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Successful Source Identification and Control of an Outbreak of Serratia mercescens Bacteremia in NICU of a Tertiary Care Hospital in Eastern India

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Introduction: S. marcescens can cause potentially fatal sepsis, especially in premature and low birth weight babies. The result of an outbreak in any hospital is grave and requires thorough environmental sampling for source identification. **Purpose:** The objective of our study was to identify the source of the Serratia marcescens outbreak among the neonates admitted to the Neonatal Intensive Care Unit (NICU) of a tertiary care pediatric hospital. Seven neonates were affected in this outbreak and the index case, unfortunately, died. **Materials &Methods:** Apart from attempts to isolate organisms from neonates with sepsis, extensive environmental sampling in the form of swabs were collected from all surfaces like walls, floors, cradles, ventilators etc. and instruments like milk collecting devices, intravenous fluid and drug bottles etc. as well as from hands, stethoscopes, mobile phones of doctors and nursing staffs. Swabs were cultured to isolate S. marcescens, and a sensitivity pattern was noted. **Results:** Among the 78 samples studied, S. marcescens was isolated from a running intravenous fluid bottle and a normal saline bottle used for reconstituting intravenous fluids for the neonates. These isolates showed the same sensitivity patterns as those obtained from the affected neonates. Elimination of sources, appropriate antibiotic therapy and constant surveillance, achieved successful outbreak control. **Conclusions:** Extensive environmental sampling to find out the point source, and after that, active surveillance is necessary to control such infections. Besides source control and appropriate antibiotic therapy, implementing and reinforcing routine measures such as hand hygiene are compulsory in these outbreaks.

Keywords: Serratia marcescens, Neonatal intensive care unit, Outbreak, Hand hygiene, Newborn, Sepsis

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Introduction

Serratia is a genus of Gram-negative, non-spore-forming, rod-shaped bacteria belonging to the tribe Klebsielleae of the family Enterobacteriaceae. It is oxidase negative and typically a glucose-fermenter; Serratia species are Voges Proskauer positive and reduce nitrate to nitrite [1,2]. To date, 14 species of the genus Serratia have been identified, among which *S. marcescens* is the most common one isolated from clinical specimens [3,4]. First described in 1819 by an Italian pharmacist Bartolomeo Bizio[5], *S.marcescens* was at first presumed to be a non-pathogenic saprophyte. Because of detectable red pigment in many strains, it has been widely used as a tracer organism for pathogens used in bioterrorism during World War I and even until 1968 [5]. It is now a well-known human pathogen, the first probable adult case report dating back to 1913 [6]. The first report of an outbreak in a pediatric ward, along with the first neonatal mortality due to hospital-acquired *S.marcescens* infection, was reported in Israel in 1951-52 by Rabinowitz and Schiffrin[7].*S. marcescens* has been implicated in about 15% of opportunistic nosocomial infections in neonatal intensive care units[8]. In neonates, it can cause conjunctivitis, sepsis/bacteremia, pneumonia, meningitis, brain abscess etc.[5, 9]. Urinary tract infections, wound infections etc., have also been noted in pediatric patients [5]. Most of the published data show that infected infants are the main reservoirs as they harbour the organisms, often asymptomatically, in their gastrointestinal tracts despite prolonged antibiotic treatment and cause cross-transmission by the hands of health care workers working in NICUs [5, 10]. Apart from the patients, almost all the equipment, washbasins, and intravenous preparations used in NICUs have been incriminated as a source of infections. These ubiquitous organisms thrive well in soil and moist surfaces [5]. Biofilm formation by S. mercescens, observed by several researchers, may be another important factor in this regard [11,12]. Epidemic outbreaks in NICUs by this organism spread rapidly and are associated with significant neonatal mortality [13,14,15]. It has been observed that there has been an increasing trend of *S.marcescens* outbreaks in NICUs throughout the last decades [16]. Management of *S. marcescens* infections is a nightmare for clinicians. Apart from its intrinsic resistance to several antibiotics, It also acquires resistance to antibiotics, including beta-lactams, Aminoglycosides, quinolones etc., and transfers it from one strain to another very rapidly by chromosomal as well as plasmid-mediated determinants [5]. Thus hospital-acquired *S. marcescens* infections often prove devastating in neonates admitted with severe illnesses to neonatal intensive care units.

In our NICU, we have encountered a similar outbreak of *Serratia marcescens* and launched a thorough investigation to identify the source. Here we shall discuss the details of this outbreak investigation and the successful management of the situation with our limited resources.

Materials And Methods

This study was done over one month (December 2019). The study was conducted in a 150-bed tertiary care teaching hospital in Kolkata, India. The study subjects were newborns admitted to the NICU in December 2019. The NICU has 20 beds admitting critically ill neonates. The unit admits between 300-400 patients annually. In December 2019, an outbreak of systemic infections caused by *Serratia marcescens* occurred in the NICU. A total of seven patients were affected by this outbreak. Clinical details of cases were recorded by using a predesigned proforma. Sepsis was determined if blood culture showed positive results with clinical features [lethargy, feed intolerance, clinical features of shock with metabolic acidosis, tachypnoea/apnoea, tachycardia, fever/hypothermia] suggestive of sepsis and presence of routine haematological/biochemical parameters consistent with sepsis [rise/fall of total leukocyte count or increase in immature forms or rising C-reactive protein, micro-ESR etc.]Extensive environmental microbiological investigation was done. Conjunctival and rectal swabs from all the patients were sent. Swabs were taken from numerous surfaces, including walls, floors, door handles, shelves, sinks, hoods, cradles, ventilators, stethoscopes, other medical devices, milk collecting devices, trolleys, and medical record books. To find out about human transmission, hand swabs and swabs from mobile phones were taken from doctors and nurses working in NICU. Intravenous fluid samples from running bottles, bottles for fluid preparation, drug bottles, soaps and disinfectants were either swabbed or cultured. Also, sample

Swabs were collected from the obstetrics ward, labour room and operation theatre, where caesarean sections were performed. A total of 78 samples were taken and cultured.

Cultures were done by automated blood culture system BACTEC 9050, and isolates, if any, were identified by standard microbiological techniques. Antibiotic susceptibility was done by Kirby Bauer disk diffusion method following CLSI guidelines. Apart from the investigation of the cause thorough sanitation procedure commenced. Possible sources were disposed of and renewed, including linens, cotton, parenteral nutrition, milk collecting devices, disinfectants, soaps etc. Hand washing, the use of alcohol-based hand sanitisers use of gloves when assisting in procedures or handling infants were reinforced.

Results

Seven neonates developed clinical sepsis with positive blood cultures, and unfortunately, the index case died.

Four out of 7 affected neonates were girls (57.14%). The mean gestational age of the babies was 36.4 weeks, the range being 32-40 weeks. Mean birth weight was 1.820 kg, the range being 1.300 kg-2.220 kg. Four patients (cases 2,3,5, and 6) had indwelling devices (requiring mechanical ventilation, central venous lines, total parenteral nutrition etc.). The clinical characteristics associated with underlying disorders in these cases are shown in Table 1.

Table 1: Clinical characteristics of the affected neonates at the time of admission.

Case No	Age(days)	Gestational age (weeks)	Underlying problem
1	4	38	Neonatal seizure
2	4	37	Hypoxic-ischemic encephalopathy
3	1	33	Preterm, very low birth weight
4	11	37	Hypoxic-ischemic encephalopathy
5	8	40	Meconium aspiration syndrome
6	5	32	Preterm, very low birth weight
7	1	38	Transient tachypnea of the newborn

The index case (case 1) was a neonate transferred from another hospital due to neonatal seizures And did not have sepsis at the time of admission. This patient developed sepsis on day 3 of admission. Blood culture showed *S. marcescens* growth sensitive to all antibiotics except Colistin and Polymyxin B. Intravenous cefotaxime and gentamicin were started following the sensitivity pattern. Within three days of receipt of the culture positivity report of the index case, other 6 cases were identified despite reinforcing all the control measures.

One neonate (case 5) developed right-sided pneumonia, and *S. mercescens* was isolated from the bronchoalveolar lavage fluid too. It was possible to do lumbar punctures in all the cases, and the reports were within normal limits.

By this time, culture reports of patients' conjunctival and rectal swabs were negative for *S. mercescens*. Swabs and samples from inanimate surfaces, equipment, antiseptics, humidifiers, and hands of all doctors and nurses were negative. But *S. marcescens* was isolated from a running IV fluid bottle of an unaffected term neonate. The same organism was also found in a normal saline bottle used for reconstituting IV fluids for the neonates.

These isolates showed the same sensitivity patterns as those obtained from the affected neonates.

The sources incriminated by our investigation were already replaced while applying the control measures.

Unfortunately, the index case died after seven days of antibiotic therapy due to septic shock. Like the index case, all other cases were started on intravenous cefotaxime and gentamicin combination as per the blood culture sensitivity report. Blood counts and C-reactive protein (CRP) were repeated frequently. Like the index case, the other cases showed no improvement, neither clinically nor in the laboratory parameters (CRP, immature/mature white blood cell ratio, white cell count etc.).So suspecting derepression of AmpC β- lactamase while on third-generation cephalosporin, the ongoing treatment plan was reviewed, and antibiotics were switched to intravenous meropenem (40 mg/kg per day in three divided doses). After fourteen days of antibiotic therapy, a complete cure was achieved.

No *S.marcescens* was isolated in the 12-months follow up period of this outbreak.

Discussion

Since the 1980s, large numbers of *S.marcescens* outbreaks have been described in neonatal and pediatric ICUs, neonatal nurseries, special care baby units, pediatric oncology wards and maternity wards [5]. There have been many reports of such outbreaks from different parts of the world in recent years affecting patients admitted to NICUs [13, 17, 18, and 19], where newborns who have an immature immune system compared to adults are treated for various health issues [19].*S. marcescens* can cause potentially fatal sepsis, meningitis or pneumonia especially in premature and low birth weight babies [10, 20]. Reported mortality rates associated with recent *S. marcescens* outbreaks in NICUs vary, ranging from 10% and 20% [19, 21, and 22]. In our study, mortality was 14.28% which is comparable to other study findings.

Moles et al., in their article analyzing neonatal faecal microbiota, showed that the presence of Serratia was strongly associated with a higher degree of immaturity and other hospital-related parameters like mechanical ventilation etc. [23]. There are several other studies, i.e. study by Voeltz et al. that concluded that risk factors for these outbreaks include the length of NICU stay, exposure to the hands of health care providers and use of prolonged antibiotic therapy that may destroy the normal gut flora of the neonates [10, 24, and 25]. In our study, among the seven study subjects, four (case 2, 3, 5, 6) (57.14%) required one or more of the followings: prolonged NICU stay, frequent handling by health care providers, mechanical ventilation, central venous line and prolonged parenteral nutrition and antibiotic therapy.

Failure to control sepsis in the index case (receiving intravenous cefotaxime- a third-generation cephalosporin and gentamicin- an aminoglycoside) was treated following an antibiotic-susceptibility pattern explained by the rapid evolution of antibiotic resistance observed in *S. marcescens*. The chromosomal ampC genes of *S. marcescens* are inducible by various beta-lactam antibiotics by a complex mechanism involving cell wall recycling [26]. The 2011 Clinical and Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing (M100-S21) [27] stated this warning: "Serratia may develop resistance during prolonged therapy With third-generation cephalosporins. Therefore, isolates that are initially susceptible may become resistant within 3 to 4 days after initiation of therapy." One such outbreak was reported in Italy from 2001 to 2002, probably due to ampC derepression or induction, where before isolation of *S. marcescens,* neonates were being routinely treated with various beta-lactam antibiotics just like our NICU.

S. marcescens can acquire resistance to Aminoglycosides most commonly via genes located on plasmids containing aminoglycoside-modifying enzymes, which by modifying the antibiotic binding sites on ribosomes, render Aminoglycosides ineffective [5]. This organism is also notorious for expressing Extended Spectrum Beta Lactamases (ESBL) by many strains [5]. In India, Rizvi and others observed 33% ESBL producing Serratia species from 2007 to 2008 by analysis of clinical samples [28]. Since the publication of the first outbreak with carbapenemase-producing *S. mercescens* in Argentina [29], Very few such cases have been reported, and carbapenems are regarded as a good treatment option in suspected *S. marcescens* infections. We, too, found success treating six of the study subjects after switching over to intravenous meropenem when the index case died.

S. marcescens can spread rapidly and cause substantial mortality and morbidity [30]. Voeltz et al. [10] stated in their article that two or more nosocomially related inpatient *S. marcescens* cases indicate a potential outbreak that should be investigated thoroughly to prevent further progress. Although in a large number of published neonatal *S.marcescens* outbreaks source could not be identified. Investigators have reported that during *S. marcescens* outbreaks, standard hygienic measures may prove insufficient to halt the aggressive spread of this organism. In such conditions, cohort nursing and even temporary closure of the unit should be considered [30].

Affected neonates have often been incriminated as the most important reservoirs in *S. marcescens* outbreaks by most of the published studies [10]. *S. marcescens* is not a natural intestinal flora of neonates [31]; rather, they acquire this bacterium through contaminated feeds [32]. Also, neonates in NICUs often suffer from bacterial conjunctivitis, and *S. marcescens* is a proven major pathogen

In these cases. However, our investigation could not find any Serratia isolates in the rectal or conjunctival swabs of the study subjects.

Hand colonization and hand carriage are incriminated as important sources of infection as the organism can live on human skin for a long period [33]. High patient density and low nurse-to-patient ratio, as observed often in developing countries, have been reported to cause the spread of pathogens by contaminated hands of health care workers [34]. *S. marcescens* has got colonization rates on the hands of healthcare workers ranging from 15.4% to 24% [35]. In our study, though, all the hand swabs yielded negative results.

Fortunately, in our study, we could identify the source. *S. marcescens* was isolated from swabs from one running fluid bottle and another fluid bottle used for mixing and preparing intravenous fluid solutions. The investigation of the first pediatric outbreak of *S. marcescens* by Rabinowitz and schiffrin in 1952 revealed a similar point source, contaminated intravenous solution as the culprit [7]. Also, in 1966, McCormack and Kunin investigated a similar outbreak in a baby nursery and incriminated contaminated saline in their report [36].

Apart from these point sources, other possible sources of *S. marcescens* outbreaks in NICU could be enlisted as follows: contaminated breast milk, formula, breast pump, parenteral nutrition, incubators, laryngoscopes, soap and soap dispensers, suction tubes, air conditioning ducts, waste jars, contaminated hand brush, multidose medications and nebulizer dropper bottles etc. In our study, swabs or samples from all these sources were cultured, but no isolate was found. We could not use typing methods such as sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), plasmid profiling etc. which are very useful in outbreak scenarios but are not readily available in all the parts of third world countries like India.

Conclusion

Serratia marcescens outbreaks in NICU pose a grave threat to clinicians and epidemiologists. Frequently the source of such an outbreak cannot be pinpointed. However, Extensive environmental sampling to find out the point source and after that, active surveillance is necessary to control Such infections. Molecular technologies, though not readily accessible in third world countries, can help to an immense extent. Conjunctival and rectal swabs from all neonates are necessary to culture. Also, the culture of swabs collected from the hands of healthcare workers is of paramount importance. Implementation and reinforcement of routine measures such as hand hygiene are compulsory in these outbreaks. Carbapenems, especially meropenem, are good empiric therapy in suspected *S. marcescens* infections.

Authors' Contributions: Authors Poddar S and Halder PP collected the data. Hassan R did the compilation of data. Poddar S, Halder PP and Hassan R wrote the primary manuscript. Ghosh A and Uttam KG wrote the final manuscript.

What does the present study add to existing knowledge? Extensive environmental sampling to find out the point source and, after that, active surveillance is necessary to control outbreaks in NICUs, especially in developing countries where molecular technologies are not readily available.

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