

Salmonellosis: An Epidemiologic Study

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Abstract

Background: Salmonella species commonly produce acute gastroenteritis. The clinical course may be affected by factors such as age, immunosuppression, and underlying disorders.

Objectives: To investigate clinical and laboratory differences in the infected population and the risk of complications according to the different age groups.

Methods: The records of 295 patients with positive cultures for Salmonella were divided into six age groups and reviewed retrospectively for the years 1994–1997. Demographic, clinical and laboratory data, extraintestinal manifestations, underlying disorders, organism source, and susceptibility to antibiotics were analyzed.

Results: We found that 88.5% were only stool positive, 9.2% had positive blood cultures, and 2.4% were positive in both blood and stool; 3.6% were found to have underlying disorders. Anemia, disturbed liver function tests and hypoalbuminemia were the most common pathologic laboratory findings. Salmonella serogroups B and D were isolated most frequently. The rate of positive blood cultures increased significantly during the years, as did resistance to ampicillin and trimethoprim-sulfamethoxazole. Salmonella infection has two peaks of incidence: at ages 1–5 and 15–65 years. Bacteremia was prominent in the extreme ages.

Conclusions: Salmonella infection has a different clinical presentation in different age groups. The significant increase in the rate of bacteremia in the extreme age groups necessitates a different attitude and management for these heterogeneous patient populations.

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Salmonella are gram-negative, rod-shaped bacteria that are ubiquitous among domestic and wild warm-blooded animals, and may cause illness in humans [1]. Salmonellosis increased steadily in many western countries during the 1970s and 1980s, with an especially sharp rise in some countries during the last 5 years due to a certain phage type of *Salmonella enteritidis* [2]. There are more than 2,200 serovars of Salmonella, but less than 200 can cause illness in humans. *Salmonella typhimurium* and *Salmonella enteritidis* account for three-quarters of reported cases, while *S. enteritidis* accounts for more than half of the total number of cases [2]. Excluding *S. typhi* and *S. paratyphi*, Salmonella infections are usually confined to the gastrointestinal tract [3], while in healthy children and adults the disease is usually a self-limited disorder. Childhood infection with *S. enteritidis* species commonly produces acute gastroenteritis which is characterized by fever, diarrhea, vomiting and lethargy [4]. However, the clinical course may be affected by factors such as age, immunosuppression, sickle cell anemia, and underlying disorders that encourage colonization [5–7]. Therefore, in the elderly the disease pattern may be different and more severe [5].

In our study we reviewed all Salmonella-positive cultures in our hospital during the years 1994–1997 in order to investigate clinical and laboratory differences in the infected population and the risk of complications according to the different age groups.

Patients and Methods

Patients

We selected patients by means of a computer-generated list of the microbiology records at Assaf Harofeh Medical Center, Zerifin, Israel, from January 1994 through December 1997. Records of 295 patients with positive cultures for Salmonella (blood, stool, urine, cerebrospinal fluid) were reviewed retrospectively. Data collection from the charts included age, gender, presenting signs and symptoms, intestinal and extraintestinal manifestations, and underlying conditions, as well as laboratory parameters. The organism source, identification, and sensitivity for antibiotics were gathered from the microbiologic records. We divided the 294 patients (one patient's age was unavailable) with positive cultures for Salmonella into six age groups: <0.25 years (n=21), 0.25–1 years (n=63), 1–5 years (n=82), 5–15 years (n=29), 15–65 years (n=72), and >65 years (n=27). All data were processed according to the different age groups and the distribution through the years 1994 to 1997.

Microbiologic methods

All samples were cultured by standard procedures [8]: feces cultures by direct plating on Mac-Conkey agar, Salmonella-Shigella agar, which is selective for Salmonella, as well as enrichment media-selenite broth. Bactec aerobic and anaerobic blood cultures medium and the BACTEC 9000 system (Becton Dickinson Biosciences, USA) were used for processing blood samples. Diaslide – a urine culture device (Savion-Yaron Diagnostic Marketing Ltd, Israel) containing CLED agar and Mac-Conkey agar – was used for urine sample plating. Growth from a single typical colony was used for testing the specific biochemical properties with the help of a computerized typing device (Api 20E Bio-Merieux, France). Salmonella colonies were serologically typed with screening sera: Polyvalent O (Difco Laboratories Inc., Detroit, USA) and Omni H (Central Laboratories, Ministry of Health, Israel). The definite identification was performed by the National Center for Salmonella at the Central Laboratories, Ministry of Health, Jerusalem, Israel. The antimicrobial susceptibilities of the strains were determined by the Kirby-Bauer agar diffusion method and interpreted according to guidelines of the National Committee for Clinical Laboratory Standards for the following antimicrobial agents: ampicillin,

trimethoprim-sulfamethoxazole and ciprofloxacin using BBL susceptibility disks (Beckton Dickinson).

Statistical analysis

The results are presented as mean ± standard deviation for continuous variables, and percentage for discrete variables. The difference between age groups and during the different years was calculated by one-way analysis of variance and chi-square test using the Mantel-Haenszel test for linear association.

Results

A total of 295 positive cultures for Salmonella was identified by the Assaf Harofeh Medical Center microbiologic computer system between January 1994 and December 1997. The mean age of patients was 16.8 years (range 0.07–96 years); 261 (88.5%) were only stool positive, 27 (9.2%) were identified in blood cultures and not in stool, and 7 (2.4%) were identified both in blood and stool cultures. No positive cultures were identified in urine and CSF. Demographic and clinical data are summarized in Table 1.

Among the 295 Salmonella-positive patients, 40 (13.5%) had underlying disorders (alone or in combination) [Table 1]. No comorbidity was found in patients under the age of 3 months. Only 3 patients under the age of 1 year were documented, 4 were 1–5 years

old, 20 were between the ages of 15 and 65, and 12 were over 65 years old [Table 1].

The presenting symptoms among the 295 cases were gastrointestinal in 206, central nervous system in 17, prolonged fever in 16, and 6 presented with other symptoms. Hemoglobin <12 g/dl was found in 160 (54.4%) and disturbed liver function test (aspartate

Table 1. Demographic and clinical data of patients

Total	295
Gender (M/F)	157/138
Mean age ± SD (yrs)	16.82 ± 24.64 (range 0.07–96)
Stool frequency	7.92 ± 4.7
Bloody diarrhea	45
Days of diarrhea	5.24 ± 4.52
Days of hospitalization	6.5 ± 6.5
Fever	251
Abdominal pain	106
Underlying disorders	40
Immunodeficiency	11/40
Hospitalization for other reason	10/40
Operated stomach	7/40
Antisecretory drugs	6/40
Diabetes mellitus	3/40
Pregnancy	3/40
S/p intestinal operation	2/40
Inflammatory bowel disease	1/40
Others	7/40

CSF = cerebrospinal fluid

Table 2. Clinical data by age group*

Age (yrs)	<0.25	0.25–1	1–5	5–15	15–65	>65	P value
N	21	63	82	29	72	27	
Mean stool frequency SD	8.1 2.9	7.8 4.7	7.3 4.6	8 3.4	8.9 5.8	6.7 3.3	NS
Days of diarrhea SD	6.3 7.1	6.2 6.4	5.3 3.9	4.3 1.7	4.8 2.9	3.7 2.3	NS
Bloody diarrhea (%)	55	34.5	10.5	3.7	7.6	0	< 0.0001
Abdominal pain (%)	4.8	0	12.3	79.3	80.6	51.9	< 0.0001
Fever (%)	85.7	92.1	92.7	96.6	88.8	74.1	0.06
Days of hospitalization	7.6 7	6.3 6.4	5.4 2.6	5.5 4	6.2 7.3	11.4 11.4	0.016

* One missing case

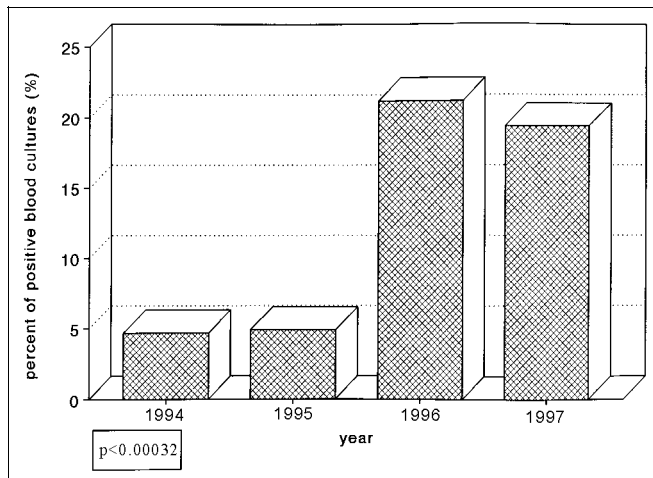


Figure 1. Rate of bacteremia among the different age groups.

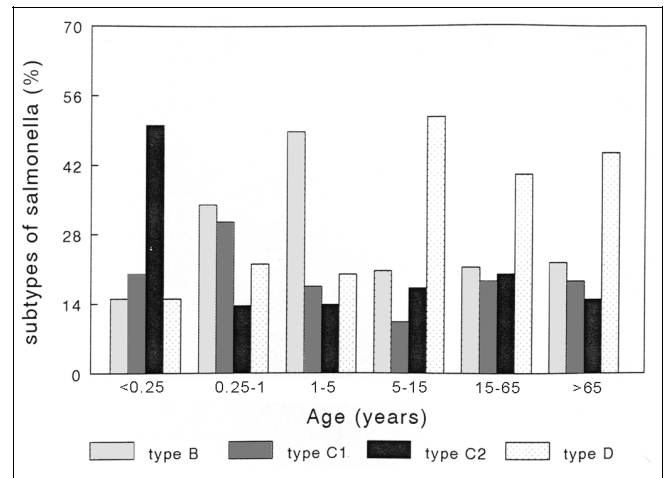


Figure 2. Distribution of Salmonella subtypes according to different age groups.

aminotransferase, alanine aminotransferase, alkaline phosphatase) or hypoalbuminemia were present in 11–27% of the patients. *Salmonella* serogroups B and D were isolated most frequently: 31.5% and 30.4% respectively, followed by *Salmonella* C1 and C2: 19.9% and 18.2% respectively.

No differences with regard to clinical and routine laboratory data were found from 1994 to 1997. However, the rate of positive blood cultures increased significantly during the years: from 4.7% in 1994, and 4.9% in 1995 to 21.2% in 1996 and 19.4% in 1997. Yet no mortality was documented among these patients. Resistance to ampicillin also increased during this period from 10.6% in 1994 up to 48.4% in 1997. Trimethoprim-sulfamethoxazole resistance increased from 2.4% to 11.3% in 1997 ($P < 0.001$). Analysis of antibiotic resistance in the different age groups revealed increased resistance to ampicillin in the old age group and to a lesser degree to trimethoprim-sulfamethoxazole.

Processing the data according to the different age groups revealed two peaks of incidence of *Salmonella* infection: age 1–5 years and 15–65 years. Table 2 presents the clinical data among the different age groups. No differences were found in either mean stool frequency or in duration of diarrhea. However, bloody diarrhea was absent in patients over the age of 65. Hospitalization was longer in infants or elderly patients.

Figure 1 demonstrates the rate of bacteremia between the different age groups. Distribution of *Salmonella* subtypes according to age groups is shown in Figure 2. *Salmonella* C2 was most frequent in infants, serogroup B in patients aged 1–5 years, and serogroup D in those over the age of 5.

Discussion

Salmonella-induced enteritis is a widespread cause of morbidity and mortality, especially in developing countries [7,9]. The rate of non-typhoidal *Salmonella* cases increased dramatically during the period 1981–1990 in the United States [10], the most common presentation of illness being gastroenteritis [1,7,11]. Sporadic illness is likely to go underdiagnosed because specimens are not taken for cultures [12]. Most outbreaks are characterized by self-limited fever and diarrhea associated with nausea, vomiting and crampy abdominal pain [1,12]. Diarrhea may be occasionally bloody or dysenteric and resolves spontaneously, but it may cause severe dehydration or disseminate and lead to death in debilitated elderly patients or neonates [12]. In our study, fever was present in 85% of cases. Bloody stools were a unique presentation in young patients, and were prominent especially in the neonatal age group where they reached 55%. None of the elderly (>65 years) had bloody stools. Abdominal pain was a frequent symptom in both young and old patients. In the majority of our patients the presenting symptoms were gastrointestinal while only 17/295 (5.9%) presented first with central nervous system manifestations, particularly lethargy and stupor, despite similar stool frequency or duration of diarrhea. Maximal hospitalization days were documented in the extreme age groups: infants younger than 0.25 years or elderly above age 65. These findings suggest that the natural history of salmonellosis may be worse at these ages and treatment must be more aggressive. Anemia (hemoglobin <12 g/dl) was present in half

of the patients, elevated transaminase ALT was found in 16.1% of patients and hypoalbuminemia (albumin <3.5 g) in 11.6%.

Excluding *Salmonella typhi* and *S. paratyphi* the clinical course of the disease may be affected by factors such as age, immunosuppression states such as hypogammaglobulinemia, AIDS, steroid treatment and other underlying disorders that encourage colonization of bacteria [5,13–16]. A review of the literature showed that the conditions predisposing to infection or complication were partial gastrectomy, oral steroid intake and diuretics in those aged 0–64 years; vagotomy with gastrojejunostomy, pernicious anemia, atrophic gastritis, chronic myeloid leukemia, non-Hodgkin's lymphoma, cimetidine treatment, and diuretics in those above age 65 [5,17]; and antibiotics and underlying liver disease in all age groups [6]. In our study we found 40/295 patients with underlying disorders alone or in combination. Immunodeficiency was the leading cause (27.5% of the total of 40 patients), followed by prolonged hospitalization due to other diseases, operated stomach, use of antiseptic drugs, diabetes mellitus, pregnancy, and inflammatory bowel disease. The rate of underlying disorders increased with age. None was present in individuals under the age of 3 months, and only three cases under the age of 1 year were documented. It is well established that young infants are at particular risk for focal complications such as meningitis [18].

In other studies the reported isolation rate of *Salmonella* from blood was higher for infants under 1 year old [3,18,19], with the peak rate in the 0–2 months old group. For patients older than 70 the isolation rate doubled compared to the rate for those between 60 and 70 years old, but was still significantly lower than the rate for patients younger than 1 year old [20]. Similarly, in our study we found two peaks for bacteremia: in those between 0 and 3 months old (23.8%) and persons above 65 years (29.6%) – which was even higher than the neonatal rate. In those aged 1–5 years, the isolation rate was minimal and did not pass 3.7%. For unexplained reasons the isolation of *Salmonella* from blood increased significantly from 4.7% in 1994 to 21.2% in 1996 and 19.4% in 1997. The four most common serotypes of *Salmonella* isolated from blood in other studies were *S. typhi*, *S. typhimurium*, *S. enteritidis* and *S. heidelberg*. In our study the most frequent subtypes of *Salmonella* that were isolated were *S. typhimurium*, *S. enteritidis*, *S. virchow* and *S. hadar*. *Salmonella* C1 was isolated most frequently in neonates as compared to serogroups D and B, which were isolated in patients above 15 and 1–5 years old, respectively.

Traditionally, antimicrobial drugs have not been recommended for *Salmonella* enterocolitis unless extraintestinal complications are present [16]. If bacteremia is present on admission an adverse course of disease may be expected in the very young and the elderly. Therefore, the modality of treatment might be different in these two extreme age groups. Resistance to ampicillin increased during the years, from 10.6% in 1994 up to 48.4% in 1997, as did resistance to trimethoprim-sulphamethoxazole, although less striking (from 2.4% to 11.3%). No resistance was found to ciprofloxacin or ceftriaxone.

ALT = alanine aminotransferase

In conclusion, Salmonella infection has a different presentation in different age groups. Therefore, a different approach and management protocol is needed for these heterogeneous patient populations.

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Capsule

The carotid as a chemoreceptor

The mammalian carotid body in the neck is a chemoreceptor that senses O₂ levels in the circulatory system and adjusts the respiratory rate accordingly. When O₂ becomes scarce, large-conductance calcium-sensitive potassium (BK) channels become inhibited, which causes cell depolarization and a cascade of responses that ultimately increases ventilation. Williams et al. find that hemoxygenase-2 (HO-2) acts as an O₂ sensor to control

BK channel activity. At normal O₂ concentrations, HO₂ uses O₂ as a substrate to generate carbon monoxide (CO), a critical channel activator. During hypoxia, when O₂ becomes scarce, HO₂ activity and CO generation fall, which inhibits BK channels and results in carotid body excitation.

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E. Israeli

Capsule

Israeli scientist leads nanotechnology

Prof. Ehud Shapiro of the Weizmann Institute of Science has been named Research Leader in the field of Nanotechnology and Molecular Electronics within the 2004 "Scientific American 50" for his work on DNA-based computing machines. The magazine's annual list recognizes outstanding acts of leadership in science and technology. Prof. Shapiro's biomolecular computing devices, made entirely of DNA and other biological molecules, are so small that more than a trillion fit into one drop of water. A recent version was programmed by Shapiro and his team to identify signs of specific cancers in a test tube, to diagnose the type of

cancer and to release drug molecules in response. Although the device is still in the very early stages and able thus far to function only in test tubes, Shapiro's team envisions future biomolecular devices that may be injected directly into the human body to detect and prevent or cure disease. Prof. Shapiro is the recent recipient of the 2004 World Technology Award for Biotechnology, and his PhD student Yaakov Benenson received a 100 Top Young Innovators Award from MIT's Technology Review Magazine.

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