

## ORIGINAL ARTICLE

Case-control analysis of endemic *Serratia marcescens* bacteremia in a neonatal intensive care unit

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**Background:** *Serratia marcescens* is an opportunistic gram-negative rod which typically infects compromised hosts.

**Objectives:** To identify risk factors, signs, and outcomes associated with non-epidemic *S marcescens* bacteremia in a neonatal intensive care unit (NICU).

**Methods:** The records of infants with *S marcescens* bacteremia while in the Yale-New Haven Hospital NICU from 1980–2004 were reviewed. A matched case-control study was performed by comparing each case of *S marcescens* to 2 uninfected controls and 2 cases of *Escherichia coli* bacteremia.

**Results:** Twenty-five sporadic cases of *S marcescens* bacteremia were identified. Eleven available isolates were determined to be different strains by pulse field gel electrophoresis. Infants with *S marcescens* bacteremia had median gestational age and birth weight of 28 weeks and 1235 grams, respectively. Compared to matched, uninfected controls, infants with *S marcescens* bacteremia were more likely to have had a central vascular catheter (OR = 4.33; 95% CI (1.41 to 13.36)) and surgery (OR = 5.67; 95% CI (1.81 to 17.37)), and had a higher overall mortality (44% vs 2%; OR = 38.50; 95% CI (4.57 to 324.47)). Compared to *E coli* matched controls, infants with *S marcescens* bacteremia had later onset of infection (median of 33 days of life vs 10;  $p < 0.001$ ), prolonged intubation (OR = 5.76; 95% CI (1.80 to 18.42)), and a higher rate of CVC (OR = 7.77; 95% CI (2.48 to 24.31)) use at the time of infection. A higher rate of meningitis (24% vs 7%; OR = 3.98; 95% CI (1.09 to 14.50)) was observed with *S marcescens* bacteremia compared to *E coli*.

**Conclusions:** *S marcescens* bacteremia occurs sporadically in the NICU, primarily in premature infants requiring support apparatus late in their hospital course. Associated meningitis is common and mortality high.

*Serratia marcescens* is a pathogenic and opportunistic gram-negative rod (GNR) of the Enterobacteriaceae family with a proclivity toward infecting immunocompromised hosts. The newborn patient population is particularly at risk secondary to deficits in, and the immature function of, several components of the natural and acquired immune systems. The preterm neonate is further compromised by an ineffective skin barrier and increased need for instrumentation to facilitate survival. The escalating frequency of premature births<sup>1</sup> coupled with therapeutic advances in their care has thereby resulted in an increase in the population at risk.

*S marcescens* bacteremia in neonatal intensive care units (NICU) has typically been observed as hospital-acquired, epidemic outbreaks.<sup>2–12</sup> These outbreaks have traditionally been linked to environmental sources<sup>2–7 9–12</sup> such as contaminated medical devices.<sup>2 4 9 10 12</sup> We have periodically observed non-epidemic cases of *S marcescens* bacteremia in our NICU. The purpose of this case-control analysis was to identify and compare cases of endemic *S marcescens* bacteremia in an NICU over a 25-year period with matched uninfected and *Escherichia coli*-infected controls in an attempt to identify risk factors, presenting signs and symptoms, and outcomes specific to *S marcescens* that may facilitate and expedite their diagnosis and intervention.

## METHODS

The Yale-New Haven Hospital (Y-NHH) newborn special care unit is a 46-bed, level IIID tertiary care referral center for infants with complex medical and surgical conditions.

### Case selection

A matched case-control study was performed by comparing each case of *S marcescens* to 2 uninfected controls and 2 cases of *Escherichia coli* bacteremia.

Given the relatively small number of cases, two controls were utilized to improve the precision of the statistical estimate. To identify cases, the medical records of all infants with blood cultures positive for *S marcescens* obtained while inpatients in the NICU at Y-NHH from January 1, 1980, to December 31, 2004, were reviewed and data pertaining to demographics, potential risk factors for infection, and outcomes were extracted.

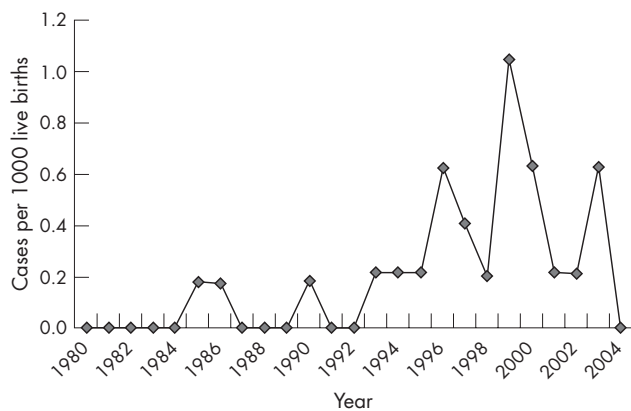
### Controls

Each case of *S marcescens* was matched and compared to two uninfected controls in an attempt to isolate potential risk factors associated with demographics and clinical care variables. Next, to compare *S marcescens* bacteremia to the most common GNR pathogen in our NICU, each case was matched and compared with two cases of *Escherichia coli* (*E coli*) bacteremia. Due to the observation that many cases of *E coli* sepsis, unlike those caused by *S marcescens*, occur during the first week of life, in the final part of this study, we compared cases of *S marcescens* sepsis with cases of *E coli* sepsis that occurred after day of life 7.

### Matching criteria

Two uninfected controls were matched to each case of *S marcescens* bacteremia using birth weight (BW;  $\pm 250$  grams), gender, and date of birth ( $\pm 1$  year). Two cases of *E coli* bacteremia were identified for each case of *Serratia* and also matched according to BW ( $\pm 350$  grams), gender, and date of birth ( $\pm 3$  years). Matching criteria for BW and date of birth

**Abbreviations:** CVC, central vascular catheter; GNR, gram-negative rod; NICU, neonatal intensive care unit; TPN, total parenteral nutrition; Y-NHH, Yale-New Haven Hospital



**Figure 1** Cases of *S. marcescens* per 1,000 live births in the Y-NHH NICU from 1980 to 2004.

differed between control groups because there were fewer *E. coli*-bacteremic subjects available. No matching could be performed for cases of *E. coli* at >7 days of life due to the small data pool.

**Definitions**

**Sepsis**

Sepsis was defined as described.<sup>13</sup> A repeat positive blood culture was defined as a positive blood culture with the same species and identical antibiotic susceptibility pattern obtained after ≥24 hours of appropriate antibiotic therapy. Multiple positive repeat blood cultures from a single patient obtained within one week were considered a single episode of sepsis.

**Meningitis**

Meningitis was documented if culture-proven or if pleocytosis (>100 white blood cells/mm<sup>3</sup>) in the cerebrospinal fluid was detected.

**Presumptive primary source of infection**

This was defined as a positive culture from a source other than blood with an identical antibiotic susceptibility pattern which predated (≤7 days) or, in the case of a central vascular catheter (CVC) culture, coincided with the onset of bacteremia

**Risk factors and signs**

Preterm labor was defined as onset of labor prior to 37 weeks' gestation. Maternal fever was defined as core temperature >38°C prior to delivery. Prolonged rupture of membranes was defined as rupture of membranes ≥18 hours prior to delivery. Choriomanionitis was identified by the isolation, under sterile conditions, of a pathogenic organism from the amniotic fluid or maternal blood and/or the presence of intrapartum fever in conjunction with two or more of the following: fetal tachycardia; uterine tenderness; malodorous vaginal discharge; or maternal leukocytosis (>15 000 leukocytes/mm<sup>3</sup>).<sup>14</sup>

The presence of a CVC, including umbilical venous and arterial catheters, percutaneous central venous catheters, Arrow® (Arrow International, Reading, PA, USA), and Broviac Silastic® (Bard Access Systems, Salt Lake City, UT, USA) catheters, (author, please include the place and country of origin) was included as a risk factor only if placed before the onset of sepsis and in place at the time of the positive blood culture. Surgery was included only if the procedure occurred ≤7 days prior to the onset of bacteremia. Prolonged mechanical ventilation was defined as the need for mechanical ventilation for >14 days prior to infection. Other potential risk factors for sepsis (i.e. urinary catheter, total parenteral nutrition) had to be in place or in use at the time a positive culture was obtained.

Apnea and bradycardia were classified as a clinical sign of sepsis only if the episodes were new in onset, or more frequent, prolonged, or severe than previously observed. Hypoglycemia was defined as blood glucose <40 mg/dl not coinciding with reduction in the glucose infusion rate or volume of enteral intake. Hyperglycemia was defined as blood glucose of >140 mg/dl that did not coincide with an increase in the glucose infusion rate or volume of enteral intake. Hypothermia was defined as a core body temperature <36.5°C. Hyperthermia was defined as a core body temperature >38°C. The absolute neutrophil count was obtained at the same time as the positive blood culture and was defined as the fraction of the sum of the segmented and band forms, or the automated neutrophil count, multiplied by the total white blood cell count. Neutropenia was defined as an absolute neutrophil count of <1500 cells/mm<sup>3</sup>.

**Death**

Death was considered related to sepsis if it occurred within 7 days of the positive blood culture or if clinical signs and symptoms of sepsis were documented in the medical record as the direct cause

**Table 1** Characteristics of cases of *S. marcescens* sepsis versus uninfected, sepsis with *E. Coli*, and sepsis with *E. Coli*>7 days of life controls

| Characteristic                                    | Median (Range)                |                              |                         |                                 |
|---|-------------------------------|------------------------------|-------------------------|---------------------------------|
|   | <i>S. marcescens</i> (n = 25) | Uninfected controls (n = 50) | <i>E. Coli</i> (n = 50) | <i>E. Coli</i> >7 days (n = 68) |
| BW (g)  | 1235(470–3350)                | 1250(590–3360)               | 1129(570–3830)          | 1470(545–4610)                  |
| GA (wks)  | 28(23–40)                     | 31(23–40)                    | 28(24–42)               | 30(23–42)                       |
| Day of life at positive culture                   | 33(13–146)                    | N/A                          | 10(1–117)*              | 22(8–117)**                     |
| Number of days from surgery to onset of infection | 15(1–65)                      | N/A                          | 27(1–61)                | 19(1–74)                        |
| Number of days with central line <sup>¶</sup>     | 16(1–43)                      | N/A                          | 8(2–49)                 | 13(1–38)                        |
| Number of days receiving antibiotics <sup>¶</sup> | 11(0–50)                      | N/A                          | 2(0–58)*                | 3(0–62)**                       |
| Platelet count                                    | 220(5–511)                    | N/A                          | 238(10–504)             | 207(8–504)                      |
| White blood cell count                            | 13.5(3–62)                    | N/A                          | 11.3(2–57)              | 11.8(0.2–56)                    |

<sup>¶</sup>Prior to onset of infection  
\*P<0.001  
\*\*P=0.001

**Table 2** Bivariable logistic regression analysis of risk factors and outcomes associated with cases of *S marcescens* sepsis versus uninfected controls

| Characteristic                 | <i>S marcescens</i><br>(n = 25) | Uninfected<br>controls<br>(n = 50) | OR (95% CI)*           | p†    |
|--------------------------------|---------------------------------|------------------------------------|------------------------|-------|
| Host and perinatal factors     |                                 |                                    |                        |       |
| Vaginal delivery               | 10 (40)                         | 19 (38)                            | 1.09 (0.41 to 2.91)    | 0.87  |
| Maternal antibiotic use        | 9 (36)                          | 15 (30)                            | 1.31 (0.48 to 3.63)    | 0.60  |
| Preterm labor                  | 16 (64)                         | 24 (48)                            | 1.93 (0.72 to 5.17)    | 0.25  |
| Prolonged rupture of membranes | 2 (8)                           | 5 (10)                             | 0.78 (0.14 to 4.35)    | 0.80  |
| Maternal fever                 | 1 (4)                           | 2 (4)                              | 1.00 (0.09 to 11.59)   | 0.96  |
| Chorioamnionitis               | 3 (12)                          | 0                                  | 0.03                   |       |
| Procedures and conditions      |                                 |                                    |                        |       |
| Intubated                      | 13 (52)                         | 22 (44)                            | 1.38 (0.53 to 3.61)    | 0.51  |
| Prolonged intubation           | 11 (44)                         | 15 (30)                            | 1.83 (0.68 to 4.96)    | 0.23  |
| Surgery                        | 12 (48)                         | 7 (14)                             | 5.67 (1.81 to 17.37)   | <0.01 |
| Urinary catheter               | 1 (4)                           | 1 (2)                              | 2.04 (0.12 to 34.07)   | 0.61  |
| CVC                            | 20 (80)                         | 24 (48)                            | 4.33 (1.41 to 13.36)   | 0.01  |
| TPN                            | 14 (56)                         | 31 (62)                            | 0.78 (0.29 to 2.07)    | 0.62  |
| Intralipids                    | 13 (52)                         | 31 (62)                            | 0.66 (0.25 to 1.75)    | 0.41  |
| H <sub>2</sub> -blockers       | 11 (44)                         | 31 (62)                            | 0.48 (0.18 to 1.28)    | 0.14  |
| Clinical outcome               |                                 |                                    |                        |       |
| Death                          | 11 (44)                         | 1 (2)                              | 38.50 (4.57 to 324.47) | 0.001 |

†Bivariable logistic regression  
\*OR: odds ratio; CI: confidence interval

of death. Sepsis-related death was calculated with the numerator representing the number of episodes of sepsis with death and the denominator as the total number of episodes of sepsis.

**Laboratory**

Blood cultures were assessed using a fluorescent-detection system for the presence of CO<sub>2</sub> (Bactec II or 9240®, Becton

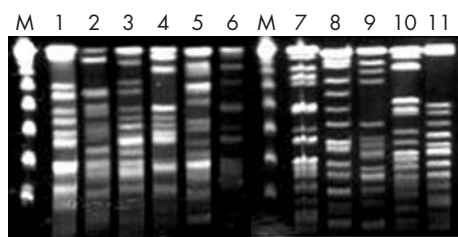
Dickinson, USA). Antibiotic susceptibility patterns were tested using the disk diffusion method.<sup>15</sup>

Strain relatedness of *S marcescens* was determined by pulse-field gel electrophoresis. Genomic DNA was digested with *SpeI* and *XbaI* (Boehringer Mannheim) and separated by electrophoresis with a CHEF-DR III apparatus (Bio-Rad, Hercules, CA, USA). The following parameters were used: temperature of

**Table 3** Bivariable logistic regression analysis of risk factors and outcomes associated with cases of *S marcescens* bacteremia versus *E Coli*-bacteremic controls

| Characteristic                 | <i>S marcescens</i><br>(n = 25) | <i>E Coli</i><br>(n = 50) | OR (95% CI)*         | p†     |
|--------------------------------|---------------------------------|---------------------------|----------------------|--------|
| Host and perinatal factors     |                                 |                           |                      |        |
| Vaginal delivery               | 10 (40)                         | 14 (28)                   | 1.40 (0.82 to 2.40)  | 0.19   |
| Maternal antibiotic use        | 9 (36)                          | 27 (54)                   | 0.48 (0.18 to 1.29)  | 0.14   |
| Preterm labor                  | 16 (64)                         | 36 (72)                   | 0.69 (0.25 to 1.92)  | 0.48   |
| Prolonged rupture of membranes | 2 (8)                           | 13 (26)                   | 0.25 (0.05 to 1.20)  | 0.06   |
| Maternal fever                 | 1 (4)                           | 7 (14)                    | 0.26 (0.03 to 2.21)  | 0.21   |
| Chorioamnionitis               | 3 (12)                          | 10 (20)                   | 0.55 (0.14 to 2.19)  | 0.39   |
| Procedures and conditions      |                                 |                           |                      |        |
| Intubated                      | 13 (52)                         | 21 (42)                   | 1.50 (0.57 to 3.93)  | 0.41   |
| Prolonged intubation           | 11 (44)                         | 6 (12)                    | 5.76 (1.80 to 18.42) | <0.01  |
| Surgery                        | 12 (48)                         | 13 (26)                   | 2.63 (0.96 to 7.20)  | 0.06   |
| Urinary catheter               | 1 (4)                           | 1 (2)                     | 2.04 (0.12 to 34.07) | 0.61   |
| CVC                            | 20 (80)                         | 17 (34)                   | 7.77 (2.48 to 24.31) | <0.001 |
| TPN                            | 14 (56)                         | 14 (28)                   | 3.27 (1.20 to 8.92)  | 0.02   |
| Intralipids                    | 13 (52)                         | 13 (26)                   | 3.08 (1.13 to 8.44)  | 0.03   |
| H <sub>2</sub> -blockers       | 11 (44)                         | 10 (20)                   | 3.14 (1.10 to 8.99)  | 0.03   |
| Repeat positive blood culture  | 13 (52)                         | 12 (24)                   | 3.43 (1.24 to 9.50)  | 0.02   |
| Presenting signs and symptoms  |                                 |                           |                      |        |
| Apnea                          | 9 (36)                          | 23 (46)                   | 0.66 (0.25 to 1.77)  | 0.41   |
| Bradycardia                    | 7 (28)                          | 16 (32)                   | 0.83 (0.29 to 2.38)  | 0.72   |
| Hypoglycemia                   | 3 (12)                          | 5 (10)                    | 1.23 (0.27 to 5.61)  | 0.79   |
| Hyperglycemia                  | 8 (32)                          | 18 (36)                   | 0.84 (0.30 to 2.32)  | 0.73   |
| Hypothermia                    | 11 (44)                         | 17 (34)                   | 1.53 (0.57 to 4.08)  | 0.40   |
| Hyperthermia                   | 8 (32)                          | 7 (14)                    | 2.89 (0.91 to 9.22)  | 0.07   |
| Neutropenia                    | 1 (4)                           | 6 (12)                    | 0.31 (0.04 to 2.69)  | 0.29   |
| Clinical outcome               |                                 |                           |                      |        |
| Meningitis                     | 6 (24)                          | 8 (16)                    | 1.66 (0.51 to 5.45)  | 0.41   |
| Death                          | 11 (44)                         | 14 (28)                   | 2.02 (0.74 to 5.51)  | 0.17   |
| Sepsis-related death           | 6 (24)                          | 11 (22)                   | 1.12 (0.36 to 3.49)  | 0.85   |

†Bivariable logistic regression  
\*OR: odds ratio; CI: confidence interval



**Figure 2** Pulse field gel electrophoresis of *S. marcescens* blood isolates. DNA was prepared from 11 blood isolates of *S. marcescens*, digested with *SpeI* and *XbaI*, subjected to pulse field gel electrophoresis, and banding patterns compared. M denotes a  $\lambda$  DNA molecular weight marker. The numbers represent individual isolates. Isolate 1 was from 1998, isolates 2 through 5 were from 1999, isolates 6 and 7 were from 2000, isolate 8 was from 2001, isolate 9 was from 2002, and isolates 10 and 11 were from 2003.

15°C with a run time of 18 h, switch time of 1–20 s, and voltage of 5.6 V/cm.

The pattern of DNA fragments for each *S. marcescens* isolate was compared with others of the same species independently by 2 investigators. Patterns that were distinctly different from each other (>3 bands different) in the same subspecies were considered to be unrelated and were defined as unique. Patterns that were identical or differed from each other by  $\leq 3$  fragments were considered to be the same strains and were defined as shared.<sup>16 17</sup>

### Statistical analysis

The SPSS v13.0 statistical software package (SPSS Inc., Chicago, IL, USA) was utilized for data analyses. Continuous data from cases and controls were analyzed using the Wilcoxon

Rank Sum test. Dichotomous variables were analyzed using odds ratio and bivariable logistic regression analysis. Despite the relatively small sample size and risk of model breakdown, independent covariates with a p-value of <0.10 as identified by bivariable analysis were subjected to multivariable logistic regression analysis. A p-value of <0.05 was considered statistically significant.

### Research ethics committee approval

This study was approved by the Human Investigation Committee of the Yale University School of Medicine.

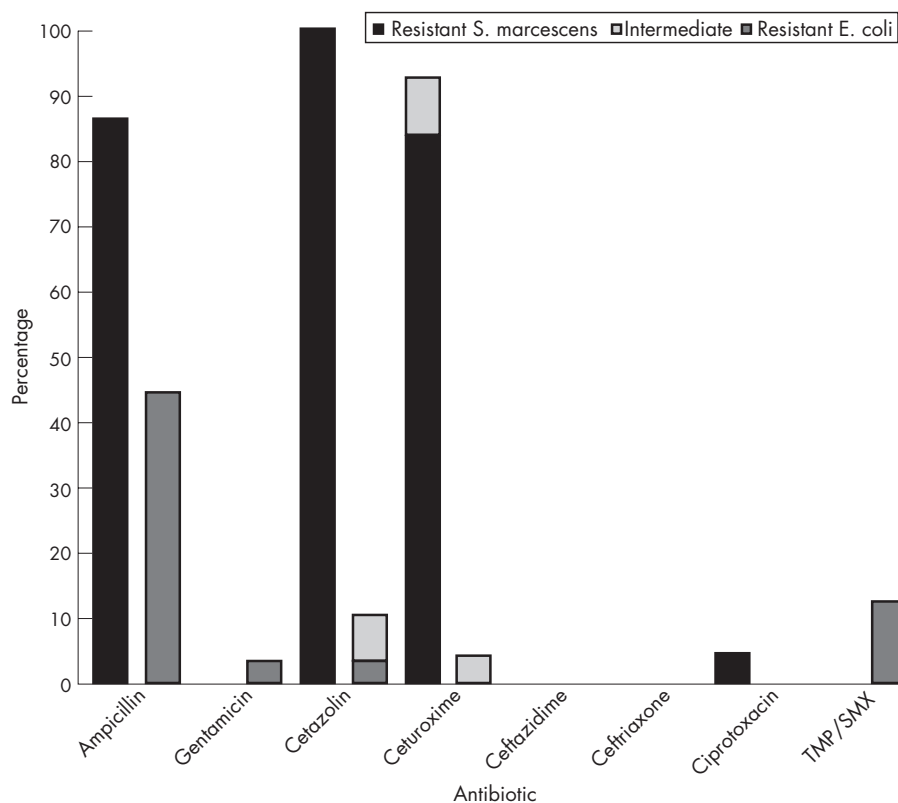
## RESULTS

### Patient characteristics, risk factors, and outcome

Twenty-five cases of *S. marcescens* bacteremia occurred in infants hospitalized in the NICU at Y-NHH between January 1, 1980 and December 31, 2004 (fig 1). Median gestational age (GA) was 28 weeks, with a body weight (BW) of 1235 grams. Infection presented at a median of 33 days of life (table 1). At the time of infection, more than 50% of infants were mechanically ventilated and receiving total parenteral nutrition (TPN) through a CVC (table 2). Meningitis occurred with 24% of cases of *S. marcescens* bacteremia (table 3). The overall mortality was 44% (table 2). Death from sepsis occurred in 24% of infants (table 3).

### Organism characteristics and antibiotic susceptibility patterns

Cases occurred sporadically over a 25-year period with a minimum of 41 days between episodes and no more than five cases in a 12-month period (1999). Eleven isolates were available for comparison analysis of organism DNA using pulse



**Figure 3** Percentage of non-susceptible (resistant and intermediate) isolates of *S. marcescens* and *E. coli* cultured at >7 days of life for each antibiotic tested.

**Table 4** Presumptive primary source of infection in 25 cases of *S marcescens* bacteremia

| Source                      | Number of Cases (%) |
|-----------------------------|---------------------|
| Central vascular catheter   | 8 (32)              |
| Respiratory                 | 3 (12)              |
| Genitourinary               | 3 (12)              |
| Conjunctiva                 | 3 (12)              |
| Gastrointestinal            | 3 (12)              |
| Ventriculo-peritoneal shunt | 1 (4)               |
| Unknown                     | 4 (16)              |

field gel electrophoresis. All 11 were determined to be different strains, including isolates from four cases in 1999 (fig 2).

Eighty-six percent of *S marcescens* isolates were resistant to ampicillin. None was resistant to gentamicin or 3<sup>rd</sup> generation cephalosporins (fig 3).

A presumptive primary source of infection was identified in 21 of 25 (84%) cases of *S marcescens* bacteremia (table 4). A CVC catheter was the believed to be the primary source of infection in 8 (32%) cases, while the conjunctiva, gastrointestinal, genitourinary, and respiratory tracts were the presumed source in 3 (12%) cases each.

**Cases of *S marcescens* and uninfected controls**

The overall mortality was higher among infected patients (44% vs 2%, OR = 38.50; 95% CI (4.57 to 324.47); table 2). Bivariable logistic regression analysis revealed that patients with *S marcescens* bacteremia were more likely to have been born to

mothers with chorioamnionitis, to have an indwelling CVC (OR = 4.33; 95% CI (1.41 to 13.36)), and to have had surgery (OR = 5.67; 95% CI (1.81 to 17.37); table 2). Multivariable logistic regression confirmed the presence of a CVC (adjusted OR = 3.25; 95% CI (1.12 to 10.65); p = 0.04) and surgery (adjusted OR = 4.07; 95% CI (1.26 to 13.10); p = 0.01) as significant independent risk factors for *S marcescens* bacteremia.

**Cases of *S marcescens* and *E coli* controls**

*S marcescens* bacteremia (median, 33 days) presented later in onset than *E coli* (median, 10 days, p < 0.001; table 1). Infants with *S marcescens* bacteremia received more total days of antibiotics prior to infection (p < 0.001; table 1) and mechanical ventilation (OR = 5.76; 95% CI (1.80 to 18.42)), and were more likely to have a CVC in place (OR = 7.77; 95% CI (2.48 to 24.31)) and be receiving TPN (OR = 3.27; 95% CI (1.20 to 8.92)), intralipids (OR = 3.08; 95% CI (1.13 to 8.44)), and H<sub>2</sub>-blockers at the time of infection (OR = 3.14; 95% CI (1.10 to 8.99); table 3). Infants with *S marcescens* bacteremia were also more likely to have a positive repeat culture, despite appropriate antibiotic therapy for >24 hours, than those with *E coli* (OR = 3.43; 95% CI (1.24 to 9.50); table 3). There were no differences in perinatal risk factors, presenting signs, or mortality (table 3). Despite relatively small numbers of cases and controls for analysis, a multivariable logistic regression was performed (with day of life at onset of infection included) and the presence of a CVC determined to be a significant independent covariate for *S marcescens* bacteremia as compared with *E coli* (adjusted OR = 4.94; 95% CI (1.20 to 20.41); p < 0.01).

**Table 5** Bivariable logistic regression analysis of risk factors and outcomes associated with cases of *S marcescens* bacteremia versus *E Coli*-bacteremic controls at >7 days of life

| Characteristic                       | <i>S marcescens</i> (n = 25) | <i>E Coli</i> (n = 68) | OR (95% CI)          | P†    |
|--------------------------------------|------------------------------|------------------------|----------------------|-------|
| <b>Host and perinatal factors</b>    |                              |                        |                      |       |
| Male sex                             | 16 (64)                      | 45 (66)                | 0.91 (0.35 to 2.37)  | 0.85  |
| Vaginal delivery                     | 10 (40)                      | 46 (68)                | 0.31 (0.15 to 1.06)  | 0.06  |
| Maternal antibiotic use              | 9 (36)                       | 29 (43)                | 0.76 (0.29 to 1.95)  | 0.56  |
| Preterm labor                        | 16 (64)                      | 41 (60)                | 1.17 (0.45 to 3.03)  | 0.75  |
| Prolonged rupture of membranes       | 2 (8)                        | 9 (13)                 | 0.57 (0.11 to 2.84)  | 0.49  |
| Maternal fever                       | 1 (4)                        | 5 (7)                  | 0.53 (0.06 to 4.73)  | 0.57  |
| Chorioamnionitis                     | 3 (12)                       | 5 (7)                  | 1.72 (0.38 to 7.79)  | 0.48  |
| <b>Procedures and conditions</b>     |                              |                        |                      |       |
| Intubated                            | 13 (52)                      | 23 (34)                | 2.10 (0.84 to 5.38)  | 0.11  |
| Prolonged intubation                 | 11 (44)                      | 9 (13)                 | 5.15 (1.79 to 14.81) | <0.01 |
| Surgery                              | 12 (48)                      | 19 (28)                | 2.36 (0.92 to 6.14)  | 0.07  |
| Urinary catheter                     | 1 (4)                        | 1 (2)                  | 2.79 (0.17 to 46.40) | 0.47  |
| CVC                                  | 20 (80)                      | 37 (54)                | 3.35 (1.13 to 9.97)  | 0.03  |
| TPN                                  | 14 (56)                      | 29 (43)                | 1.71 (0.68 to 4.31)  | 0.26  |
| Intralipids                          | 13 (52)                      | 27 (40)                | 1.65 (0.65 to 4.14)  | 0.29  |
| H <sub>2</sub> -blockers             | 11 (44)                      | 20 (29)                | 1.89 (0.73 to 4.86)  | 0.19  |
| <b>Presenting signs and symptoms</b> |                              |                        |                      |       |
| Apnea                                | 9 (36)                       | 28 (41)                | 0.80 (0.31 to 2.08)  | 0.65  |
| Bradycardia                          | 7 (28)                       | 21 (31)                | 0.87 (0.31 to 2.35)  | 0.79  |
| Hypoglycemia                         | 3 (12)                       | 3 (4)                  | 3.27 (0.44 to 12.63) | 0.30  |
| Hyperglycemia                        | 8 (32)                       | 27 (40)                | 0.72 (0.27 to 1.89)  | 0.50  |
| Hypothermia                          | 11 (44)                      | 22 (32)                | 1.64 (0.64 to 4.20)  | 0.30  |
| Hyperthermia                         | 8 (32)                       | 19 (28)                | 1.21 (0.45 to 3.28)  | 0.70  |
| Neutropenia                          | 1 (4)                        | 3 (4)                  | 0.90 (0.09 to 9.11)  | 0.93  |
| <b>Clinical outcome</b>              |                              |                        |                      |       |
| Meningitis                           | 6 (24)                       | 5 (7)                  | 3.98 (1.09 to 14.50) | 0.04  |
| Death                                | 11 (44)                      | 16 (24)                | 2.55 (0.97 to 6.73)  | 0.09  |
| Sepsis-related death                 | 6 (24)                       | 9 (13)                 | 2.07 (0.65 to 6.57)  | 0.22  |

CV: central vascular catheter; TPN: total parenteral nutrition.  
†Bivariable logistic regression

### Cases of *S marcescens* and *E Coli* controls presenting at >7 days of life

Data analyses revealed no significant differences in body weight, gestation age, or gender (tables 1 and 5). Subjects with *S marcescens* sepsis still presented with later onset infection ( $p = 0.001$ ; table 1), received more total days of antibiotic therapy prior to infection ( $p = 0.001$ ; table 1), were more likely to require prolonged mechanical ventilation, (OR = 5.15; 95% CI (1.79 to 14.81); table 5), and to have an indwelling CVC in place at the time of infection (OR = 3.35; 95% CI (1.13 to 9.97); table 5). A higher rate of meningitis was observed with *S marcescens* bacteremia as compared with later onset *E coli* (24% vs 7%, OR = 3.98; 95% CI (1.09 to 14.50); table 5). Multivariable logistic regression confirmed prolonged intubation (adjusted OR = 3.45; 95% CI (1.11 to 10.91);  $p = 0.02$ ) and the presence of a CVC (adjusted OR = 3.54; 95% CI (1.01 to 12.37);  $p = 0.048$ ) as independent risk factors for *S marcescens* bacteremia.

### Antibiotic susceptibility pattern differences between cases of *S marcescens* and *E Coli*

Antibiotic susceptibility patterns were compared between cases of *S marcescens* and *E coli* presenting at >7 days of life. Both organisms were almost uniformly sensitive to gentamicin and 3rd generation cephalosporins (fig 3). Although not typically used in the treatment of *S marcescens*, a higher percentage of ampicillin ( $p < 0.01$ ), cefazolin ( $p < 0.001$ ), and cefuroxime ( $p < 0.001$ ) resistance was observed in *S marcescens* compared with *E coli*.

## DISCUSSION

*S marcescens* is an opportunistic organism which, in adults, predominantly infects immunocompromised and debilitated hosts including postoperative patients<sup>18 19</sup> and hospitalized patients with endotracheal tubes,<sup>20-23</sup> and CVC.<sup>20 21 24</sup> These findings are mirrored in our population. *S marcescens* sepsis in the Y-NHH NICU occurred more commonly in premature, very low birth weight infants and was more likely to occur in infants who had surgery and a CVC in place at the time of infection. Presumptive primary sources of infection included support apparatus and the gastrointestinal, genitourinary, and respiratory tracts.

*S marcescens* sepsis in the NICU was associated with a significant risk of morbidity and mortality. Previous reports have documented an association between *S marcescens* bacteremia and meningoencephalitis and brain abscess formation.<sup>7 8 25 26</sup> Central nervous system infection with *S marcescens* is aggressive and may advance despite appropriate antibiotic therapy.<sup>7 25 26</sup> This is comparable to other neurotropic pathogens associated with neonatal sepsis and meningoencephalitis and brain abscess formation including K1-serotype *E Coli*, *Citrobacter* spp. and *Enterobacter sakazakii*.<sup>27</sup> In our case series, the prevalence of meningitis among infants with *S marcescens* bacteremia was 24% (as compared with a 6% overall prevalence of meningitis with all documented cases of sepsis in our NICU). This is significantly higher than observed in 68 cases of *E Coli* bacteremia occurring after 7 days of life (7% prevalence).

Mortality after *S marcescens* bacteremia has been reported to be 10% to 20%.<sup>28-30</sup> In our study, *S marcescens* bacteremia had a 24% associated mortality (as compared with an overall prevalence of sepsis-related death in our NICU of 12%).<sup>13</sup> In cases of *S marcescens* bacteremia with meningitis, the prevalence of sepsis-related mortality increased to 50%.

Episodes of *S marcescens* sepsis in the NICU have traditionally been reported as clustered epidemics with contamination of a common source leading to colonization and subsequent infection.<sup>2-7 9-12</sup> At Y-NHH, cases have occurred sporadically with no predominant strain or definable outbreak over the past quarter-century. The epidemiology of *S marcescens* bacteremia in the NICU at Y-NHH appears comparable to that observed in a study of endemic, antibiotic-resistant Gram-negative bacilli in a NICU.<sup>31</sup> This report suggested that there is gradual, but temporary, acquisition of these organisms from the NICU environment into the changing neonatal microflora with little cross-colonization.<sup>31</sup> A recent study of NICU Gram-negative bacilli infection demonstrated that contact from the hands of providers is an unlikely cause of NICU-associated GNR bacteremia.<sup>32</sup> Together, these data indicate that the source of GNR in NICU-related bacteremia is environmental and/or associated with noncutaneous reservoirs such as the gastrointestinal or respiratory tracts. As a result, prevention strategies should focus on identification and manipulation of these potential sources as well as attention to traditional hygienic issues such as hand hygiene and environmental cleanliness.

Antibiotic susceptibility patterns for *S marcescens* exhibit institutional and chronologic variability. Some centers report high rates of resistance to aminoglycosides and 3<sup>rd</sup> generation cephalosporins,<sup>23 33</sup> while others report sensitivity to these agents.<sup>34 35</sup> *S marcescens* isolates from our NICU are universally sensitive to gentamicin and 3<sup>rd</sup> generation cephalosporins, similar to the susceptibility patterns of *S marcescens* observed throughout Y-NHH.<sup>36</sup> Despite this finding, a high percentage (52%) of infants were found to have a repeat positive blood culture after >24 hours of appropriate antibiotic therapy. This may be due to factors related to the organism, to the debilitated nature of the host population, or other factors. Although the data represent a small number of cases and no differences in outcome were observed among infants with and without persistently positive cultures, antibiotic therapy with both an aminoglycoside and a 3<sup>rd</sup> generation cephalosporin should be considered if *S marcescens* bacteremia is confirmed, particularly when central nervous system infection cannot be excluded. Therapy with a 3<sup>rd</sup> generation cephalosporin should also be considered when *S marcescens* is isolated from a patient in an institution where gentamicin-resistant *S marcescens* has been observed.

## ACKNOWLEDGEMENT

We acknowledge the limitations of our study, given its retrospective nature and relatively small sample size. We attempted to address some of these issues with our study design. A matched case-control study was chosen in an attempt to control for the potential confounding effects of prematurity and gender on the susceptibility to infection. In addition, matching by date of birth was performed to control for the potential confounding effects of the differences in treatment protocols and

### What is already known on this topic

- *S marcescens* bacteremia in the NICU is typically epidemic, occurring as outbreaks in association with contaminated medical devices.
- *S marcescens* bacteremia is associated with significant morbidity and mortality in the preterm patient population

### What this study adds

- *S marcescens* bacteremia can occur sporadically in the NICU without a definable strain or outbreak.
- Compared to *E Coli*, *S marcescens* bacteremia typically occurs late in the NICU hospitalization and tends to infect more debilitated infants.

practices over the 25-year study period. Finally, a 2:1 control-to-case ratio was performed in an attempt to improve the precision of the statistical model given the small number of available cases.<sup>37</sup> Multivariable logistic regression, where appropriate, was also employed in an attempt to identify significant independent risk factors for each desired outcome of interest and the data analyzed and presented accordingly.

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