



Epidemiology of *Serratia Marcescens* in the Neonatal ICU of A Tertiary Hospital in Oman over a 10 Years Period

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Abstract

Background: *Serratia marcescens* has been described as a significant nosocomial organism. Several *S. marcescens* outbreaks in Neonatal Intensive Care Units (NICUs) were described as causing fatal meningitis, sepsis or pneumonitis in premature or low birth weight neonates with a mortality rate of 44%. The primary objective of this study is to describe the outcome (mortality and length of hospital stay) of *S. marcescens* infection in NICU at a tertiary care hospital over ten years (2009-2018). Secondary objectives are to describe the incidence of *S. marcescens* infection/colonization in NICU, study the risk factors associated with *S. marcescens* infection/colonization, and the microbiology of this organism.

Method: A retrospective, unmatched case-control study was conducted between January 2009 to December 2018. Data were analyzed using IBM SPSS Statistics 28.0. A multivariate binary logistic regression analysis was performed to determine the independent predictors of *Serratia marcescens* and mortality among *Serratia marcescens* infected patients. The Odds Ratio (OR) was reported with its 95% CI. A P-value less than 0.05 was considered statistically significant.

Result: A total of 93 cases had a positive culture of *S. marcescens* in neonates hospitalized in the NICU during the study period and 201 controls were included. 50.5% (n=47) of cases were male and 49.5% (n=46) were females. The clinical features of infection by *S. marcescens* range from asymptomatic colonization (16.1%) to potentially fatal sepsis (38.7%) and meningitis (1.1%). 13 cases (17.3 %) had colonization before infection. Mortality rate among infected neonates was 17%. Multivariate analysis showed that female gender (OR= 1.969, 95% CI= 1.020-3.801, P= 0.044), premature birth ((OR= 2.670, 95% CI= 1.156-6.167, P= 0.021). C-section (OR= 3.238, 95% CI= 1.591-6.591, P= 0.001), type of feeding and surgery (OR= 3.719, 95% CI= 1.546-8.946, P= 0.003) were independent predictors for acquiring *S. marcescens*. Female gender was an independent factor for mortality from *Serratia* infection (OR= 6.741, 95% CI= 1.307-34.767, P= 0.023).

Conclusion: *S. marcescens* is an important pathogen that has a propensity to cause difficult-to-control outbreaks in NICUs. Healthcare workers' awareness of this organism and enhancement of infection prevention and control measures is a vital requirement to prevent HAIs among susceptible neonates.

Keywords: *Serratia Marcescens*; Epidemiology; Mortality; Risk Factors

Introduction

Healthcare-associated infections (HAIs) are among the leading causes of mortalities, morbidities, and prolonged hospital stay, resulting in considerable associated economic patient care costs. *Serratia marcescens* is a gram-negative bacterium described as a significant nosocomial organism that can rapidly spread, particularly in neonatal intensive care units (NICUs). The third highest number of published outbreaks is due to *S. marcescens*, after *Klebsiella* spp. and *S. aureus* [1]. Several *S. marcescens* outbreaks in NICUs were described as causing fatal meningitis, sepsis or pneumonitis in premature or low birth weight neonates with a high mortality rate of 44% which is much higher than mortality rate caused by *Enterobacter cloacae*, another pathogen well-known to cause disease and death in premature neonates [2].

This bacterium can be transmitted to neonates via feeding, contaminated breast pumps and antiseptics, and it can spread through contact with patients [3]. Contaminated baby shampoo was identified as the source of the outbreak in the King Abdulaziz University Hospital in Saudi Arabia. Withdrawal of the shampoo product led to the termination of the outbreak [4].

The primary objectives were to describe the Outcome (30 days mortality & length of hospital stay) of *S. marcescens* infection in the NICU and the determinants of mortality among infected patients. The secondary objectives were to estimate the incidence of *S. marcescens* infection/colonization in the NICU at Royal hospital and to study the risk factors for acquisition and the microbiology of *S. marcescens* strains.

Method

Setting, study designs a retrospective case-control study in the NICU of Royal Hospital, Sultanate of Oman, from 2009 to 2018. The Royal Hospital is a tertiary hospital that provides inpatient and outpatient health care services to the country. The NICU has 35 beds, 16 of which were assigned for critical cases. The unit has no active *S. marcescens* screening; however, at the time of outbreaks, active screening surveillance is implemented till the outbreak is controlled.

Population Definitions

The target population for the study was neonates admitted to NICU at Royal hospital from 2009-2018. Cases include all neonates with a positive culture for *S. marcescens* from any sample during the study period. The case was included once if it had repeated cultures, and the infection episode was included if it had colonization before infection. Controls were randomly selected from those

neonates who were admitted in the same period and had no positive cultures for *S. marcescens* from both clinical and screening samples. The sample size was fixed due to the retrospective design. Given the relatively small number of cases, two controls were utilized to improve the precision of the statistical estimate. Each case of *S. marcescens* was compared to two uninfected controls to identify potential risk factors associated with demographics and clinical care variables. Prematurity was defined as delivery before 37 weeks and 0/7 days of gestation [5]. Procedures included echocardiography and ultrasound as they were considered a possible source of transmission of micro-organisms. The acquisition was related to the referring hospitals if the cases had a positive culture for *S. marcescens* within 48 hours of admission, while Royal hospital-acquired infection/colonization was defined as a positive culture after 48 hours of admission. Colonization is defined as a positive culture for *Serratia marcescens* in the absence of symptoms or signs of infection, and the neonate was not treated with any antibiotics. Infection was defined as a positive culture for *S. marcescens*, and signs and or symptoms of infection were present, and the neonate was treated with antibiotics. Mortality was defined as all causes of death within 30 days of a positive *S. marcescens* culture. Annual incidence proportion was calculated as the total number of positive cases divided by the total number of admitted cases in a year times 100. The annual incidence density was calculated as the total number of positive cases divided by total patient days in a year times 1000.

Statistical Analysis

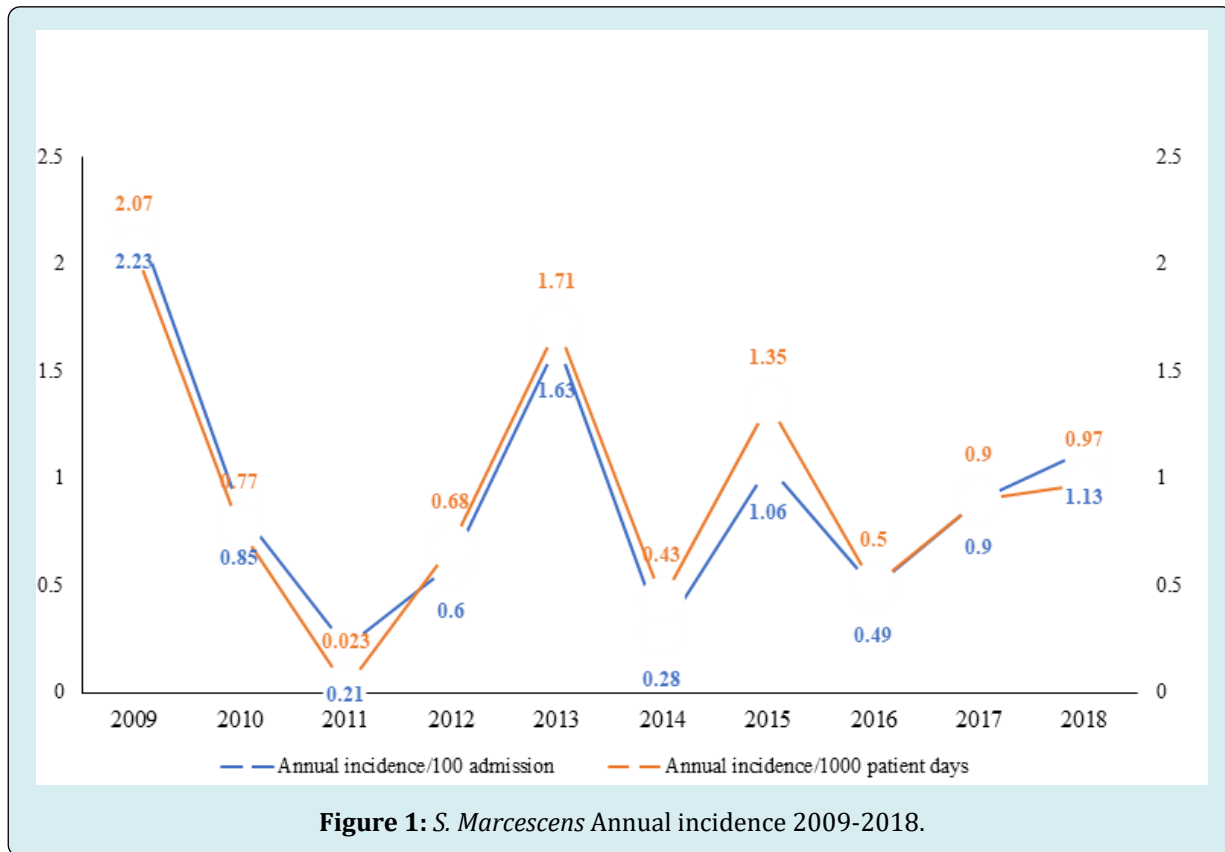
Collected data were analyzed using IBM SPSS Statistics 28.0. Continuous variables were presented as mean, median, and standard deviation, whereas categorical variables, were presented as frequency and percentage. The comparison of means between the two groups was assessed by using an unpaired t-test. The association between two categorical variables was assessed using a chi-square test (Fisher's exact/Likelihood ratio). A multivariate binary logistic regression analysis was performed to determine the independent predictors of *Serratia marcescens* and mortality among *Serratia marcescens* infected patients. The Odds Ratio (OR) was reported with its 95% CI. A P-value less than 0.05 were considered statistically significant.

Result

A total of 93 cases had a positive culture of *S. marcescens* in neonates hospitalized in the NICU during the study period, and 201 controls were included. 50.5% (n=47) of cases were male and 49.5% (n=46) were females. The annual incidence proportion fluctuated from the highest incidence of 2.23 per

100 admissions in 2009 to the lowest incidence of 0.21 per 100 admissions in 2011. The incidence density per 1000

patients' days ranged between 2.07 and 0.23, as shown in Figure 1.



During the study period, there were a total of 36 neonatal deaths among cases and controls. The overall mortality was higher among infected patients, 17.2% (n=16) vs 10.0% (n=20) in the control group. The median time from detection of *S. marcescens* to discharge from the hospital is 22 (range 8.25 to 41) days. Regarding predictors of mortality from *S.*

marcescens infection, univariate analysis showed that female gender (P=0.030) and mechanical ventilation (P= 0.025) were significant, and in multivariate analysis, only female gender was significant ((OR= 6.741, 95% CI= 1.307-34.767, P= 0.023) as shown in Table 1.

Variable	<i>Serratia marcescens</i>		p-value	Adjusted Odds Ratio (OR)	95% CI for OR		P-value
	Negative (n= 201)	Positive (n= 93)			Lower	Upper	
Gender							
Male (Reference)	119 (59.5)	47 (50.5)	0.165	1.969	1.02	3.801	0.044*
Female	81 (40.5)	46 (49.5)					
Birth weight							
<1.5 kg	61 (30.5)	42 (46.7)	0.011*	1.498	0.634	3.54	0.357
≥1.5 kg (Reference)	139 (69.5)	48 (53.3)					
Gestational age							

Term birth (Reference)	94 (46.8)	25 (27.2)	0.002*		1.156	6.167	0.021*
Premature birth	107 (53.2)	67 (72.8)		2.67			
Mode of delivery							
Vaginal Delivery (Reference)	112 (56.9)	26 (28.9)	0.0001*		1.591	6.591	0.001*
Cesarean-section	85 (43.1)	64 (71.1)		3.238			
Catheter							
No (Reference)	153 (76.1)	79 (84.9)	0.092		0.282	1.985	0.561
Yes	48 (23.9)	14 (15.1)		0.749			
Central line							
Yes (Reference)	119 (59.5)	33 (35.5)	0.0001*		0.951	5.376	0.065
No	81 (40.5)	60 (64.5)		2.261			
Procedures							
Yes (Reference)	142 (71.7)	70 (75.3)	0.574		0.215	1.079	0.076
No	56 (28.3)	23 (24.7)		0.482			
Mechanical ventilation							
Yes (Reference)	144 (73.5)	58 (62.4)	0.074		0.606	3.495	0.401
No	52 (26.5)	35 (37.6)		1.455			
Type of feeding							
Total Parenteral Nutrition TPN (Reference)	60 (30.0)	18 (19.4)	0.0001*		3.993	1.599	9.968
Enteral	38 (19.0)	37 (39.8)		4.73			
Breast Milk (BM)	25 (12.5)	16 (17.2)		4.777			
Nil Per Os (NPO)	10 (5.0)	8 (8.6)		0.311			
TPN + Enteral	62 (31.0)	5 (5.4)		9.905			
TPN + BM	5 (2.5)	9 (9.7)		0.102			
Surgery							
No (Reference)	122 (61.3)	61 (65.6)	0.518		1.546	8.946	0.003*
Yes	77 (38.7)	32 (34.4)		3.719			
Antibiotics							
Received (Reference)	175 (87.1)	90 (96.8)	0.010*		0.061	1.066	0.061
Not received	26 (12.9)	3 (3.2)		0.255			

Statistically significant

Table 1: Univariate and multivariate analysis to determine the independent predictors of *Serratia marcescens* infection.

There were significant differences between cases and controls for the acquisition of *S. marcescens* in birth weight (46.7% of those who had *S. marcescens* had a birth weight < 1.5 kg (P=0.001), premature births (P= 0.002) and born by cesarean section (P=0.0001) and had a central line (P=0.0001). All types of feeding were significant, and

exposure to antibiotics was also significant (P=0.010), as shown in (Table 2). At the time of infection, 28.7% of infants were mechanically ventilated, > 50% received Total parenteral nutrition (TPN) and (21.7%) had a central venous catheter.

Variable	Mortality		p-value	Adjusted Odds Ratio (OR)	95% CI for OR		P-value
	No (n= 77)	Yes (n= 16)			Lower	Upper	
Gender							
Male (Reference)	43 (91.5)	4 (8.5)	0.030*	6.741	1.307	34.767	0.023*
Female	34 (73.9)	12 (26.1)					
Birth weight							
<1.5 kg	33 (78.6)	9 (21.4)	0.422	0.761	0.1	5.779	0.791
≥1.5 kg (Reference)	41 (85.4)	7 (14.6)					
Gestational age							
Term birth (Reference)	21 (84.0)	4 (16.0)	1	0.872	0.083	9.179	0.909
Premature birth	55 (82.1)	12 (17.9)					
Mode of delivery							
Vaginal Delivery (Reference)	21 (80.8)	5 (19.2)	0.757	1.156	0.223	6.003	0.863
Cesarean-section	54 (84.4)	10 (15.6)					
Catheter							
No (Reference)	66 (83.5)	13 (16.5)	0.703	2.553	0.261	24.921	0.42
Yes	11 (78.6)	3 (21.4)					
Central line							
Yes (Reference)	26 (78.8)	7 (21.2)	0.567	1.252	0.216	7.266	0.802
No	51 (85.0)	9 (15.0)					
Procedures							
Yes (Reference)	55 (78.6)	15 (21.4)	0.107	0.339	0.029	3.989	0.39
No	22 (95.7)	1 (4.3)					
Mechanical ventilation							
Yes (Reference)	44 (75.9)	14 (24.1)	0.025*	0.172	0.024	1.219	0.078
No	33 (94.3)	2 (5.7)					
Type of feeding							
Total Parenteral Nutrition TPN (Reference)	13 (72.2)	5 (27.8)	0.394	1.146	0.159	8.235	0.892
Enteral	30 (81.1)	7 (18.9)					
Breast Milk (BM)	15 (93.8)	1 (6.3)					
Nil Per Os (NPO)	7 (87.5)	1 (12.5)					
TPN + Enteral	5 (100)	0 (0)					
TPN + BM	7 (77.8)	2 (22.2)					
Surgery							
No (Reference)	50 (82.0)	11 (18.0)	1	0.389	0.056	2.71	0.341
Yes	27 (84.4)	5 (15.6)					
Antibiotics							
Received (Reference)	74 (82.2)	16 (17.8)	1				
Not received	3 (100)	0 (0)					

*Statistically significant, NE - Not estimated due to non-occurrence of event.

Table 2: Univariate and multivariate analysis to determine the independent predictors of mortality among *Serratia marcescens* infected patients.

Multivariate analysis showed that gender (female neonates, OR= 1.969, 95% CI= 1.020-3.801, P= 0.044),

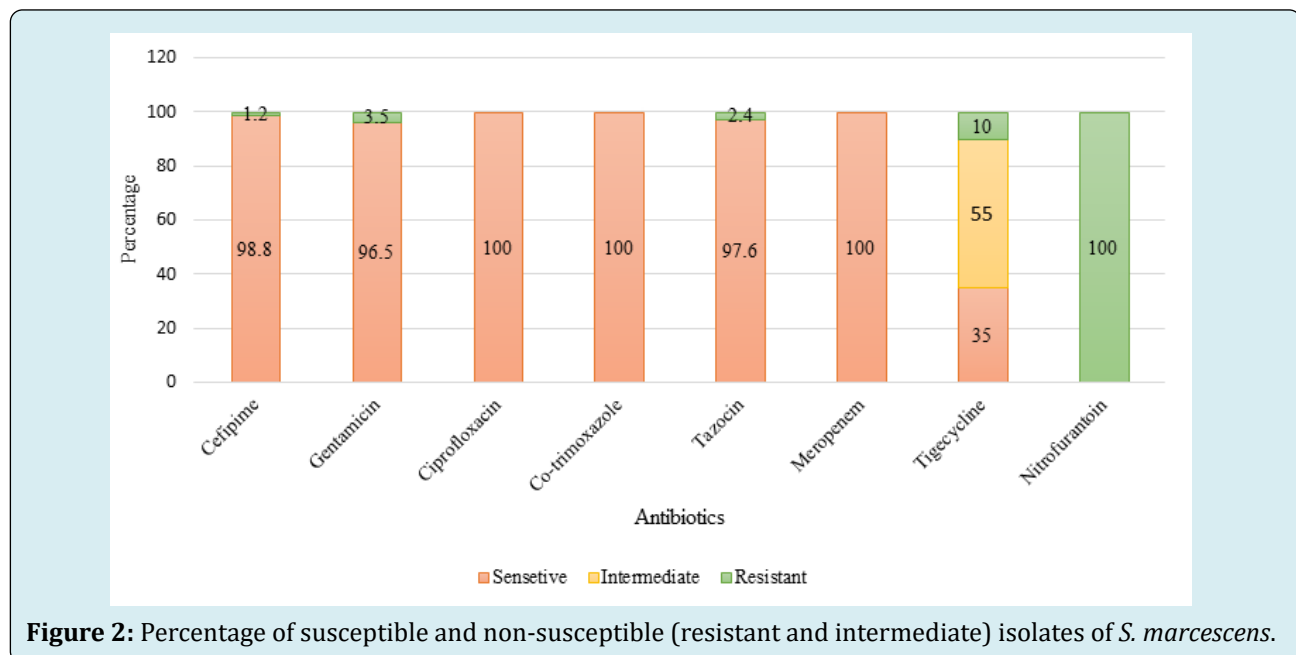
premature birth ((OR= 2.670, 95% CI= 1.156-6.167, P= 0.021). C-section (OR= 3.238, 95% CI= 1.591-6.591, P=

0.001); were independent factors for *Serratia* acquisition. Regarding the type of feeding, Enteral has four times increased risk of getting *Serratia marcescens* compared to TPN (OR= 3.993, 95% CI= 1.599-9.968, P= 0.003), whereas BM (OR= 4.730, 95% CI= 1.512-14.799, P= 0.008) and NPO (OR= 4.777, 95% CI= 1.243-18.358, P= 0.023) has five times increased risk of getting *Serratia marcescens* compared to TPN. The combination of TPN and Enteral has 69% reduced risk of getting *Serratia marcescens* compared to TPN alone (OR= 0.311, 95% CI= 0.102-0.951, P= 0.041). However, the combination of TPN and BM has a ten times higher risk of getting *Serratia marcescens* than TPN alone (OR= 9.905, 95% CI= 2.167-45.275, P= 0.003). Patients who underwent surgery have a four times higher risk of getting *Serratia marcescens* than those who did not (OR= 3.719, 95% CI= 1.546-8.946, P= 0.003).

Bacteremia was the commonest infection 38.7% (n=36) followed by conjunctivitis 29.0% (n=27). 15 (16.1%) cases had colonization, and 4 (4.3%) cases had wound infection. Meningitis, pneumonia, and urinary tract infection were 1 (1.1%) each. 87% (n=81) of cases were acquired in our hospital, while 13% (n=12) were acquired in other hospitals. 13 (14%) cases had colonization of *S. marcescens* before infection as shown in (Table 3). All tested *S. marcescens* isolates were resistant to ampicillin and amoxicillin/clavulanate, and all were susceptible to ciprofloxacin, co-trimoxazole and meropenem of the tested isolates: 1.2% were resistant to cefepime, 3.5 % were resistant to gentamicin, 2.4 % resistant to tazocin and 10 % resistant to tigecycline. One *S. marcescens* isolated from urine tested resistant to nitrofurantoin (Figure 2).

		n (%)
Type of positive Sample	blood	36 (38.7)
	CSF	1 (1.1)
	ET	10 (10.8)
	eye	27 (29.0)
	Peritoneal fluid	1 (1.1)
	pleural fluid	1 (1.1)
	screen	5 (5.4)
	sputum	5 (5.4)
	urine	2 (2.2)
	wound	5 (5.4)
Type of Infection	VAP	8 (8.6)
	Bacteremia	36 (38.7)
	GU	1 (1.1)
	Eye infection	27 (29.0)
	Wound infection	4 (4.3)
	colonization	15 (16.1)
	Meningitis	1 (1.1)
	pneumonia	1 (1.1)
colonization before infection	Yes	13 (14.0)
	No	80 (86.0)
Type of Acquisition	Royal Hospital	81 (87.0)
	Other hospitals	12 (13.0)
Detection of <i>S. marcescens</i> from > 1 site	Yes	18 (19.4)
	No	75 (80.6)

Table 3: Microbiology of *S. marcescens* cases.



Discussion

Most of the epidemiology of *S. marcescens* among neonates are described in the literature is from outbreak settings [6-11]. Our study highlighted the epidemiology for a ten-year period. The annual incidence and incidence proportion were fluctuating over the years due to occurrence of outbreaks throughout the study period that were ultimately controlled. In a recently reported outbreak, no source was identified [6].

The mortality rate in this study was high as reported by *M. Luisa* and colleagues that mortality due to *S. marcescens* infections can vary markedly and range from 0 to 45% [10].

In newborns, the main risk factors for the acquisition of *Serratia* infection are: immaturity of the immune system and low birth weight (<1500 g) in preterm newborns, length of stay, and the use of antibiotics. ⁽¹⁰⁾ In our study the significant risk factors were female gender, C-section, all types of feeding including newborn who are NPO and neonates who had surgery. All these might indicate more handling and care is given to those neonates with element of breaches or non-compliance to infection prevention and control practices during care delivery some of which were highlighted previously. ⁽⁶⁾ *S. marcescens* colonizes the preterm infant gut within the first days after birth, following a colonization pattern very similar to that observed in other members of the Family Enterobacteriaceae. Moles et al. found 69% of the infants were colonized by *S. marcescens* at least in a sampling time during the studied period. The colonization rate increased to ~ 75% when only infants born at < 30 gestational weeks and < 1500 g were considered [11]. The most frequent site of infection in our cohort, as reported in other literature, was bloodstream infection however, conjunctivitis was the second most common.

A few limitations were observed in this report including the study was retrospective in nature and was conducted in one center only which might affect the generalizability of the results. The data for rate of colonization might underestimate as our hospital does not a stable active screening for *S. marcescens* protocol in the NICU. In addition, we could not do sub analysis for bacteremia as we did not study non-*S. Marcescens* bacteremia among the controls. The strength of this work is that *S. marcescens* was studied for 10-year periods and the only one of its kind in the country.

Conclusion

S. marcescens is an important nosocomial pathogen, especially in NICUs, that has a propensity to cause difficult-to-control outbreaks. Healthcare workers' awareness of this

organism and enhancement of infection prevention and control measures is a vital requirement to prevent HAIs among susceptible neonates.

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