A 10-year retrospective review of *Salmonella* infections at the Children's Hospital in London, Ontario

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OBJECTIVES: To describe *Salmonella* infections in children presenting to the Children's Hospital (London Health Sciences Centre, London, Ontario), to assess risk factors for infection and to examine whether younger children, particularly infants younger than 12 weeks of age, experience higher morbidity than older children.
METHODS: A 10-year retrospective review of children with *Salmonella* infections at the Children's Hospital was conducted. Patient demographics, risk factors for infection, clinical characteristics, bacteriology and outcome were collected from the hospital charts and laboratory records. Data were separated into groups based on age and recent use of antibiotics to analyze differences in outcomes.
RESULTS: Sixty-six children with *Salmonella* infections presented to the Children's Hospital over a 10-year period. Common risk factors for *Salmonella* infection included having sick contacts, living in a rural area, recent travel, contact with pets (especially reptiles) and exposure to local water. Younger age was associated with an increased likelihood of admission to hospital, treatment with antibiotics and a longer course of antibiotic therapy. This was true when comparing older infants with those younger than 12 weeks of age. Patients recently treated with antibiotics and those with significant underlying medical conditions were more likely to be admitted.
CONCLUSIONS: A wider knowledge of the epidemiological risk factors for *Salmonella* infection may improve diagnosis. Higher admission rates were expected in children younger than 12 weeks of age, those recently treated with antibiotics and those who had a significant underlying medical condition. A prospective, multicentre study is needed to further address questions regarding increased illness severity and appropriate management of *Salmonella* infections in children younger than 12 weeks of age.

Key Words: *Children; Risk factors;* Salmonella *infections*

Une analyse rétrospective des infections à Salmonella sur dix ans au *Children's Hospital* de London, en Ontario

OBJECTIFS : Décrire les infections à Salmonella chez les enfants qui consultent au *Children's Hospital* du *London Health Sciences Centre*, de London, en Ontario, pour évaluer les facteurs de risque d'infection et examiner si les jeunes enfants, notamment les nourrissons de moins de 12 semaines de vie, présentent une morbidité plus élevée que les enfants plus âgés.
MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse rétrospective sur dix ans des enfants ayant une infection à *Salmonella* au *Children's Hospital*. Ils ont obtenu la démographie des patients, les facteurs de risque d'infection, les caractéristiques cliniques, la bactériologie et les issues dans les dossiers hospitaliers et de laboratoire. Ils ont divisé les données selon les groupes d'âge et l'utilisation récente d'antibiotiques pour analyser les différences d'issues.
RÉSULTATS : Soixante-six enfants ayant une infection à *Salmonella* ont consulté au *Children's Hospital* sur une période de dix ans. Les facteurs de risque communs d'infection à *Salmonella* incluaient les contacts avec des personnes malades, le domicile dans une région rurale, un voyage récent, le contact avec des animaux (surtout des reptiles) et l'exposition à l'eau locale. Un âge plus jeune s'associait à une probabilité accrue d'hospitalisation, d'antibiothérapie et d'antibiothérapie plus longue. Cette observation s'avérait lorsque les chercheurs comparaient les nourrissons plus âgés à ceux de moins de 12 semaines de vie. Les patients récemment traités aux antibiotiques et ceux qui avaient une maladie sous-jacente importante étaient plus susceptibles d'être hospitalisés.
CONCLUSIONS : Si on connaît mieux les facteurs de risque épidémiologiques de l'infection à *Salmonella*, on pourrait peut-être améliorer le diagnostic. On s'attendait à des taux d'hospitalisation plus élevés chez les nourrissons de moins de 12 semaines de vie, ceux qui avaient reçu une antibiothérapie récente et ceux qui avaient une maladie sous-jacente importante. Une étude prospective multicentrique s'impose pour mieux évaluer les questions portant sur la gravité accrue de la maladie et la prise en charge pertinente des infections à *Salmonella* chez les nourrissons de moins de 12 semaines de vie.

Childhood infections with *Salmonella* species are very common. *Salmonella* generally causes an acute, self-limited gastroenteritis; however, it is also one of the most common causes of childhood bacteremia following *Streptococcus pneumoniae* (1). *Salmonella* bacteremia may lead to focal extraintestinal infections, such as meningitis or osteomyelitis, which are associated with higher morbidity and mortality (2).

Salmonella infections have risen in frequency in industrialized nations due to changes in modern farming and food production practices, ecology, eating patterns and demographics (3). Although the major sources for outbreaks tend to be food related, an increasing number of infections in recent years have been associated with foreign travel and exotic pets (4,5). A higher risk of *Salmonella* bacteremia has also been consistently demonstrated in children who are immunocompromised or are predisposed to underlying diseases, such as sickle cell disease (6,7). However, no Canadian studies have been published to date describing the risk factors for *Salmonella* infection in our population.

The present study was prompted by the frequent occurrence of *Salmonella* infections in children who were younger and more severely ill, leading to an increased use of resources at the Children's Hospital, London Health Sciences Centre (LHSC) in London, Ontario. In Ontario, the overall incidence rate of *Salmonella* infections in 2003 was 13.3 per 100,000 population, with a higher rate

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of 47.4 per 100,000 in children younger than four years of age (8). Several studies (3,9,10) have shown a higher rate of bacteremia in children in their first year of life, but this has not consistently led to increased complications or morbidity.

The first objective of the study was to describe our sample of Canadian children with *Salmonella* infections in terms of clinical characteristics previously reported as risk factors and sources of infection. The second objective was to examine whether younger children, particularly infants younger than 12 weeks of age, experienced higher morbidity than older children. Markers of increased morbidity included higher rates of admission to hospital, longer hospital stays and more severe symptoms. Our final objective was to examine whether children who recently received antibiotics experienced a higher morbidity due to *Salmonella* infections.

METHODS

The present study design was a retrospective chart review of children with *Salmonella* infections at the Children's Hospital, LHSC. The hospital is a pediatric tertiary care referral centre that services a 29,000 square kilometre area in southwestern Ontario, which includes a large rural population. The catchment area has a population of 1.4 million, including 400,000 children. There are approximately 39,000 pediatric emergency room visits, 15,000 ambulatory clinic visits and 3725 inpatient admissions each year. Ethics approval for the study was obtained from the Review Board of the University of Western Ontario, London, Ontario.

The microbiology department at the hospital kept an up-to-date list of all patients with positive cultures for *Salmonella* starting from 1997. This list was used to identify patients who presented to the hospital in the 10-year period from August 1, 1997 to July 30, 2007. Patients were included if they were younger than 19 years of age and had *Salmonell*a species isolated from any site, and were assessed at the hospital. Two exclusion criteria were also identified: the participants must not have been diagnosed with and treated for *Salmonella* infection in the previous three months, and they could not have a concurrent bacterial infection that might explain the presenting complaints.

The hospital charts and laboratory records of eligible participants were reviewed, and patient ages, risk factors for *Salmonella* infections, clinical characteristics, bacteriology and outcome were collected. Risk factors for *Salmonella* infections included sickle cell anemia, asplenia, recent antibiotic use, sick contacts, First Nations background, exposure to reptiles, recent travel and exposure to potentially contaminated water. Clinical characteristics consistent with increased severity of illness at presentation (temperature, heart rate, ill appearance, signs of dehydration, abnormal white blood cell counts and other abnormal laboratory investigations) were defined according to recent publications from the International Consensus Conference on Pediatric Sepsis (11) and the Rational Clinical Examination series (12). Outcome measures included hospital admission, duration of hospital stay, the occurrence of complications and focal disease, specifically meningitis and osteomyelitis.

Data were collected using chart abstraction forms and were transferred to an electronic data set. Data were separated into groups based on age (older and younger than 12 weeks, and older and younger than 12 months) and recent use of antibiotics to analyze outcomes consistent with increased morbidity. SPSS version 15.0 (SPSS Inc, USA) was used for data analysis. Categorical data were summarized using percentages. Normally distributed continuous variables were reported as mean ± SD, while skewed continuous variables were described as medians with ranges. The χ^2 test or Fisher's exact test was used to compare differences in proportions for categorical variables. The Mann-Whitney U test was used to compare skewed continuous variables between age categories. $P<0.05$ was considered to be statistically significant.

TABLE 1
Patient demographics and culture results (n=66)

Patient demographics	n (%)
Male patients	37 (56.1)
Patients younger than 12 weeks of age	6 (9.1)
Patients younger than 12 months of age	18 (27.3)
Patients presenting with complaints	
Diarrhea	62 (93.9)
Fever	54 (81.8)
Bloody stools	45 (68.2)
Vomiting	23 (34.8)
Location of initial assessment	
Emergency room	61 (92.4)
Outpatient clinic	1 (1.5)
Inpatient ward	4 (6.1)
Stool culture results	
Number of stool cultures obtained	62 (93.9)
Stool cultures from which *Salmonella* was isolated	61 (98.4)
Blood culture results	
Number of blood cultures obtained	30 (45.5)
Blood cultures from which *Salmonella* was isolated	8 (26.7)
Cerebrospinal fluid (CSF) culture results	
Number of CSF cultures obtained	6 (9.1)
CSF cultures from which *Salmonella* was isolated	0 (0)

RESULTS

Sixty-eight children younger than 19 years of age with *Salmonella* infection were identified. Two were excluded for relapses of infections treated in the previous three months, leaving 66 patients for analysis. Patient demographic data are presented in Table 1. Nine per cent of patients were younger than 12 weeks of age, and 27% were younger than 12 months of age. Fifty-six per cent were male. Presenting complaints included diarrhea (93.9%), fever (81.8%) and bloody stools (68.2%).

Stool cultures were performed for 62 patients and were positive in 98.4%. Twenty-one different *Salmonella* species were isolated from stool cultures, including *Salmonella typhimurium* (34.9%), *Salmonella enteritidis* (12.9%), *Salmonella heidelberg* (11.3%) and *Salmonella enterica* subspecies *houtenae* (4.8%). Blood cultures were drawn in 30 patients and a bone marrow aspirate was sent for culture in another patient with a prolonged febrile illness. Approximately 27% of blood cultures were positive and isolates included *S heidelberg* (25%), *S typhimurium* (12.5%), *Salmonella thompson* (12.5%), *Salmonella schwarzengrund* (12.5%) and *Salmonella kiambu* (12.5%). There were two isolates of *Salmonella typhi* in the study group – the first was isolated from a patient's blood culture and the second from another patient's bone marrow aspirate. Lumbar

TABLE 2
Distribution of patient characteristics within the study sample previously documented as risk factors for *Salmonella* infection (n=66)

Patient characteristics	n (%)
Sick contacts with similar symptoms	19 (28.8)
Living in a rural area	12 (18.2)
Recent travel	10 (15.2)
Pets at home	7 (10.6)
Reptiles or exotic pets	5 (7.6)
Swimming in fresh water	5 (7.6)
Drinking well water	5 (7.6)
Immigrants	3 (4.5)
Contact with raw chicken	2 (3.0)
Attending daycare	2 (3.0)
Farm contact	1 (1.5)
Specific underlying medical conditions	
Sickle cell anemia	0 (0.0)
Asplenia	1 (1.5)
Malignancy	1 (1.5)
First Nations	0 (0.0)

punctures were performed in six patients, and all cerebrospinal fluid cultures were negative.

Previously described risk factors for *Salmonella* infections were identified (Table 2). Twelve patients came from rural areas and 10 had a history of recent travel – five of these within Ontario and the others to Barbados, the Czech Republic, the Dominican Republic, Portugal and the Philippines. Three patients were immigrants. The first child had immigrated to Canada from Peru within the previous two years; the second child was a recent immigrant from Ghana who presented with a protracted febrile illness and grew *Salmonella typhi* from a bone marrow aspirate. The third patient, who presented with typhoid fever, had emigrated from the Philippines more than five years earlier, but had recently returned from a vacation there.

Five children reported recently swimming in fresh water, including a 15-year-old who swam in a pond with a turtle and later developed *S heidelberg* gastroenteritis and bacteremia. Five patients drank well water, and one patient had documented contact with a farm. Seven patients had pets and five of these patients had reptiles, including lizards and iguanas. All three patients who grew *S enterica* subspecies *houtenae* in their stool cultures had pet reptiles. Interestingly, two patients reported contact with raw chicken. A teenage girl was splashed with raw chicken while working at a fast food restaurant, and an infant was bathed in a kitchen sink after a chicken was cleaned in the same sink. Two patients attended daycare and 19 had known sick contacts with similar symptoms – 14 in their immediate family and five among other contacts.

Fifteen patients had significant medical histories, including one patient with chronic immune thrombocytopenic purpura and splenectomy, another with acute lymphoblastic leukemia and a third patient with undiagnosed liver masses. Other important underlying medical conditions included asthma, cystic fibrosis, trisomy 21, hyperthyroidism, congenital heart disease, chronic diarrhea, prematurity with chronic liver disease and recent surgery. Children were more likely to be admitted to hospital if they had a significant medical history than if they were previously healthy (53.3% versus 23.5%; P=0.03) but were not more likely to have a positive blood culture.

TABLE 3
Comparison of clinical outcomes for patients younger and older than 12 weeks of age

Clinical outcomes	<12 weeks, n=6	>12 weeks, n=60	P
Patients admitted to hospital, %	83.3	25	0.01
Median duration of admission, days (range)	9 (3–21)	5 (2–14)	0.17
Patients treated with antibiotics, %	83.3	33.3	0.03
Median duration of antibiotics, days (range)	11 (10–21)	7 (2–38)	0.05
Blood cultures that grew *Salmonella* species, %	33.3	20.8	0.91

TABLE 4
Comparison of clinical outcomes for patients younger and older than 12 months of age

Clinical outcomes	<12 months, n=18	>12 months, n=48	P
Patients admitted to hospital, %	55.6	20.8	0.01
Median duration of admission, days (range)	7.5 (2–21)	4.5 (2–14)	0.48
Patients treated with antibiotics, %	61.1	31.3	0.03
Median duration of antibiotics, days (range)	11 (7–21)	7 (2–38)	0.03
Blood cultures that grew *Salmonella* species, %	28.6	18.8	0.84

Children younger than 12 weeks of age were more likely to be admitted to hospital (83.3% versus 25%; P=0.01), treated with antibiotics (83.3% versus 33.3%; P=0.03) and have a longer duration of antibiotic therapy (median: 11 days, range: 10 to 21 days versus median: seven days, range: two to 38 days; P=0.05) compared with older children (Table 3). There were trends toward longer durations of admission and more positive blood cultures in children younger than 12 weeks of age compared with those older than 12 weeks of age. A three-week-old infant with sepsis secondary to *S typhimurium* bacteremia was admitted to the paediatric critical care unit, and an 11-week-old infant with *S schwarzengrund* bacteremia was diagnosed with presumed meningitis based on clinical presentation. No other patients developed complications or focal infections. There were no statistically significant differences in clinical features, suggesting more severe illness at presentation in children younger than 12 weeks of age.

Patients younger than 12 months of age were more likely to be admitted to hospital (55.6% versus 20.8%; P=0.01), treated with antibiotics (61.1% versus 31.3%; P=0.03) and undergo a longer duration of antibiotic therapy (median: 11 days, range: seven to 21 days versus median: seven days, range: two to 38 days; P=0.03) compared with older children (Table 4). There were no statistically significant differences in the clinical or laboratory features, suggesting an increased severity of disease at presentation in children younger than 12 months of age.

Patients were also more likely to be admitted to hospital if they had recently been treated with antibiotics than if they had no previous antibiotic use (70.0% versus 23.2%; P=0.01). These do not necessarily represent cases of failed oral therapy, but rather, oral antibiotics may have been a marker for patients

who had chronic illnesses. Two were antibiotic prophylaxis – one child was taking trimethoprim-sulfamethoxazole for *Pneumocystis* pneumonia prophylaxis during chemotherapy, and the second child was on penicillin due to asplenia. These patients were not more likely to have a longer duration of admission, positive blood culture, complications or present with signs of more severe illness.

DISCUSSION

In our study, younger age was associated with an increased likelihood of admission to hospital, treatment with antibiotics and a longer course of antibiotic therapy. Younger infants were not more likely to present with clinical or laboratory characteristics, suggesting an increased severity of illness. Therefore, it is not possible to attribute the increased rates of admission and longer courses of antibiotics to higher rates of *Salmonella* bacteremia or more severe disease in younger infants. Finally, the rates of focal infection and complications were low in all age groups, and there were no deaths.

One important explanation for the higher admission rates is the general practice that infants younger than 12 weeks of age presenting with fever should undergo a full septic workup, including blood and cerebrospinal fluid cultures, and be admitted to hospital for empirical parenteral antibiotics. Four of the six patients younger than 12 weeks of age were febrile at presentation and would have been treated accordingly. There has been significant controversy in the literature regarding the empirical use of antibiotics for *Salmonella* gastroenteritis and bacteremia. It is clear that antibiotics do not shorten the duration of gastroenteritis, improve symptoms, shorten fecal excretion or decrease the risk of persistent bacteremia. Several authors cite the higher morbidity associated with bacteremia and extraintestinal infections as reasons to routinely treat infants younger than 12 weeks of age (6,13). Others suggest that *Salmonella* bacteremia is unlikely to cause complications in most healthy children, and antibiotic therapy should be reserved for children who are febrile and toxic on presentation, regardless of age (2,7). In our study, two of the four infants younger than 12 weeks of age who were febrile at presentation were eventually found to be bacteremic and experienced higher morbidity. Experiences such as these may influence the practice of physicians and highlight the difficulties in developing algorithms for management based on retrospective studies.

It is not surprising that children with a significant medical history were more likely to be admitted to hospital. Underlying conditions such as asplenia and malignancy not only increase the risk of *Salmonella* infection, but are also associated with higher morbidity. As a result, these patients were likely to be admitted for observation and initiation of antibiotic therapy. It is intriguing that children in our study group who were recently treated with antibiotics were more likely to be admitted to hospital. Antibiotics alter the normal gastrointestinal flora and, thus, the recent use of antibiotic agents is a known risk factor for *Salmonella* infections. Antibiotic prophylaxis may be a marker for serious underlying disease that resulted in greater clinical concern and, thus, admission to hospital.

Many of our results are consistent with previous epidemiological studies. *Salmonella* infections are more common in younger children and more than 50% of our study patients were younger than five years of age. Of 1632 cases of *Salmonella* in Ontario in 2003, *S typhimurium* was isolated in 20.6%, *S heidelberg* in 17.3% and *S enteritidis* in 7.2% of cases (8). The most common serotypes isolated in our patients were similar – *S typhimurium* (34.9%), *S enteritidis* (12.9%) and *S heidelberg* (11.3%). *S typhi* was isolated in only two of our patients.

Potential sources of infection in our study included sick contacts, living in a rural area, recent travel and exposure to pets. Living in a rural area may be associated with additional risk factors such as exposure to farms and food animals. *Salmonella* Newport isolates have been described in rural Ontario related to dairy farms and ingestion of unpasteurized dairy products or undercooked beef (14). Foreign travel is also a well-established risk factor for enteric infections. Travellers who visit friends and family in foreign countries may be at a higher risk of infection because they are more likely to stay in rural areas, remain for longer periods, drink local water and eat foods prepared in homes (4).

Exposure to reptiles and amphibians has been implicated in more than 6% of human *Salmonella* infections, and such exposure was documented in 7.6% of patients in our study. Seventeen of the stool isolates from our hospital were identified as serotypes often linked to these animals, including *S enterica* subspecies *houtenae*, *Salmonella paratyphi* var *java*, *Salmonella montevideo* and *S enteritidis*. Up to 90% of reptiles and amphibians harbour *Salmonella* in their gastrointestinal tracts (4). The estimated number of households with reptiles has been increasing steadily in the United States – the number doubled to almost two million households between 1991 and 2001 (15). Small turtles, in particular, are considered to be 'safe' by families because they do not bite or scratch; consequently, younger children are often allowed to handle these animals and, thus, are more likely to develop *Salmonella* infections. However, awareness of the association between these exotic pets and *Salmonella* infections is not well-established in the community, even among physicians, despite educational materials from the Canadian Paediatric Society (15,16).

Potential risk factors for bacterial gastrointestinal infections were generally poorly documented in the charts. For example, of the 66 hospital charts included in the study, there was no documentation regarding exposure to well water in 66.7%, asplenia in 80.3%, household pets in 86.4% and recent farm contact in 90.9%. It is unclear whether these omissions were due to a lack of familiarity with risk factors for *Salmonella* and other enteric infections. However, even well-known risk factors, such as the recent use of antibiotics and foreign travel, were not documented in approximately one-third of the charts. It may have been that the physician reported only the pertinent positive responses. Ultimately, it is important to identify potential sources of infection and to document these risk factors accordingly.

The present study had several limitations that were related to its retrospective design. The small sample size, particularly of infants younger than 12 weeks of age, limited the generalizability of our results. There was also inconsistency in which laboratory investigations were ordered by the assessing physician. As a result, it was not possible to use laboratory markers of sepsis other than white blood cell counts to compare illness severity in the different age groups. Blood was not drawn for cultures in 54.5% of patients in our study, thereby limiting our ability to interpret whether bacteremia may have played a role in the

study outcomes. Given the potential for increased morbidity, an important practice point is that blood cultures should be included in the investigations of children presenting with fever, diarrhea and epidemiological risk factors for *Salmonella* infections.

A wider knowledge of the risk factors and sources for *Salmonella* infection may improve diagnosis, and a high index of suspicion should be maintained for children with epidemiological risk factors. Higher admission rates can be expected in children younger than 12 months of age, those recently treated with antibiotics and those who have a significant underlying medical condition. A prospective, multicentre study is needed to further address questions about increased illness severity and appropriate management of *Salmonella* infections in children.

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