A cluster of necrotizing enterocolitis in neonatal intensive care unit of one of the hospitals in Salerno, Italy

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Abstract

From January to May 2012, a cluster of 12 cases of necrotizing enterocolitis (NEC) occurred in the Neonatal Intensive Care Unit of one of the Hospitals in Salerno, Italy. Six of twelve infants developed severe NEC (stage II – III). All cases, but one, were preterm of less than 37 week gestation (91.7%); five cases (41.7%) had a very low birth weight (VLBW) less than 1,500 g and five between 1500 g and 2500 g (Low birth weight - LBW). The main risk factors associated with NEC was central venous line. Klebsiella pneumoniae was isolated from the clinical samples of 10 cases, of which 9 (90%) were extended-spectrum β-lactamase (ESβL) producers. K. pneumoniae were also isolated from various sites of environmental samples, suggesting the causal role of this pathogen in the development of NEC in addition to other risk factors.We describe an outbreak of NEC in a tertiary care neonatal unit, along with the case-control study performed and microbiological investigation to identify noninfectious and infectious risk factors potentially involved in the outbreak.

Keywords: *Cluster; Necrotizing enterocolitis (NEC); Neonatal Intensive Care; Klebsiella pneumoniae; case-control study*

1.Introduction

Neonatal necrotizing enterocolitis (NEC), characterized by intestinal necrosis and pneumatosis intestinalis, is the most common gastrointestinal emergency in the newborns. It mainly affects premature infants with low birth weight (<1500 g) [1, 2].

The incidence of the disease in the neonatal period ranging from 1 to 5% among newborn on neonatal intensive care units, and between 0.3 and 2.4 cases per 1000 live births [3].; more than 90% of all cases occurring in preterm infants [4,5,6].

The exact pathogenesis of NEC is not clearly established, but appears to be multifactorial, involving neonatal intestinal ischemia, microbial colonization of the gut, and excess protein substrate in the intestinal lumen associated with oral formula milk feeding [7].

Most cases of NEC are sporadic, but outbreaks do occur [8,9]. Observations made during these epidemics suggest that they are infectious outbreaks. Many pathogens, including bacteria and virus, have been linked to epidemic necrotising enterocolitis in Neonatal Intensive Care Unit (NICU) and *Klebsiella pneumoniae* is one of the most frequent of these pathogens during the last decade [10,11].

We describe a cluster of NEC associated with the isolation of *Klebsiella pneumoniae*, which occurred from January to May 2012 among the neonates admitted to Neonatal Intensive Care Unit (NICU) of one of the Hospitals in Salerno, Italy.

Table 1. Clinical characteristics of the newborns with necrotizing enterocolitis (NEC) from January to May 2012, Salerno, Italy.

P.	Gestational age (wks)	Birth weight (g)	Pathological conditions	Age of onset (gg/mm/yy)	Signs and symptoms of NEC	Diagnosis
1	31	1620	Respiratory distress	11/01/12	abdominal distension, gastric residual	Suspected case (Stage I)
2	26	850	Respiratory distress	19/01/12	abdominal distension, gastric residual	Suspected case (Stage I)
3	30	1680	Respiratory distress	28/01/12	abdominal distension	Suspected case (Stage I)
4	37	3550	Hypoxic encephalopathy, Respiratory distress	09/02/12	abdominal distension, emesis, blood in stool	Suspected case (Stage I)
5	33	1845	Respiratory distress	06/03/12	abdominal distension	Suspected case (Stage I)
6	30	1410	Respiratory distress	01/04/12	abdominal distension, gastric residual	advanced case (Stage III)
7	36	3000	Respiratory distress	11/04/12	abdominal distension, blood in stool, pneumatosis intestinalis	Proven cases (Stage II)
8	35	1715		18/05/12	abdominal distension, gastric residual, emesis pneumatosis intestinalis	advanced case (Stage III)
9	33	2070	Respiratory distress	18/05/12	abdominal distension, gastric residual, pneumatosis intestinalis	advanced case (Stage III)
10	30	1470	Respiratory distress	20/05/12	pneumatosis intestinalis	Proven cases (Stage II)
11	29	645	Respiratory distress	21/05/12	abdominal distension, blood in stool, pneumatosis intestinalis	Proven cases (Stage II)
12	34	1260	Respiratory distress	25/05/12	abdominal distension, gastric residual	Suspected case (Stage I)

2.Materials and Methods

Setting/Study design

In May 2012, five cases of NEC were observed among infants hospitalized in the NICU of one of the Hospitals in Salerno, as a result on 24th May were stopped admitting new patients, while those already hospitalized remained there. On this date 12 babies were already hospitalized in the NICU. The unit is a 14-bed tertiary care referral center and admit premature neonates with low birth weight less than < 2500 g and/or low gestational age < 37 weeks, both inborn and outborn.

We immediately carried out an epidemiological investigation to identify the risk factors associated with NEC and the mode of transmission.

A case-control study including all infants with NEC was performed. Environmental samples (room air, incubators, work surfaces, resuscitation equipment, sinks, breast pump and milk formula already partially used in packaging) were also collected at the time of our investigation. Hand impression, nasopharyngeal and rectal swabs were taken from the medical and nursing staff of the NICU.

Case-Control Study

The study population consisted of all 167 newborns admitted at the NICU during the period 1st January to 24th May 2012. All medical records and folders nursing of the 167 neonates were reviewed to find all cases NEC.

A case-control study including all infants with NEC was performed. A case patient was defined as a neonate admitted at the NICU, over the period from 1st January to 24th May 2012, who met criteria for NEC staging as per the modified Bell criteria by Walsh and Kliegman.

Infants with stage I disease (suspected NEC) had clinical signs and symptoms suggestive of the disease, such as abdominal distension, gastric residual, vomiting and/or blood in the stool and radiological signs are absent or normal. Infants with stage II disease (definite NEC-"medical") had diagnostic abdominal radiographs showing pneumatosis intestinalis. Infants with stage III disease (advanced NEC-"surgical") were critically ill with impending or intestinal perforation [12]. Controls were defined as neonates matched for gestational age (± 2week)

to the index cases. For each NEC infant two control infants matched.

Table 2. Odds ratios of necrotizing enterocolitis (NEC) occurred among infants in the neonatal intensive care unit from January to May 2012, Salerno – Italy.

	NEC			
Variables	Cases	No Cases	Odds Ratio	95% CI
Sex				
Male	7	11		
Female	5	13	1.7	0.4-6.7
Nationality				
Italian	10	21		
Foreign	2	3	0.7	0.1-5.0
Gestational age				
<37	11	22		
37+	1	2	1.0	0.1-12.3
birth weight				
<2500	10	19	1.3	0.2-8.0
>2500	2	5		
Respiratory distress				
Yes	10	15		
NO	2	9	3.0	0.5-16.9
Mechanical ventilation				
Yes	4	7		
NO	8	17	1.2	0.3-5.4
Central venous catheter				
Yes	5	1		
NO	7	23	16.4	1.6-165.1
Vescical catheter				
Yes	0	0		
NO	12	24	-	-
umbilical catheter				
Yes	5	5		
NO	7	19	2.7	0.6-12.3

Microbiological Investigations

We reviewed the results of all clinical cultures taken from the 167 neonates admitted to the NICU from January to May 2012 (blood culture, urine culture, rectal swab, nasopharyngeal culture, peritoneal fluid). At the time of our investigation, we also carried out environmental samples (room air, incubators, work surfaces, resuscitation equipment, sinks, breast pump and milk formula already partially used in packaging) and collected from the medical and nursing staff of the NICU, hand impression, nasopharyngeal and rectal swabs were. The samples were processed in the hospital's Microbiology laboratory.

Data Analysis

We analyzed the characteristics of the newborns such as: sex, gestational age, birth weight, Apgar score, nationality, pathological condition, invasive therapeutic procedures before the onset of symptoms (mechanical ventilation, central venous catheters, umbilical catheters and vescical catheters), feeding history, clinical and radiological findings and duration of hospital stay.

Epi Info version 3.5 (Atlanta, GA) was used to conduct the statistical analysis for the case control study. Odds Ratios (OR) with 95% confidence interval were calculated.

3.Results

From January to May 2012, a total of 12 cases of NEC were identified among 167 babies admitted in NICU (Table 1). Six of twelve infants developed severe NEC (stage II – III). The characteristics of the 12 infants with NEC are described in Table 1. Seven (58.3%) infants were male, eleven (91.7%) were preterms, born within 26 to 36 weeks of gestation, two (16.7%) had birth weight less than 1000g, three (25%) between 1000 and 1500g and seven between 2500 and 3550g.

All cases were feeding with milk formula and five also with breast milk (mixed feeding). Ten babies with NEC had a central venous catheter or an umbilical catheter, none had vescical catheter. Four preterm infants having a birthweight between 850 and 2050g had required mechanical ventilation.

The mean age of onset was 13.3 days (range 2-22) and signs and symptoms of the disease were: abdominal distension (91.7%), respiratory distress (83.3%), gastric residual (50%), blood in stool (25%) and emesis (16.7%). For five cases (41.7%) radiological findings showed intestinal pneumatosis. No fatalities occurred. All NEC cases received antibiotic treatment; four infants in critical condition were transferred to the pediatric surgery unit of the hospital level of a company of national importance, of which 3 were underwent surgical therapy.

The case control study demonstrated no significant differences between cases and controls for nationality sex, birth weight, gestational age, Apgar score, pathological conditions, mechanical ventilation and umbilical catheter. The presence of a central venous catheter was instead significantly associated (Table 2) with NEC (OR 16.4, 95% IC 1.6-165.1). A total of 10 (83.3%) on 12 infants with NEC had positive cultures for *Klebsiella pneumonia* compared with 4 of 24 controls (OR 25.0, 95% IC 3.9-160.5); antimicrobial susceptibility tests showed that isolates were ESBL producing *K. pneumonia*

Table 3. Microorganisms isolated from infants with NEC.

P.	Diagnosis	Microrganismi isolati				
		Blood culture	Rectal swab	Urine culture	Nasopharyngeal culture	Peritoneal fluid
1	Suspected case (Stage I)	*Klebsiella pneumoniae ESβL*				
2	Suspected case (Stage I)			*Klebsiella pneumoniae ESβL*		
3	Suspected case (Stage I)			*Klebsiella pneumoniae ESβL*		
4	Suspected case (Stage I)	*Coagulasi negative Staphilococci*	*Rotavirus*			
5	Suspected case (Stage I)	*Klebsiella pneumoniae ESβL*		*Klebsiella oxytoca ESβL, Enterobacter multidrug resistant*		
6	advanced case (Stage III)	*Klebsiella pneumoniae*	*Rotavirus*	*Klebsiella pneumoniae ESβL*	*Klebsiella pneumoniae ESβL*	
7	Proven cases (Stage II)			*Enterobacter multidrug resistant*		
8	advanced case (Stage III)				*Klebsiella pneumoniae*	
9	advanced case (Stage III)	*Klebsiella pneumoniae*			*Klebsiella pneumoniae*	*Klebsiella pneumoniae ESβL*
10	Proven cases (Stage II)		*Klebsiella pneumoniae ESβL*	*Klebsiella pneumoniae ESβL*		
11	Proven cases (Stage II)	*Klebsiella pneumoniae ESBL*	*Klebsiella pneumoniae ESBL*			
12	Suspected case (Stage I)	*Coagulasi negative Staphilococci*	*Klebsiella pneumoniae ESβL*	*Klebsiella pneumoniae*		

in 9 cases and 4 controls (OR 15.0, 95% IC 2.8-81.4). ESβL Klebsiella pneumoniae was isolated from blood cultures, rectal swabs, urine cultures and nasopharyngeal culture. In one of three newborns, undergoing surgery ESβL *Klebsiella pneumoniae* was also isolated from the peritoneal fluid. Other organisms were isolated in these patients included other multidrug resistant microorganism and rotavirus (Table 3). Subsequent screening of the environment yielded *K. pneumoniae* from various sites (incubators, resuscitation equipment, sinks, work surfaces, breast pump and milk formula already partially used in packaging) but not in room air and among medical and nursing staff. Antimicrobial susceptibility were not tested in the NICU environment isolated.

4.Discussion

Klebsiella pneumoniae has been incriminated in NICU acquired infections. This organism colonizes the bowel and skin and is probably transmitted by the hands of medical and nursing staff of the NICU [13,14,15]. The *Klebsiella* species, in addition to its virulence and ability to acquire antibiotic resistance determinants, are able to survive on skin and watery surfaces and resist desiccation, making them easily transferable through equipments and the hands of health care workers[16]. *Klebsiella pneumoniae* was isolated from clinical sample of neonates con NEC and from environmental samples during the study period. The widespread presence of *K. pneumoniae* in the intensive care unit suggested the causal role of K pneumonia in this outbreak and environmental reservoir of this microorganism. Although *K. pneumoniae* was not isolated from hands of healthcare workers during the study period and no one among the staff presented symptoms, given the widespread environmental contamination, seems quite plausible a role of personnel in transmitting the infection from one child to another. This finding reinforces the importance of hand hygiene practices but also implementing strict environmental cleaning and additional contact precautions.

In this study cannot evaluated in transmitting of

bacteria the role of mothers admitted in the maternity wards for breastfeeding babies, even if *K. pneumoniae* was been isolated from breast pump. Certainly there was no monitoring of good hand hygiene practices among these mothers before handling their babies and so it was possible contamination of these infants and subsequently of NICU. In addition, since the ICU caters to both inborn and outborn infants, there may be a constant replenishment of the NICU environment with *K. pneumoniae* from other hospitals through colonised infants, as has been reported in other studies. The antimicrobial susceptibility tests of isolates from the environment were not performed and, due to lack of facilities at our institution, not even the molecular typing of these microorganisms. Therefore, it was not possible to identify whether these organisms have originated from a single strain. Since the NEC still has a mortality rate of 10 to 55% [3,17], it is fundamental that healthcare workers in neonatology and NICU wards be made aware of the potential of the epidemics to occur and be taken that all necessary preventive measures including the cohorting of infants, cohorting nursing care for affected infants to with NEC infants only, and enforcing routine procedures for antisepsis [8].

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