were reported in patients that used azithromycin in the previous or our recent new trials.

5. CONCLUSION

Typhoid fever is changing in Egypt; food handlers constitute the major risk factors, while the classical form of the disease is not the common presentation, with a low yield of blood culture and increasingly resistant to fluroquinolone and ceftriaxone.

CONSENT

All the patients were informed about the search, and verbal consent was taken from everyone.

ETHICAL CONSIDERATIONS

This search project was approved by the ethical committee, Faculty of Medicine, Suez, Canal University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Butter T. Typhoid fever, In J.B. Wyangaarden, L.H.Smith, and J.C. Bennett (ed.), Cecil text book of medicine, 19th ed. W.B. Saunders Co, Philadelphia. 1992;1690-1692.
2. Pearson RD, Guerrant RL. Enteric fever and other causes of abdominal symptoms with fever, P. In G.L. Mandell, J.E. Benett, and R.Dolin (ed.), Principles and practice of infectious diseases, 5th ed. Churchill Livingstone, Newyork, N.Y. 2000;1136-1150.
3. Akinyemi K, Smith S, Oyefolu A, Coker A. Multidrug resistance in Salmonella enterica serovar Typhi isolated from patients with typhoid fever complications in Lagos, Nigeria. Public Health. 2005;119:321-327.
4. Feng YC. The epidemiology of typhoid fever in the Dong ThapProvince, Mekong Delta region of Vietnam. The American Journal of Tropical Medicine and Hygiene. 2000;62:644-648.
5. Hornick RB. Typhoid fever, p.803-818. In A.S. Evans and P.S. Brachman (ed.), Bacterial infections of human epidemiology and control, 2nd ed. Plenum Medical Book Company, New York, N.K; 1991.
6. David A. Pegues, Samuel I. Miller. Samonellosis. In: Harrison's Principles of Internal Medicine, 18th ed. 2012;1275-1276.
7. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella Typhi: A worldwide epidemic. Clin Infect Dis. 1997;24(suppl 1):106-109.
8. Lynch MF, Blanton EM, Bulens S, Polyak C, Vojdani J, Stevenson J, et al. Typhoid fever in United States, 1999-2006. JAMA. 2009;302(8):859-65.
9. Ranjbar M, Alizadeh M, Amir H, Hashemi SH, Dadashpoor M, Madrakian AR, et al. Clinical features of patients with typhoid fever and drug resistance of the causative isolates in Westren Iran. Tropical Doctor. 2009;39:223-224.
10. Pang T, Puthucheary SD. Significance and value of the Widal test in the diagnosis of typhoid fever in endemic area. J. Clin. Pathol. 1983;36:471-475.
11. Dobson AJ. Calculating sample size. Trans Menzeiz Foundation. 1984;7:75-79.
12. Edelman R, Levine MM. Summary of an international workshop on typhoid fever. Reviews of Infectious Diseases. 1986;8: 329-49.
13. Mahmoud SZ. Typhoid & paratyphoid fevers in Assiut; thesis for master degree in Tropical Medicine 1999 (unpublished data).
14. Dutta TK, Beeresha, Ghotekar LH. Atypical manifestations of typhoid fever. J Postgrad Med. 2001;47(4):248-51. [Medline].
15. Mulligan TO. Typhoid fever in young children. Br Med J. 1971;4(5788):665-7. [Medline].
16. Maskey AP, Day JN, Tuan PQ, Thwaites GE, Campbell JI, et al. *Salmonella enterica* serovar Paratyphi A and *S. enterica* serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. Clin Infect Dis. 2006;42:1247.
17. Mathura KC, et al. Clinical study of typhoid fever. OROZCO R, et al. Rev Med Chil.

1959. Show full citation .... Kathmandu Univ Med J (KUMJ); 2003.
18. WHO; 2003.
19. Butler T, Islam A, Kabir I, et al. Patterns of morbidity and mortality in typhoid fever dependent on age and gender: review of 552 hospitalized patients with diarrhea. Rev Infect Dis. 1991;13(1):85-90. [Medline].
20. Butler T, Knight J, Nath SK, et al. Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. Rev Infect Dis. 1985;7(2): 244-56. [Medline].
21. Crum NF. Current trends in typhoid Fever. Curr Gastroenterol Rep. 2003;5(4):279-86. [Medline].
22. Huang DB, DuPont HL. Problem pathogens: Extra-intestinal complications of Salmonella enterica serotype Typhi infection. Lancet Infect Dis. 2005;5(6):341-8. [Medline].
23. Abdel Wahab MF, el-Gindy IM, Sultan Y, el-Naby HM. Comparative study on different recent diagnostic and therapeutic regimens in acute typhoid fever. J Egypt Public Health Assoc. 1999;74(1-2):193-205. [Medline].
24. Escamilla J, Florez-Ugarte H, Kilpatrick ME. Evaluation of blood clot cultures for isolation of *Salmonella typhi, Salmonella paratyphi*-A, and Brucella melitensis. J Clin Microbiol. 1986;24(3):388-90. [Medline].
25. Dolecek C, La, TTP, Rang NN, et al. A multi-center randomized controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in childern and adults in Vietnam. PLoS ONE. 2008;3:e2188.
26. Chinh NT, Parry CM, Ly NT, et al. A randomised controlled comparison of azithromycin and ofloxacin for multidrug-resistant and nalidixic acid resistant enteric fever. Antimicrobial Agents and Chemotherapy. 2000;44:1855-9.
27. Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrobial Agents Chemother. 1999;43: 1441-1444.
28. Parry CM, Hein MB, Dougan MD, White NJ, Farrer MT. Typhoid fever. N Engl J Med. 2002;347:1770-82.

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