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Magnitude of bacteraemia is associated with increased mortality in non-typhoid salmonellosis: a one-year follow-up study

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We examined whether the number of positive bottles in a routinely used three-bottle blood culture (BC) set predicted one-year mortality in adult patients with non-typhoid *Salmonella* (NTS). Data from 1994 through 2003 in North Jutland County, Denmark, were retrieved from health databases and medical records. We used the number of positive BC bottles as an index of magnitude of NTS bacteraemia: Index 0 (reference) patients had a negative BC coincident with an NTS-positive faecal culture and index 1, 2, or 3 patients had increasing levels of NTS bacteraemia. For all patients and for patients with gastroenteritis we computed Kaplan-Meier curves to summarize survival over time and Cox regression analysis to estimate mortality in crude analyses and in analyses adjusted for comorbidity and age. There were 115, 43, 21, and 41 patients with index 0, 1, 2, and 3, respectively. One-year cumulative mortality was 4.4%, 14.0%, 28.6%, and 41.5% for indices 0 to 3. Adjusted one-year mortality rate ratios (with 95% confidence intervals) were 1.7 (0.5–5.8), 5.2 (1.5–17.4), and 5.3 (1.9–14.9) for index 1, 2, and 3 patients, respectively. These estimates remained robust for patients with gastroenteritis. We conclude that higher magnitude of bacteraemia predicted one-year mortality in NTS patients.

Key words: Magnitude of bactaeremia; non-typhoid salmonellosis; mortality.

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Most studies focusing on predictors of outcome among patients hospitalized with non-typhoid *Salmonella* (NTS) have primarily addressed age, immunosuppression, and comorbid diseases (1). The complex interrelationship between age, immune status, comorbidity, and bacteraemia makes it difficult to separate the prognostic impact of each factor. Several older studies of various pathogenic bacteria reported that a higher magnitude of bacteraemia was associated with increased mortality, but differences among groups were not taken into account, mortality after hospital discharge was not reported, and NTS bacteraemia was not addressed specifically (2–9). Recently we found that mortality rises as the number of positive blood culture (BC) bottles per initial BC set increases in patients with NTS bacteraemia (10). This led us to elaborate further on magnitude of NTS bacteraemia as a separate prognostic factor.

In the present study we made use of the local BC practice since 1992 in which 30 mL blood is obtained by venipuncture and then distributed

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equally between two aerobic bottles and one anaerobic bottle. Because *Salmonella* grows readily both aerobically and anaerobically, the number of positive bottles is an appropriate semiquantitative index of bacterial density in the blood sample. Patients with a negative BC coincident with an NTS-positive faecal culture served as the reference cohort because of their confirmed NTS exposure and their physicians' attention to bacteraemia risk.

We examined whether magnitude of NTS bacteraemia was a prognostic factor for mortality during a one year follow-up period, taking into consideration comorbidity, age, and presence of gastroenteritis.

METHODS

Study population

The Danish health care system is tax financed and provides care free of charge for all residents. Acutely ill patients are admitted to the nearest hospital in their county of residence. During the 10-year study period (1994–2003), North Jutland County, Denmark, had an average population of ~500,000, served by eight public hospitals. Bacteriological services for the entire county were provided by the Department of Clinical Microbiology (DCM), Aalborg Hospital.

The bacteraemic cohort comprised all patients in North Jutland County with NTS isolated by BC during the study period (10). All were hospitalized in connection with their NTS bacteraemia. The reference cohort consisted of all inpatients in the County from 1995 through 2003 with NTS detected in a faecal culture and a negative BC drawn ±1 day from the faecal culture. Patients with only one bottle sampled per BC were excluded, 24 without and 6 with NTS in the blood bottle, all of whom were 0–9 years old and alive after one year.

Record linkage

All Danish residents have a unique 10-digit personal identification number (incorporating age and gender), which permits accurate linkage between relevant administrative and health registries. The Danish Civil Registration System contains continuously updated records of the vital status of all Danish residents, including date of emigration or death, if relevant, allowing us to ascertain patient status after one year of follow-up (11).

Microbiological procedures

During the study period two BC systems were in use, the Colorbact® system (Statens Serum Institut [SSI], Copenhagen, Denmark) until December 1995 and the BacT/Alert® system (bioMérieux, Marcy l'Etoile, France) thereafter (12). Both systems used two aerobic bottles and one anaerobic bottle per BC, except for younger children, for whom only one aerobic bottle was sampled (12, 13). In the Colorbact system the actual volumes sampled for the three bottles were 18–21 mL (12, 13), but after the introduction of the BacT/Alert system the target volume of 30 mL has been assured by regular quality control measurements (unpublished results).

Procedures for faecal cultures have been described in detail previously (14). In brief, faeces were cultured in NTS selective broth, followed by culture on indicative solid media and identification according to the Kaufmann-White scheme (15).

Microbiological data

Identification of bacteraemic patients from the North Jutland County Bacteraemia Database has been described in detail previously (10, 16).

The national reference laboratory at SSI maintains a country-wide database with information on all NTS-positive cultures, including serotype and culture receipt date, but not culture type. After excluding 40 known NTS-bacteraemic patients, we assumed that all remaining cultures were faecal. Patients with NTS-positive faecal cultures were retrieved from this database from 1995 through 1997. For 1998–2003 we retrieved the same information on patients with NTS-positive faecal cultures from the DCM laboratory information system ADBakt (Autonik, Sköldinge, Sweden). Unlike the SSI database, this database includes culture type. From 1995 on, all negative BC results were also recorded in the DCM laboratory information system.

Hospital discharge data

Since 1977, non-psychiatric hospital discharge diagnoses have been recorded in the Hospital Discharge Registry of North Jutland, using the International Classification of Diseases (ICD) system [ICD-8 until 1994 and ICD-10 thereafter (ICD-9 was never implemented in Denmark)] (17). By linking patients with NTS-positive faecal cultures to this registry we were able to identify patients hospitalized with an NTS-related diagnosis ±1 month of the culture receipt date. The main NTS-related diagnoses (NTS infection or diarrhoea due to presumed infectious cause) were retrieved using ICD-8 codes 003 and 009 and ICD-10 codes A02 and A09. Diagnoses of selected major comorbid diseases recorded in the 5-year period before the first NTS-positive culture were also retrieved for study patients. We classified comorbidity using the Charlson index, which includes 19 major disease categories (e.g., cardiovascular diseases, cancer, diabetes, and AIDS) and assigns scores to each of them (with higher scores associated with more severe disease categories) (18).

Medical records

We used the medical records of the study patients to extract data on comorbidity, clinical and labora-

tory variables, and medicine administered during hospitalization (10).

Statistical analysis

The analytical unit was a patient, each of whom encountered the study population criteria only once. The initial event was receipt date of the first culture (BC for bacteraemic patients and faecal culture for reference cohort patients). The primary exposure was magnitude of bacteraemia as measured by the number of NTS-positive BC bottles (index 0, 1, 2, or 3) in the initial BC set. Outcome was death within 30, 180, and 365 days following the initial event.

Charlson index scores were categorized into three levels (0, 1–2, and >2 points) and four age groups were used (0–15, 16–64, 6–80, and >80 years).

We first estimated associations between the index and important covariates (age, gender, Charlson index scores, gastroenteritis, and main NTS serotype) using cross-tabulations. We then focused on Charlson index scores, age, and gastroenteritis, as these key covariates had been identified previously as prognostic factors for survival (10).

For the four index cohorts, we calculated crude cumulative mortality and cumulative mortality standardized to the distribution of Charlson index scores and age in the index 0 cohort.

We computed Kaplan-Meier survival curve estimates based on the index and key covariates. Cox proportional-hazards regression analysis was used to compute mortality rate ratios (MRR) and 95% confidence intervals (CI). First, the impact of the index was evaluated in crude analyses, after which we adjusted the model by including Charlson index scores and age. We repeated all analyses, excluding patients without gastroenteritis. Proportionality assumptions for all the models (assessed graphically and by Schoenfeld residuals) were found to be adequate (19).

Tests for trend for the indices 0–3, 0–2, and 1–3 were performed by repeating the adjusted Cox proportional-hazards regression analysis using the index as a continuous variable.

The software program Stata/SE 8.2 for Windows (Stata Corporation, College Station, TX, USA) was used for all analyses.

Ethical considerations

The study was conducted according to the guidelines of the regional scientific ethics committee for use of clinical and laboratory data, and approved by

TABLE 1. *Main characteristics of the study population with non-typhoid* Salmonella *(NTS), North Jutland County, Denmark, 1994–2003*

	Index[1]				
Factor	0	1	2	3	Total (%)
Age group (years)					
0–15	6 (5.2)[2]	1 (2.3)	0 (0)	2 (4.9)	9 (4.1)
16–64	79 (68.7)	23 (53.5)	11 (52.4)	13 (31.7)	126 (57.3)
65–80	23 (20.0)	12 (27.9)	8 (38.1)	15 (36.6)	58 (26.4)
>80	7 (6.1)	7 (16.3)	2 (9.5)	11 (26.8)	27 (12.3)
Gender					
Female	60 (52.2)	21 (48.8)	7 (33.3)	16 (39.0)	104 (47.3)
Male	55 (47.8)	22 (51.2)	14 (66.7)	25 (61.0)	116 (52.7)
Charlson index scores[3]					
0	81 (70.4)	23 (53.5)	10 (47.6)	15 (36.6)	129 (58.6)
1–2	29 (25.2)	14 (32.6)	7 (33.3)	19 (46.4)	69 (31.4)
>2	5 (4.4)	6 (14.0)	4 (19.1)	7 (17.1)	22 (10.0)
Gastroenteritis					
Yes	115 (100.0)	31 (72.1)	14 (66.7)	29 (70.7)	189 (85.9)
No	0 (0)	12 (27.9)	7 (33.3)	12 (29.3)	31 (14.1)
Main serotype					
S. Enteritidis	68 (59.1)	20 (46.5)	8 (38.1)	24 (58.5)	120 (54.6)
S. Typhimurium	36 (31.3)	4 (9.3)	4 (19.1)	8 (19.5)	52 (23.6)
Exotic[4]	11 (9.6)	19 (44.2)	9 (42.9)	9 (22.0)	48 (21.8)
Total no. patients	115	43	21	41	220

[1]Number of NTS-positive bottles in the initial blood culture drawn during hospital admission.
[2]Number of patients (%).
[3]Comorbidity as measured by Charlson index scores (18).
[4]All zoonotic serotypes other than *S.* Enteritidis and *S.* Typhimurium.

the Danish Data Protection Agency (Record no. 2004–41–4004).

RESULTS

Among the study population of 220 patients, 115, 43, 21, and 41 had an index of 0, 1, 2, and 3, respectively (Table 1). Two index 1 patients had NTS detected in faeces 6 and 11 months after the actual NTS episode, but this did not result in hospital admission. Complete follow-up information was obtained for all patients except for one index 0 patient who emigrated on day 229.

The index rose with increasing age and level of Charlson index score (Table 1). While the study population had equal numbers of females and males, more males were represented among index 2 and index 3 patients. All index 0 patients, but only approximately 70% with indices 1 to 3, had gastroenteritis. *Salmonella* (*S.*) Typhimurium occurred more commonly than exotic serotypes (all serotypes other than *S.* Enteritidis or *S.* Typhimurium) in index 0 patients, while the reverse was seen in patients with indices 1 to 3. *S.* Enteritidis was equally distributed among the four index cohorts.

Regardless whether the follow-up period was 30, 180, or 365 days, cumulative mortality and MRR generally rose as the index increased (Table 2 & Fig. 1). The risk estimates remained consistent in both the crude and adjusted analyses. In tests for trend, p-value for indices 0–3 was ≤0.01 after 180 and 365 days; this p-value remained the same in separate analyses for indices 0–2 and 1–3 after 365 days.

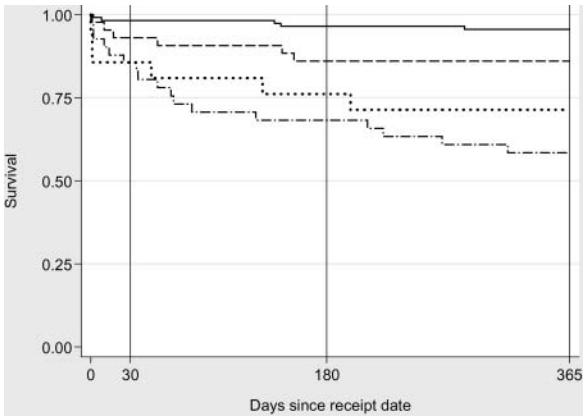

Fig. 1. Kaplan-Meier survival curves for 220 hospitalized patients with three bottles sampled for the initial blood culture drawn during hospital admission, North Jutland County, Denmark, 1994–2003. Index 0 (solid line): Patients with non-typhoid *Salmonella* (NTS) in a faecal culture and an NTS-negative blood culture drawn ±1 day from the NTS-positive faecal culture. Indices 1 to 3: Patients with 1 (dashed line), 2 (dotted line), and 3 (dashed and dotted line) NTS-positive blood bottles, respectively. Receipt date is the date the faecal culture (index 0) or blood culture (indices 1 to 3) was received.

Because index 0 patients were selected according to an NTS-positive faecal culture only,

TABLE 2. *Study population with non-typhoid* Salmonella*, North Jutland County, Denmark, 1994–2003: Cumulative mortality (CM), standardized cumulative mortality (SCM), mortality rate ratio (MRR) with 95% confidence intervals (CI) computed from Cox proportional-hazards regression analysis, and p for trend (for adjusted analyses)*

		All patients					Gastroenteritis patients only				
Period	Index[1]	CM	SCM[2]	Crude MRR (95% CI)	Adjusted[3] MRR (95% CI)	p for trend	CM	SCM	Crude MRR (95% CI)	Adjusted MRR (95% CI)	p for trend
30-day	0	2/115 (1.7)[4]	1.7[5]	1 (ref.)	1 (ref.)	0.07/	2/115 (1.7)	1.7	1 (ref.)	1 (ref.)	0.10/
	1	3/43 (7.0)	6.8	4.1 (0.7–24.5)	2.6 (0.4–16.0)	0.07/	1/31 (3.2)	6.5	1.8 (0.2–20.4)	1.4 (0.1–16.0)	0.30/
	2	3/21 (14.3)	7.0	9.1 (1.5–54.5)	5.5 (0.9–34.2)	0.54[6]	1/14 (7.1)	10.4	4.3 (0.4–47.8)	2.4 (0.2–28.3)	0.32
	3	6/41 (14.6)	4.5	8.8 (1.8–43.4)	4.2 (0.8–22.3)		4/29 (13.8)	4.9	8.1 (1.5–44.4)	4.0 (0.7–23.2)	
180-day	0	4/115 (3.5)	3.5	1 (ref.)	1 (ref.)	0.01/	4/115 (3.5)	3.5	1 (ref.)	1 (ref.)	0.01/
	1	6/43 (14.0)	9.8	4.2 (1.2–14.9)	2.1 (0.6–7.7)	0.02/	3/31 (9.7)	9.1	2.8 (0.6–12.7)	1.9 (0.4–8.4)	0.23/
	2	5/21 (23.8)	13.5	7.8 (2.1–29.7)	4.8 (1.2–18.4)	0.16	2/14 (14.3)	11.7	4.4 (0.8–24.0)	2.2 (0.4–12.8)	0.12
	3	13/41 (31.7)	10.1	10.7 (3.5–32.8)	4.5 (1.4–14.4)		9/29 (31.0)	11.5	10.5 (3.2–34.1)	5.0 (1.5–16.9)	
365-day	0	5/114 (4.4)[7]	4.4	1 (ref.)	1 (ref.)	$<10^{-3}$/	5/114 (4.4)	4.4	1 (ref.)	1 (ref.)	10^{-3}
	1	6/43 (14.0)	9.9	3.4 (1.0–11.1)	1.7 (0.5–5.8)	0.01/	3/31 (9.7)	9.2	2.3 (0.5–9.6)	1.5 (0.4–6.3)	0.08/
	2	6/21 (28.6)	20.2	7.8 (2.4–25.7)	5.2 (1.5–17.4)	0.02	3/14 (21.4)	18.4	5.4 (1.3–22.8)	3.2 (0.7–14.1)	0.01
	3	17/41 (41.5)	13.2	11.7 (4.3–31.6)	5.3 (1.9–14.9)		13/29 (44.8)	16.4	12.9 (4.6–36.3)	7.2 (2.5–20.6)	

[1] Blood culture density index, *cf* Table 1.
[2] Cumulative mortality standardized to distribution of age and Charlson index scores (18) in the index 0 cohort.
[3] Adjusted for Charlson index scores (18) and age.
[4] Number of deaths/total (%).
[5] %.
[6] Index 0–3/Index 0–2/Index 1–3.
[7] n=114, as one patient emigrated on day 229.

whereas index 1–3 patients were selected according to BC results, occurrence of gastroenteritis could confound the results. Of the 67 patients with indices 1 to 3 recorded after August 1997, 42/50 (84%) of those with gastroenteritis had faeces cultured, but only 2/17 (12%) of those without gastroenteritis had such cultures. When we repeated the analyses, excluding patients without gastroenteritis, the risk estimates were not affected (Fig. 2 & Table 2).

DISCUSSION

Our study showed that higher magnitude of bacteraemia was associated with increased mortality among patients with NTS infections. These findings accord with bacteraemia studies in adults conducted several decades ago, which used very different methodologies (2–9). No study used multivariate analyses to control for potential confounders such as comorbidity and age, mortality after hospital discharge was not reported, and they did not include NTS among the diverse list of pathogens (*inter alia Staphylococcus aureus*, pneumococci, and Gram-negative rods) (2–9). In three studies, the prognostic impact of magnitude of bacteraemia in adults was reported for patient cohorts stratified by the authors' clinical evaluation of the prognosis (5–7). For Gram-negative bacteria, DuPont and Spink found that mortality increased in parallel with higher CFU/mL in patients with a good or intermediate prognosis, while most patients with a poor prognosis died regardless of the magnitude of bacteraemia (5). Interestingly, when the same study group included all bacteraemic patients the same trend was reported for Gram-negative bacteria, but less clearly for Gram-positive bacteria or polybacteraemia (6).

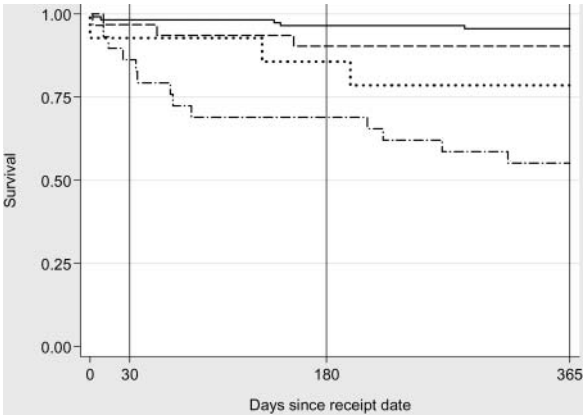

Fig. 2. Kaplan-Meier survival curves for 189 hospitalized gastroenteritis patients with three bottles sampled for the initial blood culture drawn during hospital admission, North Jutland County, Denmark, 1994–2003. Legend: see Fig. 1.

Most studies focusing on magnitude of bacteraemia as a prognostic factor have relied on direct measurements of CFU/mL blood, derived either from pour-plate methods (2–7) or from plating on solid agar (20, 21). However, these quantitative methods are labour intensive and are rarely used for routine diagnostic purposes (22–24). Furthermore, their sensitivity is compromised by the small blood sample volumes (~1 mL). Because magnitude of bacteraemia in adults is low, culturing of 20–30 mL blood is recommended (23, 25–27).

Routine sampling of three blood bottles per BC in North Jutland County hospitals was implemented in 1992 (12, 13), spurred by American and Danish studies showing the critical importance of blood sample volume (25, 26). This approach has since been adopted by others (28). In our laboratory, all blood bottles were weighed from March 2000 through February 2002. Amongst the 1,173 weighed BC sets from this study there were no weight differences between BC indices 1, 2, and 3 (unpublished results). In addition, the index distribution did not differ when the two BC systems were compared (data not shown). We therefore believe this semi-quantitative index reflects bacterial density in the samples (26), and accordingly can be used as an appropriate measure of magnitude of NTS bacteraemia.

Some bacteraemia studies have attempted to relate cause of death to either infection or to factors such as underlying disease (29). This appears simplistic in view of the difficulty of separating the impact of individual factors on mortality among bacteraemic patients. The increasing cumulative mortality paralleling magnitude of NTS bacteraemia observed in our study up to one year after infection makes it difficult to argue that either microbial virulence or host response *per se* was responsible. Ours is one of the few studies to use a standard comorbidity index (the Charlson index) with proven value in prognostic studies (30). Still, we were not able to determine if magnitude of NTS bacteraemia was

causally related to mortality or functioned as a marker of an underlying disease process unaccounted for in the Charlson index.

Several studies suggest that the absence of gastroenteritis worsens the prognosis for NTS bacteraemic patients (10, 31–34). However, when we restricted our analysis to gastroenteritis patients, the risk estimates remained essentially unchanged.

The main strengths of our study were the use of data from both administrative registries and medical records (which reduced possible misclassifications), virtually complete follow-up, and its applicability to the general population.

Our study also had a number of limitations. First, the wide CI reflect the limited precision of our risk estimates. Second, we also had to rely on previously identified confounders (10) without adjusting for other covariates. Third, as a higher proportion of NTS infections will probably remain undetected as their severity declines (35), the prevalence found in the reference cohort may be underreported in relation to the general population, though this is less important from the clinician's bedside point of view. Finally, while the definition of bacteraemic patients was clear-cut the novel approach used to identify the reference cohort may be questioned. We believe that narrowly limiting the time span between sampling of blood and faeces for culture and subsequently excluding patients without gastroenteritis made the reference cohort more homogeneous. However, this also resulted in exclusion of patients who with wider time spans might have had blood samples taken in connection with their clinical NTS symptoms.

CONCLUSIONS

Increasing magnitude of NTS bacteraemia was associated with higher mortality after 30, 180, and 365 days. It is important to determine the prognostic utility of an analogous index derived from multiple BC sets with only two bottles each, which is used in several other hospitals and countries.

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