

# Acute Diarrhea and Malnutrition: Lethality Risk in Hospitalized Infants

Ulysses Fagundes-Neto, MD, PhD, and Jacy A.B. de Andrade, MD, PhD

Department of Pediatric Gastroenterology, Umberto I Hospital, São Paulo Federal University/Escola Paulista de Medicina, São Paulo, BRAZIL

**Key words:** acute diarrhea, lethality, malnutrition, enteropathogenic *Escherichia coli*

**Objectives:** Acute diarrhea is a very frequent disease in developing countries and is the first cause of death in infants under two years of age. This study was designed to evaluate the clinical and epidemiological factors associated to the death of 17 out of 511 infants hospitalized due to severe acute diarrhea between January 1989 and December 1995.

**Patients and Methods:** The patients were divided into two groups according to their clinical evolution: Group I—Death and Group II—Survival. The following parameters were evaluated: birth weight, gender, age, duration of diarrhea (days) prior to admission, nutritional status, hydration, presence of an enteropathogenic agent in the stools, food intolerance and duration of hospitalization.

**Results:** The analyzed factors have shown a significant association with death for the following variables: age, relative factor of death (RFD)=4.0 for infants less than six months of age, identification of an enteropathogenic *Escherichia coli* (EPEC) strain in the stools (RFD=3.3), severe malnutrition at admission to the hospital (RFD=4.5), occurrence of food intolerance during hospitalization (RFD=2.7). Some enteropathogenic agent was identified in the stools of 253 infants (54.9%), among the 461 (90.2%) studied. Group I revealed the presence of an enteropathogenic agent in 75% of the cases. The most frequent agents identified in Group I were: EPEC (56.3%) and *Shigella* (12.5%), while in Group II EPEC was identified in 26.5% of the patients.

**Conclusions:** The association of some factors, such as age less than six months, severe malnutrition, food intolerance and the identification of EPEC strains in the stool culture, indicate a high risk of death in infants hospitalized due to severe acute diarrhea.

## INTRODUCTION

The magnitude of the impact of the diarrheic diseases on infantile morbidity and mortality rates in developing countries is represented by more than one billion episodes and approximately 3.3 million deaths a year, respectively [1]. In the majority of the developing countries of the Americas, Asia and Africa, infantile mortality rates have always been associated with the frequency of diarrheic disease [2]. Diarrhea is the most important cause of death in children under five years of age [3,4]. In Brazil, acute diarrhea is responsible for the deaths of 20,000 children under five years of age each year, and this

number is fifty times higher than that estimated for children of the same age in the United States of America [5]. In Brazil, infants under one year of age represent the age group with a higher risk of death due to diarrhea (5.5 deaths per 1,000 inhabitants) [5].

The impact of diarrheic diseases is more severe in the earliest periods of life, taking into account both the number of episodes per year and the hospital admission rates [6]. The present knowledge concerning fluid and electrolyte losses and their replacements during an acute episode of diarrhea has proved to be an excellent tool for the treatment of the first stage of the disease, mainly on the community level [7]. However, in

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Abbreviations: NCHS=National Center of Health Statistics, WHO=World Health Organization, PCM=protein calorie malnutrition, RFD=risk factor of death, A/E=attaching and effacing, EPEC=enteropathogenic *Escherichia coli*, EIEC=enteroinvasive *Escherichia coli*, ETEC=enterotoxigenic *Escherichia coli*, EHEC=enterohemorrhagic *Escherichia coli*.

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Address reprint requests to: Ulysses Fagundes Neto, M.D., Ph.D., Av. Cons. Rodrigues Alves 1239, São Paulo, SP, BRAZIL.

those more severe cases that need hospitalization, the risk of perpetuation of diarrhea is beyond the efficacy of oral hydration, since food intolerance and nutritional aggravation are the most frequent clinical complications. In order to propose guidelines that may decrease significantly the infantile mortality rates, a better understanding of the interaction between the enteropathogenic agents and the host seems to be highly desirable.

The aim of this study was to determine the epidemiological and clinical factors potentially associated with lethality in hospitalized infants due to severe acute diarrhea.

## **Patients and Methods**

From January 1989 to December 1995, 511 children under five years of age hospitalized due to severe diarrhea in the Metabolic Unit of the Umberto I Hospital, São Paulo, Brazil, were prospectively studied. All patients had diarrhea lasting less than 14 days at the moment of admission. The patients' mean age was 5.5 months; 87.5% were under one year of age and 75.0% were under six months of age. According to the clinical evolution during hospitalization patients were divided into two groups:

Group I: 17 infants (3.3%) who died during hospitalization; the mean age was 3.8 months.

Group II: 404 infants (96.7%) who had a satisfactory evolution and were discharged from hospital in good clinical conditions; the mean age was 7.1 months.

## **Evaluation of Hydration Conditions**

After a clinical history was obtained and a physical examination was performed by a pediatric gastroenterologist, patients were admitted to the Metabolic Unit to stay until diarrheal disease had ceased. At the time of admission, the degree of dehydration was clinically estimated as mild (<6%) by general appearance, absence of tears and moist mucous membranes, or moderate (6% to 9%) by presence of sunken anterior fontanel and/or eyes and changes in skin elasticity. Children with severe dehydration (10% or more), as judged by signs of moderate dehydration and abnormalities of pulse and/or mental status received intravenous rehydration therapy. Oral hydration and/or intravenous therapy were given to all patients. The amount of fluid given was calculated to replace the estimated hydration deficit and the continuing fecal losses. The patients were rehydrated between four and six hours after admission to the hospital. Rehydration was gauged clinically by the presence of tears, return of skin turgor and moist mucous membranes, weight gain and increased urine output. This judgment was made by the same physician who examined the patient on admission to the study. As soon as the infants were rehydrated, refeeding was initiated and oral hydration or intravenous solutions or both were given in quantities equal to stool losses.

## **Refeeding Protocol and Criteria for Food Intolerance**

Feeding was continued during hospitalization, and supportive therapy was instituted whenever required. The refeeding protocol provided maintenance calories during the first day of treatment. Thereafter, oral intake was increased gradually, and patients were fed up to 120 kcal/kg/day during the second or third day of treatment, and during the subsequent days food intake was determined by the *ad libitum* criteria. The initial feeding was based on cow's milk formula full strength dilution and when patient's age allowed solid foods were included into the diet. Cow's milk feeds were withdrawn from infants who exhibited signs of cow's milk intolerance and replaced by a lactose-free, casein-based formula. When the latter was not tolerated, a protein-hydrolysate-based, lactose-free formula was offered. Total Parenteral Nutrition was indicated whenever intolerance to the protein-hydrolysate-based formula was detected.

The criteria for food intolerance included persistence of diarrhea for a 72-hour observation period associated with weight loss and presence of reducing substances in stools and/or fecal pH <6.0 [8] while formula intake of at least 70 kcal/kg/day was provided.

The following parameters were evaluated in relation to the clinical outcome of the patients: Birth weight, gender, age, duration of diarrhea prior to hospital admission, nutritional status, hydration conditions, enteropathogenic agents identified in the stool culture, food intolerance and duration of hospital admission.

## **METHODS**

### **Nutritional Status Evaluation**

The nutritional status was evaluated after fluid and electrolyte losses were corrected, according to Gomez' criteria [9] and the National Center for Health Statistics (NCHS) [10] growth chart.

### **Stool Culture and Rotavirus Test**

At admission, stool specimens were collected and were examined for the usual enteric pathogens (*Salmonella*, *Shigella*, *Yersinia enterocolitica*, *Campylobacter*, *Cryptosporidium* and ova and parasites) using standard techniques [11]. Three to five colonies, biochemically identified as *Escherichia coli* were serotyped according to standard methods, using commercial available polyvalent and monovalent sera (Probac do Brasil, São Paulo, Brazil) against O antigens of enteropathogenic (EPEC), enteroinvasive (EIEC), enterotoxigenic (ETEC) or O157 enterohemorrhagic (EHEC) serogroups of *E. coli*. H antigens were identified by standard assays, using H 1 to H 5 antisera prepared at the Center for Diseases Control, Atlanta,

Georgia [12]. Rotavirus antigen was identified with an enzyme-linked immunoassay [13].

### Statistical Analysis

Data analysis and statistical evaluation were calculated using parametric and non-parametric tests according to the nature of the distribution of the studied variables. The  $\chi^2$  test and the Fisher exact test considering the Cochran restrictions were used. The risk factor of death (RFD) was utilized to estimate the degree of association between the studied variables and death occurrence (Confidence interval=95%). This project was approved by the Research and Ethics Committee of the Escola Paulista de Medicina.

## RESULTS

The evaluation of the nutritional status revealed that only 143 patients (28%) were wellnourished at admission to the hospital. The remaining 368 malnourished patients (72%) were classified as follows: protein-calorie malnutrition PCM I 174 (34%), PCM II 125 (24.5%) and PCM III 69 (13.5%). The qualification of the nutritional status of the patients according to the age is shown in Table 1.

The following variables showed a significant association with RFD: age, severe malnutrition (PCM III), presence of EPEC in the stool culture and food intolerance (Table 2).

The RFD was 4.0 times higher for the infants under six months of age ( $4.5\% \times 1.1\%$ ) ( $p < 0.05$ ) and 3.6 times higher for the patients suffering severe malnutrition when compared with the wellnourished ones and those suffering moderate degrees of malnutrition at the moment of hospital admission ( $p < 0.05$ ).

In the present study an enteropathogenic agent was isolated in the stool culture in 253 patients (54.9%). The distribution of the different enteropathogenic agents according to the clinical outcome of the patients is shown in Table 3. EPEC serogroups were the most frequent agents identified in the stools (27.5%), mainly the following specific serogroups: O111 (19.3%) and O119 (5.2%). In Group I the etiologic investigation resulted positive in 75% of the cases, and EPEC serogroups were the most frequent, present in 56.3% of the cases, followed by Shigella (12.5%). In Group II the etiologic investigation resulted positive in 54.1% of the cases; EPEC serogroups were

also the most frequent enteropathogenic agents, in 42.2% of the cases and, again, followed by Shigella (7.6%). The RFD was 3.4 times higher in those cases in which some EPEC serogroup was identified in the stools in comparison with cases in which the etiologic investigation resulted negative.

The associative comparison between age groups, under or above six months, and the presence of EPEC serogroups in the stool culture was positive in 33.2% (78/235) of the patients under six months of age and in 21.7% (49/226) of the patients above six months of age. These values showed significant differences when the statistical tests were applied ( $p < 0.05$ ).

Food intolerance was detected in 11 patients (64.7%) belonging to Group I and in 194 patients (39.7%) belonging to Group II. The RFD was 2.7 times higher for the patients who revealed food intolerance in comparison to those that did not show this clinical complication. The frequency of food intolerance was higher and statistically significant in patients under six months in comparison to those above six months of age, respectively: 53.9% vs. 27.1% ( $p < 0.01$ ). There was also a significant positive association between the identification of EPEC serogroups in the stool culture and the presence of food intolerance.

Sepsis was the most frequent cause of death, being responsible for 58.8% (10/17) of the fatal outcomes; in 60% (6/10) of the cases a microorganism was identified in the blood culture, and the most frequent were *Staphylococcus aureus* (3/6) and *Proteus mirabilis* (3/6).

## DISCUSSION

Diarrhea remains one of the most common illnesses of children and one of the major causes of infant and childhood mortality in developing countries. Considering the usually scanty resources available in the Third World, a reduction in diarrhea-related mortality may be possible by identifying high-risk subjects and targeting them for intensive intervention. In the present study, we were able to identify four factors significantly associated with death, namely, age, severe malnutrition (PCM III), presence of EPEC in the stool culture and food intolerance.

Sachdev *et al.* [14], utilizing univariate and multivariate analysis, were also able to find four factors statistically related

**Table 1.** Nutritional Status of the Patients According to the Age

| NUTRITIONAL STATUS                              | PCM I | PCM II | PCM III               | WELLNOURISHED | TOTAL                |
|---|-------|--------|-----------------------|---------------|----------------------|
| Total   | 174   | 125    | 69                    | 143           | 511                  |
| % Death   | 0     | 3.5    | 10.1                  | 2.8           | 3.3                  |
| WELLNOURISHED $\times$ PCM I + PCM II + PCM III |       |        | * $\chi^2$ CALC=16.92 |               | $\chi^2$ CRITIC=7.82 |
| WELLNOURISHED $\times$ PCM II                   |       |        | $\chi^2$ CALC=0.83    |               |                      |
| WELLNOURISHED + PCM I + PCM II $\times$ PCM III |       |        | * $\chi^2$ CALC=11.53 |               | $\chi^2$ CRITIC=3.84 |
| PCM I $\times$ WELLNOURISHED + PCM II           |       |        | $\chi^2$ CALC=4.56    |               |                      |

**Table 2.** Variables That Showed a Significant Association with Death in Infants Hospitalized Due to Severe Acute Diarrhea

| EV*                          | Group I <sup>1</sup><br>(n) | Group II <sup>2</sup><br>(n) | %<br>Total <sup>3</sup> | EV/death (%) <sup>4</sup> | Death/EV (%) <sup>5</sup> | $\chi^2$ | RFD <sup>6</sup> |
|------------------------------|-----------------------------|------------------------------|-------------------------|---------------------------|---------------------------|----------|------------------|
| Age <6 months<br>p=0.04      | 15                          | 320                          | 2.9                     | 88.2                      | 4.5                       | 4        | 4                |
| EPEC in the Stools<br>p=0.01 | 9                           | 118                          | 1.8                     | 52.9                      | 7.1                       | 6.8      | 3.4              |
| PCM III p=0.01               | 7                           | 62                           | 1.4                     | 41.2                      | 10.1                      | 11.5     | 3.6              |
| Food Intolerance<br>p=0.04   | 11                          | 194                          | 2.1                     | 64.7                      | 5.4                       | 4.24     | 2.7              |

$\chi^2$  critic=3.84 (p=0.05)

\* EV=Evaluated Variable

<sup>1</sup>=Death

<sup>2</sup>=Survival

<sup>3</sup>=Percentage of patients that showed the evaluated factor and died

<sup>4</sup>=Percentage of patients that showed the evaluated factor and died in relation of the total of death

<sup>5</sup>=Percentage of death (patients that showed the evaluated factor)

<sup>6</sup>=Risk Factor of Death

**Table 3.** Distribution of the Different Enteropathogenic Agents according to the Clinical Outcome of the Patients

| ENTEROPATHOGENIC AGENTS | GROUP I | GROUP II | TOTAL | DEATH % |
|-------------------------|---------|----------|-------|---------|
| EPEC                    | 9       | 118      | 127   | 7.1     |
| Shigella                | 2       | 34       | 36    | 5.9     |
| Salmonella              | 0       | 16       | 16    | 0       |
| EHEC                    | 0       | 1        | 1     | 0       |
| EIEC                    | 0       | 2        | 2     | 0       |
| ETEC                    | 0       | 5        | 5     | 0       |
| Campylobacter           | 0       | 20       | 20    | 0       |
| Cryptosporidium         | 0       | 2        | 2     | 0       |
| Rotavirus               | 0       | 13       | 13    | 0       |
| Mixed                   | 1       | 30       | 31    | 3.2     |
| Negative                | 4       | 204      | 208   | 2.4     |
| Total                   | 16      | 445      | 461   | 3.5     |

GROUP I: DEATH    GROUP II: SURVIVAL

EPEC=Enteropathogenic Escherichia coli

ETEC=Enterotoxigenic Escherichia coli

EHEC=Enterohemorrhagic Escherichia coli

EIEC=Enteroinvasive Escherichia coli

to deaths in hospitalized children due to acute diarrhea. Associated major infection, severe wasting, severe stunting and protracted diarrhea were the major risk factors for death in children under five years of age, in New Delhi. Although there are similarities in the findings of both studies, we could point to some different interpretations for the reported results. In the New Delhi study, a precise etiological diagnosis of diarrhea was not attempted, and the mortality rate was 10.4%. Severe malnutrition and persistence of diarrhea associated with non-enteral infection were important factors for death from diarrhea. In our study, a detailed etiological investigation was undertaken, and EPEC serogroups emerged as the most frequent enteropathogenic agent associated with food intolerance as a risk factor for death, mainly in infants under six months of age. Persistence of diarrhea as currently defined by WHO experts [15] is most probably due to food intolerance after an

episode of acute diarrhea, presumably induced by an enteropathogenic agent. It is well known that persistence of diarrhea due to food intolerance is associated with malabsorption of nutrients, a very common cause of nutritional aggravation leading to severe malnutrition [16, 17]. Victora *et al.* [18], studying deaths due to diarrhea among children in Brazil, found that among 90% of those who reached a health-care facility, persistent diarrhea was responsible for 62% of the mortality, suggesting that deaths from acute dehydration were prevented. Persistent diarrhea and malnutrition are the major clinical components of food intolerance as a consequence of the morphological and functional lesions that occur on the small bowel mucosa causing malabsorption of the nutrients of the diet. Thus enteric infection constitutes the triggering factor that generates a vicious cycle represented by persistence of diarrhea, food intolerance and severe protein-calorie malnutrition. The presence of these major clinical complications is responsible for the most important risk factors for death in hospitalized infants due to severe acute diarrhea. On the other hand, nonenteral infections are frequently acquired during prolonged hospital stays, most often on account of inappropriate hospital hygiene conditions associated with immunological deficiencies of the patients, a common complication observed in severe malnutrition states. Systemic infection acts, in general, as the final stage in this chain reaction that evolves into death.

Age has been considered a controversial risk factor for death from acute diarrhea. Sachdev *et al.* [14] did not document any significant relation of younger age (less than six months) with mortality, but reports of a total of 22 longitudinal studies in 12 countries found median global values for mortality highest among infants less than one year of age [19]. In our present series, RFD was four times higher for infants under six months. The frequency of food intolerance was by far greater in patients under six months in comparison to those above this age, respectively: 53.9% vs. 27.1%, and the RFD was 2.7 times higher

for the patients that revealed food intolerance. Another interesting aspect that should be stressed in our results is that identification of EPEC serogroups in the stool culture was significantly more frequent in infants under six months of age than in those above this age (33.2% vs. 21.7%, respectively) ( $p < 0.05$ ). There was also a significant positive association between an identification of EPEC serogroups in the stool culture and the presence of food intolerance.

EPEC infections are unusual in most industrialized countries, but they are a major cause of infantile diarrhea in developing countries [20]. In São Paulo, Brazil, EPEC strains are the major enteropathogenic agents in infants under one year of age, with the highest prevalence occurring in those under six months of age [21]. EPEC strains can induce a copious secretory diarrhea severe enough to require intravenous hydration, since the failure rate of oral rehydration therapy can be as high as 26% [22]. In general, less than 10% of acute episodes of diarrhea in children under five years of age require hospitalization; however, EPEC gastroenteritis is also associated with a higher rate of hospitalization, reaching 34% of the cases in our experience in a previous study in Brasilia, Brazil [22]. This fact indicates that EPEC organisms are relatively more virulent than most of the other known enteropathogenic agents and can potentially evolve into protracted illnesses. Acute diarrhea episodes induced by EPEC strains are also highly related to persistence of diarrhea due to the association of a secretory process and food intolerance, leading to severe nutritional aggravation in up to 30% of the cases [22]. EPEC strains are able to adhere to human intestinal tissue, inducing a typical lesion of attaching and effacing (A/E) [23]. The A/E lesion leads to dissolution of the brush border membrane and loss of microvillus structures of bacterial attachment, causing cuplike projections of the apical membrane [24]. The presence of A/E lesion is associated with fluid secretion and derangement of the digestive-absorptive enzymatic equipment, which is responsible for the persistence of diarrhea associated with malabsorption of the nutrients [25]. Recently, Fagundes-Neto *et al.* [26] reported the nutritional impact and ultrastructural alterations in the small bowel epithelium in infants with severe acute diarrhea due to EPEC strains that evolved to persistent diarrhea. Patients had cow's milk intolerance as well as casein, lactose-free formula intolerance. Diarrhea ceased and patients started to gain weight when a protein-hydrolysate, lactose-free formula was introduced into the diet. Ultrastructural abnormalities in the intestinal epithelium included the presence of bacteria attached to long disoriented microvilli, pedestal formation and partial effacement of the microvilli surface. Lifshitz *et al.* [27], since the early seventies, have been advocating the use of lactose-free formula for young infants with severe acute diarrhea, because of the frequent occurrence of lactose malabsorption/intolerance reported, mainly in patients under six months of age. We have always followed this nutritional policy, an

aggressive dietary treatment, such as the utilization of a specifically designed lactose-free formulas, at the onset of gastroenteritis in high-risk infants with severe diarrhea, namely, patients who are malnourished, under six months of age and/or infected with EPEC strains. We can speculate that this is one very important reason why the mortality rate in the present series is approximately 3%, a reasonable result for severe acute diarrhea in hospitalized infants, the majority under six months of age.

The identification of these major risk factors of death in our series clearly shows that there is a strong interaction among them. In summary, enteric infection acquired in early stages of life, in infants belonging to low-income families, is commonly associated with the presence of EPEC serogroups in the stools. EPEC infection is prone to cause food intolerance that results in perpetuation of diarrhea and nutritional aggravation requiring a prolonged hospital stay. Prolonged hospitalization and malnutrition predispose patients to systemic infection, which in turn is responsible for fatal outcomes. In the present study, we emphasized the identification of the enteropathogenic agent and the prompt detection of food intolerance to allow high priority in choosing the best diet to assure efficient nutritional support, in order to avoid persistence of diarrhea and nutritional aggravation. Following these guidelines has enabled us to keep our mortality rates close to those reported for hospitalized patients with severe acute diarrhea in industrialized countries.

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