

Risk Factors of Enteric Fever in Children Less Than 15 Years of Age

(A cross sectional study based on 530 children under Risk of
Enteric Fever)

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Abstract

This is hospital based cross sectional prospective study of children less than 15 years old who were diagnosed as case of Enteric Fever. The main objective of study was to find out the effect of significant risk factors on ENTERIC FEVER (EF). The 530 children (275 Typhoid fever patients and 255 Non-Typhoid) entering the Hospitals under the risk of Enteric Fever during the period Feb-July 2005 were studied. There are 314 male and 216 female patients. Study was conducted in three major institutions, General Hospital, Children Hospital and Mayo Hospital of Lahore. Data was collected through questionnaire. Logistic Regression technique was used to find the significant risk factors. The probabilities by using Logistic models were also found. This study shows that risk factors of EF include age, educational status of parents, consumption of street vendors' food, water intake, history of contact with patient of EF in family and availability of Dispensary Facility.

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1. Introduction

Background

Enteric Fever, also called Typhoid Fever, is caused by *Salmonella typhi*, bacteria belonging to the family Enterobacteriaceae. Typhoid has had a strong impact on human history. It is widely held responsible for the decline of the ancient Athens civilization. In modern history, Typhoid has played havoc in the lives of Princes and paupers alike, from British Royalty to massive outbreaks all over the world. (Wikipedia)

Transmission

Salmonella typhi infects only humans. It is transmitted by ingestion of food or water contaminated with feces from an infected person. These bacteria survive and multiply in the bloodstream, get absorbed in the digestive tract, and are eliminated in stool. The different sources of *Salmonella typhi* are:

- 1). Inadequate sanitation facilities result in the contamination of drinking water by sewage.
- 2). Poor personal hygiene, specifically the neglect to wash hands before handling food may also lead to the spread of *Salmonella*.
- 3). In addition, some people may transmit *Salmonella* even after recovering from EF (5% according to the Centre of Disease and Control). These people are termed “carriers.” They are themselves asymptomatic, but can infect others (Wikipedia). Although uncommon, carriers may also eliminate *Salmonella* via their urine.(Brusch)
- 4).The other sources of these bacteria are contaminated shellfish, improperly canned meat and polluted water. (Weaver M 1993).

In addition to the above-mentioned sources, another class of population is susceptible to *Salmonella*. These patients have stomach ulcers, thus leading to low levels of stomach acids, which otherwise play part in the human body’s natural defense against this bacterium. Therefore, patients taking antacids, Histamine blockers, and proton pump inhibitors, or those who have had a gastrectomy (stomach surgery) or have achlorhydria (decreased stomach acid) due to any cause, are more susceptible to develop EF. (Brusch)

Clinical Features and Diagnosis

Unfortunately, the initial symptoms of EF are quite common, fever, malaise, myalgias, headache, constipation,

anorexia, rash, and less commonly, diarrhea. Left untreated, the patient ends up with intestinal perforation and death. The definite way to diagnose EF is via blood and stool cultures that take several weeks. A quicker, but less certain way is to carry out the Widal test.

Purpose of Study

We chose to research the risk factors of EF because this is one of the major health problems faced by Pakistan currently. The population of our country is predominantly rural based (66% according to the Economic Survey of Pakistan, 2004). Above the age of 15, 61% of urban and 30.8 % of the rural population is literate. The literacy rate is slightly higher for the population under 15. (1998 census). Overall, 23.9 % people are below the poverty line. (Economic Survey of Pakistan, 2005-2006). Therefore, a large segment of the population does not have access to proper sanitation facilities and timely medical attention, and is unfortunately, ignorant about the importance of personal hygiene.

To make matters worse, Pakistan is heading for more trouble since strains of Salmonella have emerged which are resistant to conventional antibiotics. (Muhammad Amer Mushtaq, 2005) The use of newer and stronger antibiotics will be a burden on the individual as well as the state.

We have tried to unmask means by which EF may be prevented in, so that public awareness campaigns can be organized to this end.

Keeping in view the importance of EF as a major health problem and its impact on society, numerous research workers from all over the world has given their input in this connection. Among these Capasso (1980), Ross (1986), Hoffman (1986), Murphy (1989), Deshmukh (1994), Butler (1991), Braddick (1993), Watier (1995), Bhutta (1996), Sinha (1999), Christopher (1999), Gupta (2001), Willke (2002), Hussain (2002), Nsing (2002), Nye (2002), Singh (2003), Wong (2003), Ohanu (2003), Albert (2003), Murdoch (2004), Hosoglu (2004), Mandal (2004), Malhotra (2004), Vollaard (2004), Thaver (2005), Brooks (2005), Chen (2005), Trann (2005) have done tremendous work in this area.

2. Materials and Methods

This is a cross sectional study with analytic and descriptive components. This is hospital based data collected from 3 major institutes of our town General Hospital, Children Hospital and

Mayo Hospital. Study was conducted in span of 6 months from Feb 2005 to July 2005 under the supervision of Medical experts. A detailed questionnaire was devised. The included components are: Age (AGE), Gender (GEND), Educational status of Father (FEDU), Educational status of mother (MEDU), Family Size (FS), Duration of Fever (DURF), Socio-Economic condition (SOEC), Typhoid History (TYPH), Water Intake (WI), School Going (SG), Hand washing before eating (HW), Vaccination (VAC), Eating habits (EH), Toilet Facility (TF), Sanitation Condition (SC), Medical Facilities (MEDF) and Attitude towards health center (ATHC). Data was particularly scrutinized before the entry. Diagnosis was based upon examination, Medical History, and positive Widal test. Typhoid disease was taken as dependent variable and its categories are “present” and “absent”. The AGE and FS were taken as numeric variables and all others as categorical variables. The categorical variables were also coded before analysis as given in Table A-1. The data was analyzed by descriptive, bivariate and Multiple Logistic Analyses. The statistical methods: Odd Ratios, Multiple Logistic Regression and Wald Statistics were used at 5% level of significance. The Probabilities of EF are obtained by using Logit model.

a) Logistic Regression

Logistic regression can be used whenever an observed outcome is restricted to two values. Which usually represent the occurrence or non-occurrence of some outcome event and independents are dichotomy or continuous. The most of the applications of logistic regression are in medical field. It has been used to calculate the risk of developing disease as a function of certain personal and behavioral characteristics.

The specific form of the logistic regression model is:

$$E(Y / x) = \pi(x) = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}}$$

A transformation of $\pi(x)$ is the logit transformation of simple model, as follows

$$g(x) = \ln \left[\frac{\pi(x)}{1 - \pi(x)} \right]$$

$$g(x) = \beta_0 + \beta_1 x$$

For multiple logistic model,

$$\Pr(\text{Event}) = \pi(x) = \frac{e^{g(x)}}{1 + e^{g(x)}}$$

$$g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$$

b) Odds Ratio

The odds ratio is a measure of risk. It is that someone who is exposed to the factor under study will develop the outcome as compared to someone who is not exposed. It is defined as:

$$OR_{A \text{ vs } B} = \frac{\text{odds}(A)}{\text{odds}(B)}$$

$$OR_{A \text{ vs } B} = \frac{\Pr(A)}{1 - \Pr(A)} \div \frac{\Pr(B)}{1 - \Pr(B)}$$

95% confidence limit for odds ratio may be calculated as:

$$\exp\left[\hat{\beta} \pm 1.96 \times SE(\hat{\beta})\right]$$

c) Wald Statistic

The Wald statistic is commonly used to test the significance of individual logistic regression coefficients for each independent variable. That is to test the null hypothesis in logistic regression that a particular logit (effect) co-efficient is zero. It is the ratio of the logit co-efficient to its standard error.

$$W = \frac{\hat{\beta}_1}{SE(\hat{\beta}_1)}$$

This will be distributed as chi-square with p+1 degrees of freedom under the hypothesis that each of the p+1 coefficients is equal to zero. (Hosmer & Lemeshow 1989).

The EF is taken as dichotomous dependent variable. The probabilities of EF are calculated by the logistic method. The forward selection likelihood ratio procedure is applied to obtain the significant factors. The Wald's statistic is used to test the significance of individual logistic regression coefficients for each risk factor. The null hypothesis that a particular logit coefficient is zero is tested. The factors with insignificant effect are dropped from the multiple logistic model. The Wald statistic is used for this purpose.

3. Result

The findings of descriptive and bivariate analyses are described as below. The analyses are completed for overall patients, male patients and female patients.

a) Descriptive Analysis

There are 530 patients for analyses out of which 216(40.8%) are females and 314(59.2%) are males. The 275(51.9%) patients have confirmed EF. Out of 314 male patients 155 confirmed EF. Out of 216 female patients 96 have confirmed EF.

b) Bivariate Analysis

The association of every risk factor was tested with EF. For this purpose Chi-Square test was applied and Phi values were computed to find the highly significant variable associated with EF. In overall, male and female patients analyses WI has the largest phi value. So it is highly associated with EF among all the significant risk factors.

c) Overall Patients Analysis

By analyzing patients collectively considering both males and females following results are obtained:

The value of $\chi^2=10.654$ with d.f 2 and p-value is .005. Thus, fitted model is appropriate even at 1% level of significance.

As shown in Table A-2, 1.132 odd ratio of age means that with the increase of one year in age the risk of EF is increased 1.132 times provided all other factors are kept constant and the significant change after 10 years as $e^{10 \times 0.124} = 3.456$. This indicates that with an increase of 10 years in age the risk of EF increases 3.456 times.

The coefficient for FEDU is positive. Odd ratios of FEDU(1), FEDU(2) and FEDU(3) show that their children have 13.34, 19.87 and 15.93 times more chance of getting EF, as compare to fathers having education masters or above.

The coefficient for SOEC-2 is negative. The odd ratio is .012, which means that the children who do not belong to SOEC-1 have .988 times more chance of getting EF. Similarly, the odd ratio for SOEC-3 is 0.016 which indicates that the child who does not belong to SOEC-1 has .984 times more chance of getting EF.

The coefficient for TYPH is 2.196. The odd ratio shows that the children who have TYPH have 2.196 times more chance of getting an EF as compare to the children who do not have TYPH.

The coefficient for EH-3 is negative. Odd ratio for these children is .143 which shows that the children who have EH-3 have 0.857 times more chances of getting EF as compare to those children who don't have EH-3.

The coefficient for SANC-3 is 10.651. The odd ratio indicates that the children who face SANC-3 have 10.651 times more chance of getting EF as compare to children who enjoy SANC-1.

The coefficient for MEDF-3 is negative. The odds ratio is .28. It shows the children who fall in category MEDF-3 have .72 times chance of getting EF as compared to those who do not fall in this category.

For Wald test statistic P-Value of risk factors AGE, FEDU, SOEC, TYPH, EH-3, SANC-3 and MEDF-3 indicate that all these risk factors are statistically significant.

$$Z = .124 (AGE) + 2.590 (FEDU-1) + 2.989 (FEDU-2) + 2.768(FEDU-3) - 4.395(SOEC-2) - 4.140(SOEC-3) + .787(TYPH) - 1.947(EH-3) + 2.366(SANC-3) - 1.267(MEDF-3)$$

Example

Suppose AGE =5, FEDU-1=0, FEDU-2 =0, FEDU-3=1, SOEC-2=1, SOEC-3=0, TYPH=1, EH-3=1, SANC-3=1 and MEDF-3=0

$$Z = .124(5) + 2.590(0) + 2.989(0) + 2.768(1) - 4.395(1) - 4.14(0) + .787(1) - 1.947(1) + 2.366(1) - 1.267(0) = 0.199$$

The Probability of the occurrence of EF is

$$= \frac{1}{1 + e^{-z}} = \frac{1}{1 + e^{-0.199}} = .5496$$

Hence there is a 54.96% chance of the occurrence of EF.

d) Male Patients Analysis

Gender has irruption on the results. When applied Multiple Logistic Analysis to males exclusively, risk factors were not the same as described in overall patients analyses.

The value of $\chi^2 = 7.135$ with d.f 1 and p-value is .008. Thus, fitted model is appropriate even at 1% level of significance.

As shown in Table A-3, the coefficient for AGE is positive and the value of odd ratio is 1.13. It means that with the increase of one

year in AGE, the risk of EF is increased 1.13 times provided all other factors are kept constant. Since one year increase does not give any significant change therefore, the change after 10 years as $e^{10 \times .123} = 3.421$ is evaluated. This indicates that with an increase of 10 years in AGE the risk of EF is increases by 3.421 times.

The coefficient for TYPH is 3.475. The odd ratio shows that the children who have TYPH have 3.475 times more chance of getting an EF as compared to the children who do not have TYPH.

The coefficient for WI-3 is positive. The odds ratio is 32.49. It shows that the children who have the facility of WI-3 have 32.49 times more chance of getting EF as compare to WI-6.

The coefficient for HW is positive. The odd ratio is 2.96. It shows that the children having habit of HW-0 have 2.96 times more chance of getting EF as compared to those children having habit of HW-1.

The coefficient for EH-3 is negative. The odd ratio is .05. It shows that the children who have the habit to take EH-3 have .95 times more chance of getting EF as compared to those children who don't have the habit of EH-3.

The coefficient for SANC-3 is positive. The odd ratio indicate that the children who face SANC-3 have 14.07 times more chance of EF as compared to children who do not face SANC-3.

The coefficient for MEDF-3 is negative. The odds ratio is .15. It shows the children who fall in category MEDF-3 have .85 times chance of getting EF as compared to those who do not fall in this category.

The Wald test statistic and p-Value indicate that risk factors AGE, TYPH, WI, HW, EH-3, SANC-3 and MEDF-3 are statistically significant.

$Z = .123 (AGE) + 1.246 (TYPH) + 3.481 (WI) + 1.086 (HW) - 2.932 (EH-3) + 2.644 (SANC-3) - 1.899 (MEDF-3)$

Example

Suppose AGE=5, TYPH=0, WI=1, HW= 1, EH-3=1, SANC-3=0 and MEDF-3=1

$Z = .123(5) + 1.246(0) + 3.481(1) + 1.086(1) - 2.932(1) + 2.644(0) - 1.899(1) = .351$

The Probability of having EF is:

$$= \frac{1}{1+e^{-z}} = \frac{1}{1+e^{-.351}} = .586$$

Hence there is 58.6% chance of having EF.

e) Female Patients Analysis

Similarly in female spectrum of risk factors were slightly different.

The value of $\chi^2=12.23$ with d.f. = 4 and p-value is .016. Thus, fitted model is appropriate even at 2% level of significance.

As shown in Table-4, the risk factors AGE, SOEC-2, EH-3 and MEDF-3 are significant.

The coefficient of AGE is positive. The odds ratio is 1.35. Thus, as the AGE increases by one year the chance of TF is increased 1.35 times.

The coefficient for SOEC-2 is negative. The odds ratio is .011. It means that the children who belong to SOEC-2 have .99 times chance of getting EF as compared to others.

The coefficient for EH-3 is negative. The odd ratio is .20. It shows that the children who have the habit to take EH-3 have .80 times more chance of getting EF as compared to those children who don't have the habit of EH-3.

The coefficient for MEDF-3 is negative. The odds ratio is .18. It shows the children who fall in category MEDF-3 have .82 times chance of getting EF as compared to those who do not fall in this category.

The Wald test statistic and P-Value indicate that risk factors AGE, SOEC, EH-3, and MEDF-3 are statistically significant.

Z = .296 (AGE)– 4.544 (SOEC-2)-1.611 (EH-3)– 1.718 (MEDF-3)

Example

Suppose AGE=5, SOEC=1, EH-3=0 and MEDF-3=1

Z = .296(5)-4.544(1)-1.611(0)-1.718(1) = -4.788

The Probability of having EF is:

$$= \frac{1}{1+e^{-z}} = \frac{1}{1+e^{-4.788}} = .00826$$

Because probability is less than .5 so we can say that EF is not likely to occur.

4. Discussion

In overall multivariate analysis AGE, FEDU, TYPH, SANC-3, SOEC, EH-3 and MEDF-3 are significant risk factors for EF.

In the multivariate analysis of male patient's AGE, TYPH, WI, HW, EH-3, SANC-3 and MEDF-3 are significant risk factors.

In the multivariate analysis of female patients' AGE, SOEC, EH-3 and MEDF-3 are significant risk factors.

The probabilities of having EF are also calculated. For overall and male patients the probability of having EF is greater than .5. So, the chance of the occurrence of EF is higher than for female patients for which the probability is less than .5.

For overall, male and female patients' WI appears as a most significant risk factor - Bivariate analysis.

Enteric perforation is more common in males than in females. In the present study M:F (Male-female ratio) ratio was 1.45:1, that is consistent with the ratio of 6.41:1 reported by Singh (2003) and 4:1 reported by Adesunkanmill (1997). This is due to the fact that enteric fever is more common in males, possibly because of more exposure to infection.

The greatest incidence of infection was in children less than 15 years of age and similar to those of a community-based study conducted in India by Sinha (1999) and also contrast with Walsh (2000) and Bhutta (1996) study which have suggested peak incidence in children 5 to 15 years of age.

Cochrane (1982) and World Bank reports that parents' education and socio economic condition have strong effect on health seeking behavior, and this study also found significant effect of parents' education and socio Economic condition health seeking behavior.

The study revealed that intra household spread of typhoid were poor hand washing hygiene and outside the household were consumption of foods from street vendors. This corroborates the Albert report in Indonesia (2004) in which these two factors were also statistically significant.

It is also recognized that untreated water access Enteric Fever as Trann (2005) submitted that drinking untreated water plays a major role in getting Enteric Fever. According to him, improving quality of drinking water must be a priority to decrease the burden of typhoid fever.

It is also emphasized that *Salmonella Typhi* survive in sewage system as according to Weaver (1993) and Casner (2001) the actual source of this bacteria is sewage system.

This study shows that Typhoid spread through history of contact with patient of EF in family as shown in report of Indiana State Dept of Health (2004).

In this study long distance to the dispensary (5 km) increased the risk of Typhoid fever, as it shown in report of Thomas (2004) in Iraq during war.

The study gives the result that EF is not due to any single risk factor but this disease may cause due to more than one risk factors. Such as age, educational status of parents, consumption of street vendors' food, water intake history of contact with patient of EF in family and availability of Dispensary Facility.

Thus we infer that EF spreads through consumption of unhygienic food and beverages which are being handled by typhoid carrier. Since overall quality of food and hygienic is less than optimal in our country.

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TABLE - 1: Coding Scheme of the Variables

| No | Variable | Code Number |
|----|---|--|
| 1 | <u>Age (AGE)</u> | <u>Years</u> |
| 2 | <u>Age Code</u> | <u>0=<5, 1=5-15</u> |
| 3 | <u>Gender (GEND)</u> | 0 = female, 1= male. |
| 4 | Educational Status of Parents (EDU) | 1=illiterate, 2=Matric, 3=Intermediate, 4=Graduation, 5=Masters &above |
| 5 | <u>Family Size (FS)</u> | <u>Number of Persons</u> |
| 6 | <u>Family Size Code</u> | <u>0=<5, 1= 5-10, 2=>10</u> |
| 7 | Socio-Economic Condition (SOEC) | 1=high, 2=Middle, 3=Low |
| 8 | Any Family member had Typhoid (within year) | 0=No, 1=Yes |
| 9 | <u>Water Intake (WI)</u> | 1=Hand Pump Water, 2 = Wasa Water,3=Mineral Water,4=Filtered Water, 5=Motor water, 6= Boiled Water |
| 10 | <u>School Going (SG)</u> | 0=No, 1=Yes |
| 11 | Hand Washing before eating (HW) | 0=No, 1=Yes |
| 12 | Vaccination against Typhoid (VAC) | 0=No, 1=Yes |
| 13 | <u>Eating Habits (EH)</u> | 1=Seal Food, 2=Home Food, 3= Street Vendors Food |
| 14 | <u>Toilet Facility (TF)</u> | 1=WC, 2=Non-WC, 3=No Facility |
| 15 | Sanitation Condition (SANC) | 1=Satisfactory, 2= Good, 3= Bad |
| 16 | <u>Medical Facility (MEDF)</u> | 1=Hospital, 2=HealthCenter,3=Dispensary,4=Doctors |
| 17 | Attitude Towards Health Center (ATHC) | 1= Don't Like, 2= Weekly, 3=Monthly, 4=Annually,5=Rarely |

TABLE -2: LOGISTIC REGRESSION OUTPUT

| Variable | $\hat{\beta}$ | Wald | d.f | p-Value | Odds Ratio | 95% Confidence Limits | |
|------------------------------------|---------------|-------|-----|---------|------------|-----------------------|--------|
| | | | | | | LCL | UCL |
| Age | 0.12 | 10.49 | 1 | 0.001 | 1.13 | 1.05 | 1.22 |
| Educational status father (FEDU-1) | 2.59 | 4.98 | 1 | 0.026 | 13.34 | 1.37 | 129.73 |
| Educational status father (FEDU-2) | 2.99 | 6.87 | 1 | 0.009 | 19.87 | 2.12 | 185.89 |
| Educational status father (FEDU-3) | 2.77 | 5.87 | 1 | 0.015 | 15.93 | 1.7 | 149.66 |
| Socio Economic(SOEC-1) | -4.40 | 5.39 | 1 | 0.02 | 0.01 | 0.00 | 0.51 |
| Socio Economic(SOEC-2) | -4.14 | 4.54 | 1 | 0.033 | 0.02 | 0.00 | 0.72 |
| Typhoid History (TH) | 0.79 | 5.77 | 1 | 0.016 | 2.20 | 1.16 | 4.17 |
| Eating Habits (EH-3) | -1.95 | 24.19 | 1 | 0.000 | 0.14 | 0.07 | 0.31 |
| Sanitation Condition (SANC-2) | 2.37 | 20.77 | 1 | 0.000 | 10.65 | 3.85 | 29.46 |
| Medical Facility (MEDF-3) | -1.27 | 9.31 | 1 | 0.002 | 0.28 | 0.13 | 0.64 |

TABLE -3: LOGISTIC REGRESSION OUTPUT FOR MALE PATIENTS

| Variable | $\hat{\beta}$ | Wald | d.f | p-Value | Odds Ratio | 95% Confidence Limits | |
|-------------------------------|---------------|-------|-----|---------|------------|-----------------------|--------|
| | | | | | | LCL | UCL |
| Age | .123 | 6.80 | 1 | .009 | 1.13 | 1.03 | 1.24 |
| Typhoid History (TH) | 1.25 | 7.25 | 1 | .007 | 3.48 | 1.40 | 8.61 |
| Water Intake(WI-2) | 3.48 | 11.42 | 1 | .001 | 32.49 | 4.32 | 244.46 |
| Hand Washing (HW) | 1.09 | 7.31 | 1 | .007 | 2.96 | 1.35 | 6.51 |
| Eating Habits (EH-3) | -2.93 | 20.89 | 1 | .000 | 0.05 | 0.02 | 0.19 |
| Sanitation Condition (SANC-2) | 2.64 | 16.08 | 1 | .000 | 14.07 | 3.87 | 51.25 |
| Medical Facility (MEDF-3) | -1.90 | 9.97 | 1 | .002 | 0.15 | 0.05 | 0.49 |

TABLE -4: **LOGISTIC REGRESSION OUTPUT FOR FEMALE PATIENTS**

| Variable | $\hat{\beta}$ | Wald | d.f | p-Value | Odds Ratio | 95% Confidence Limits | |
|-----------------------------|---------------|-------|-----|---------|------------|-----------------------|------|
| | | | | | | LCL | UCL |
| Age (AGE) | 0.30 | 12.83 | 1 | .000 | 1.35 | 1.14 | 1.58 |
| Socio Eco Condition(SOEC-1) | -4.54 | 6.16 | 1 | .013 | 0.02 | 0.00 | 0.38 |
| Eating Habits (EH-3) | -1.61 | 8.04 | 1 | .005 | 0.20 | 0.07 | 0.61 |
| Medical Facility (MEDF-3) | -1.72 | 8.07 | 1 | .005 | 0.18 | 0.06 | 0.59 |