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# Nosocomial necrotising enterocolitis outbreaks: epidemiology and control measures

**Abstract** Necrotising enterocolitis (NEC) is one of the most serious gastrointestinal diseases among newborns and it mainly affects those in intensive care units. The aetiology of the disease has been reported to be multifactorial and both sporadic cases and nosocomial outbreaks have occurred. In this report, we review 17 epidemics of NEC reported in the literature between 1973 and 1999. The number of confirmed cases ranged from 1 to 32 with an average of 10.5 confirmed cases. On average, 16.15% of cases required surgery (range 0–66.6%). The average mortality rate was 6.25% (range 0–87.5%). The mean age at disease onset was 9.5 days (range 6.6–29 days). Most of the infants had low birth weight (median weight 1,395 g; range 1,112–2,788 g, calculated on the reported mean weights). The main risk factors associated with NEC were: low birth weight, low gestational age, low Apgar score, perinatal complications, hyaline membrane disease, and umbilical catheterisation. The bacteria involved often included *Enterobacteriaceae*, particularly *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* type 3305573. The causative role of *Clostridia* in NEC is controversial. With regard to viral agents, coronarovirus, rotavirus and enterovirus, such as echovirus type 22, were isolated during some of the epidemics. The recommended control measures for NEC epidemics are those used for epidemics of other orofaecally transmitted infections.

**Conclusion** Understanding the epidemiology of necrotising enterocolitis is fundamental if adequate preventive control measures are to be developed and applied.

**Key words** Control · Epidemiology · Necrotising enterocolitis · Neonates · Outbreak

**Abbreviation** *NEC* necrotising enterocolitis

## Introduction

Necrotising enterocolitis (NEC) is one of the most serious gastrointestinal diseases among newborns. It mainly affects those with low birth weight and generally occurs as sporadic cases, though epidemics have also been reported. The incidence of NEC is relatively high in the neonatal period, ranging from 1–5% among newborns on intensive care units and from 0.3–2.4 per 1,000 live-births (median 1.3 per 1,000) [28]. Most of the newborns affected by this disease are premature (62–94%), although sporadic cases of NEC have been reported among full-term newborns [32] and there is a linear correlation between incidence, low birth weight and low gestational age. NEC requires surgery in 23–70% of cases depending on the gestational age; although the mortality rate has significantly decreased in the last 30 years, it continues to be high (9–28% in the 1990s) [28].

The universally accepted case definition is that proposed in 1978 by Bell and collaborators [2], according to

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whom the disease is characterised by the following: systemic symptoms, ranging from apnoea, bradycardia and temperature instability to diffuse intravascular co-agulation and septic shock, intestinal symptoms (e.g. abdominal distension and bloody stools) and radiological findings such as pneumatosis intestinalis and gas in the portal vein. Based on the severity of symptoms, different grades of the disease, from suspected to advanced, have been defined (Table 1).

The aetiology of NEC is multifactorial, attributable to both infective and non-infective factors (e.g. ischaemic lesions of the gastrointestinal tract in premature newborns or in those with specific predisposing factors, formula milk feeding, and the presence of a pathogen or of imbalances in the intestinal microbial flora) [28].

Within the last few decades, various NEC epidemics have been reported in the literature. Given the potential severe clinical impact and the preventability of these events, we conducted a systematic review of the scientific literature to evaluate the epidemiological characteristics of the epidemics reported, the methods adopted for their investigation and the control measures used, with the aim of providing indications for the proper and rapid identification and management of NEC epidemics.

## Materials and methods

NEC epidemics were identified by a literature search of PubMed, the online site of the National Library of Medicine. Since NEC epidemics are not very common, we did not restrict the search to period of time or language. The following terms were used: "necrotising enterocolitis" (all fields: 1,729 records were identified), "newborn", "neonate" or "neonatal" (all fields: 382,420 records), and "disease outbreaks" (MeSH term: 27,037 records). The search identified 38 articles that included all three terms: three of these articles could not be traced [3, 15, 20] and 20 were excluded from

the analysis because they were not strictly related to epidemics. We reviewed a total of 15 articles, published in English language journals and reporting on 17 epidemics.

## Results

Table 2 describes the principal characteristics of the 17 epidemics (i.e. number of cases, mean age and weight at onset and clinical impact of the disease). For all the epidemic investigations, the case definition of confirmed NEC developed by Bell et al. [2] was adopted; however, it is not clear whether the investigations also included suspected cases of NEC and/or simple cases of gastroenteritis.

Of the 17 epidemics analysed, 11 lasted from 8 to 10 weeks [4, 6, 9, 11, 13, 16, 17, 21, 27]; one epidemic lasted for 20 weeks [13] and four lasted for less than 8 weeks [1, 8, 10, 23] (in one case the duration of the epidemic was not mentioned [24]); no seasonal trend was evident. The number of confirmed cases ranged from 1 [4] to 32 [6], with an average of 10.5 confirmed cases. In five of the epidemics, additional cases of NEC were suspected but not confirmed [4, 8, 9, 16, 17]. In eight of the epidemics, additional cases of gastroenteritis due to the same pathogen were diagnosed [4, 6, 8, 9, 10, 11, 23, 24].

Surgery was required in 0% [4, 10] to 66.6% [12] of cases (median 16.15%). The mortality rate ranged from 0% [4, 11, 13, 16] to 87.5% [27] (median 6.25%). The highest mortality rates were reported in the 1970s, whereas the mortality rate of the epidemics described in recent years was less than 10% [1, 6, 8, 10, 17, 24].

The mean age at disease onset ranged from 6.6 [13] to 29 days [1] (median 9.5 days). Most of the affected newborns had low birth weight (median 1,395 g, range 1,112–2,788 g calculated on the reported mean weights),

**Table 1** Clinical staging of NEC according to [29]

| Stage | Systemic signs | Intestinal signs | Radiological signs |
|---|---|---|---|
| Suspected NEC – Stage I | | | |
| Stage IA | Temperature instability, apnoea, bradycardia, lethargy | Elevated pre-gavage residuals, mild abdominal distension, emesis, haem-positive stools | Normal or intestinal dilatation, mild ileus |
| Stage IB | Same as Stage IA | Bright red blood from rectum | Same as Stage IA |
| Definite NEC – Stage II | | | |
| Stage IIA (mildy ill) | Same as Stage IA | Same as Stage IA + absent bowel sounds, +/− abdominal tenderness | Intestinal dilatation, ileus, pneumatosis intestinalis |
| Stage IIB (moderately ill) | Same as stage IIA + mild metabolic acidosis, mild thrombocytopenia | Same as stage IIA + absent bowel sounds, definite abdominal tenderness, +/− abdominal cellulitis or right lower quadrant mass | Same as stage IIA + portal vein gas, +/− ascites |
| Advanced NEC – Stage III | | | |
| Stage IIIA (severely ill, bowel intact) | Same as stage IIB + hypotension, bradycardia, severe apnoea, combined respiratory and metabolic acidosis, DIC, neutropenia | Same as stage IIB plus signs of generalised peritonitis, marked tenderness, and distension of abdomen | Same as stage IIB + definite ascites |
| Stage IIIB (severely ill, bowel perforated) | Same as stage IIIA | Same as stage IIIA | Same as stage IIIA + pneumoperitoneum |

**Table 2** Investigations of NEC epidemics and selected findings. (*NM* not mentioned)

| Reference | Year | Epidemic: Season/duration | NEC cases (n) | Cases of gastroenteritis (n) | Mean age at onset (days)[a] | Surgical treatment (%) | Mortality rate (%) | Mean weight (g)[a] |
|---|---|---|---|---|---|---|---|---|
| [27] | 1973 | Summer, 8 weeks | 8 | NM | NM | NM | 87.5 | < 2,500 |
| [16] | 1977 | Winter, 8 weeks | 8 confirmed; 4 suspected | NM | 8.7 ($\pm 9.5$) | 25 | 0 | 2,788 ($\pm 940.6$) |
| [13] | 1979 | Autumn, 8 weeks | 10 | NM | 6.6 | NM | 0 | $\geq 2,000$ |
| [13] | 1979 | Winter, 10 weeks | 14 | NM | 24.9 | NM | 21 | $\geq 2,000$ |
| [13] | 1979 | Winter/spring, 20 weeks | 15 | NM | 7.9 | NM | 20 | $\geq 2,000$ |
| [21] | 1980 | Winter, 8 weeks | 12 | NM | 10.3 | 16.7 | 16.7 | 1,667 |
| [6] | 1981 | Spring, 10 weeks | 32 | 12 | NM | 15.6 | 3.1 | NM |
| [23] | 1983 | Summer, 4 weeks | 8 | 3 | NM | 36.4 | 18.2 | 1,712 ($\pm 600$) |
| [8] | 1983 | Autumn, 2 weeks; | 7 confirmed | 2 | 9.7 $\pm 10.4$ (confirmed) | NM | 6.25 | 1,800 $\pm 1,014$ (confirmed) |
|  |  | Winter, 3 week | 7 suspected |  | 24 $\pm 33$ (suspected) |  |  | 1,043 $\pm 240$ (suspected) |
| [1] | 1984 | Spring, 4 weeks | 20 | NM | 29 $\pm 14$ ( < 30 weeks gestation) 12.6 $\pm 6$ ($\geq 30$ weeks gestation) | 10 | 5 | 1,279 $\pm 448$ |
| [10] | 1984 | Spring, 5 weeks | 2 | 14 | NM | 0 | 6 | NM |
| [9] | 1984 | Winter, 8 weeks | 9 confirmed, 6 suspected | 15 | NM | NM | NM | 1,112.2 $\pm 99.7$ (confirmed), 1,735.8 $\pm 573.4$ (suspected) |
| [11] | 1985 | Summer, 8 weeks | 7 | 4 | NM | 27.2 | 0 | NM |
| [17] | 1987 | Spring, 10 weeks | 12 confirmed, 21 suspected | NM | NM | 15 | 9 | 1,360 |
| [24] | 1987 | Spring, (NM) | 7 | 8 | NM | NM | 1.4 | NM |
| [4] | 1997 | Autumn, 8 weeks | 1 confirmed, 7 suspected | 4 | NM | 0 | 0 | 1,395 (confirmed), 2,000 (suspected) |
| [12] | 1999 | Spring, 8 weeks | 6 confirmed | NM | 5.3 $\pm 1.96$ | 66.6 | 33.3 | 1326.6 ($\pm 262.8$) |

[a] Where not included, the standard deviation was not reported

although some epidemics involved newborns with a birth weight over 2,000 g and Apgar scores of more than 7 [13, 16]. Many of the epidemic investigations reported risk factors associated with NEC, the most common of which were: low birth weight [4, 9, 17, 24, 27], low gestational age [1, 4, 9, 27], low Apgar score [26], perinatal complications [21, 27], hyaline membrane disease [21], and umbilical catheterisation [21]. However, many of the investigations reported no risk factors in that there were no clinical differences between cases and healthy controls [6, 13, 16, 23].

Table 3 shows the pathogens isolated during the epidemic investigations, the epidemiological and laboratory methods used, the risk factors identified and the control measures adopted. Only seven of the epidemics were investigated with a proper case-control study [1, 9, 13, 17, 24], one of which also included the microbiological monitoring of cases, hospitalised newborns and/or hospital staff [24]. Seven epidemics were investigated only by microbiological monitoring [6, 8, 10, 11, 16, 23, 24, 27], and three included only an analysis of the epidemiological characteristics of the NEC cases [4, 18, 27]. With regard to the causal agent (Table 3), the bacteria involved often included *Enterobacteriaceae*, particularly *Escherichia coli* (non-typable [27], a heat labile toxin producer [8], and serogroup 0142 H6 [10]), *Klebsiella pneumoniae* (either alone [13] or with viral agents [23] or other types of bacteria [12]) and *Enterobacter cloacae* type 3305573 [21]. Different species of *Clostridia* were

isolated during some of the epidemics (i.e. *Clostridium butyricum* [16]; *Clostridium difficile* was reported in other epidemics not included in this review [14, 20]). The viral agents involved were coronarovirus [6], rotavirus [23, 24] and enterovirus such as echovirus type 22 [4]. In six of the epidemics, the causal agent was not identified [1, 9, 11, 13, 17]; in some cases, the laboratory investigations led to the isolation of one or more microorganisms but their causal role was not demonstrated as they were also isolated in healthy controls or from sites where they are commonly commensal.

All but one of the investigations [12] performed stool cultures (Table 3). Two investigations included rectal swabs [9, 24] to search for intestinal pathogens, such as *Salmonella*, *Shigella*, enterotoxic *Staphylococcus aureus*, *Campylobacter* and *Yersinia* [9, 24]. In most cases, blood cultures were taken for aerobes and anaerobes; cultures were carried out more rarely for urine [1, 10], CSF [1], peritoneal liquid [17], and nasal and pharyngeal swabs [10]. In one epidemic [12], all isolates were subjected to molecular fingerprinting. For four epidemics, microbiological investigations were carried out on environmental samples or on milk [1, 16, 24, 27]. Only some of the investigations included the search for *Clostridia* and their toxins using anaerobic cultures [1, 16], gas-liquid chromatography [16] or immunoenzymatic techniques (e.g. ELISA) [8]. With regard to *Clostridium butyricum*, isolation required a very long period of time: the first of the six samples that were positive on gas-liquid

**Table 3** Epidemic investigations: study design, risk factors, diagnostic methods, pathogens, and control measures. (*NM* not mentioned)

| Reference | Study design | Risk factors | Diagnostic methods | Pathogen | Control measures |
|---|---|---|---|---|---|
| [27] | Case description | Low birth weight, gestational age, Apgar, perinatal complications | Stool culture on all neonates and adults, and enviromental culture | E. coli (not typable) | Emphasis on hand washing, use of gloves and masks; isolation of cases; cohorting |
| [16] | Case description | None of the usual risk factors | Stool and blood cultures for aerobes and anaerobes in cases, microbiological monitoring of nursing staff and milk samples; gas-liquid chromatography of blood and faeces | Cl. butyricum | Closure of the ward |
| [13] | Case-control study | None of the usual risk factors | Stool and blood cultures | No significant pathogen | Emphasis on hand washing; isolation of cases |
| [13] | Case-control study | None of the usual risk factors | Stool and blood cultures | K. pneumoniae | Emphasis on hand washing; isolation of cases |
| [13] | Case-control study | None of the usual risk factors | Stool and blood cultures | No significant pathogen | Emphasis on hand washing; isolation of cases |
| [21] | Case description | Prematurity, hyaline membrane disease, perinatal complications, umbilical catheterisation | Stool and blood cultures; search for rotavirus. | Enterobacter chloacae type 3305573 | Strengthening of hygienic measures; isolation of cases |
| [6] | Case description | None of the usual risk factors | Stool culture, electron microscopy, serological tests on NEC cases, suspected cases, healthy newborns, hospital staff and four mothers | Coronavirus | Emphasis on hand washing, use of gloves and masks; isolation of cases; cohorting |
| [23] | Case description, comparison infected/not infected | None of the usual risk factors | Stool and blood cultures on cases, healthy newborns and nursing staff; ELISA on nursing staff | K. pneumoniae, rotavirus | Isolation of cases |
| [8] | Case description | NM | Stool cultures on cases, healthy neonates and nursing staff; ELISA (search for Aereomonas hydrophila, Clostridium difficile β toxigenic type C, Clostridium perfrigens) | E. coli heat labile toxin | NM |
| [1] | Case-control study | Chronological age; post-conceptional age (gestational age + chronological age) | Stool, CSF, urine, blood (aerobes and anaerobes) and enviromental cultures; search for enterovirus and rotavirus; Cl. difficile | No significant pathogen | Emphasis on hand washing, use of gloves and masks; closure of the ward; isolation of cases; cohorting |
| [10] | Case description | NM | Stool cultures on all infants and nursing staff, urine, blood cultures; nasal and pharyngeal swabs on all infants; search for adenovirus, enterovirus, coronavirus | E. coli O142H6 | NM |
| [9] | Case-control study | Low birth weight; gestational age | Stool cultures, rectal swabs; search for adenovirus and enterovirus | No significant pathogen | NM |
| [11] | Case description | NM | Stool cultures, rectal swabs on cases and nursing staff; search for Cl. difficile (toxin); ELISA (search for rotavirus, coronavirus, adenovirus, coxsackie virus A and B); electron microscopy; serology | No significant pathogen | Emphasis on hand washing, use of gloves and masks; closure of the ward |
| [17] | Case control study | Low birth weight; use of diuretics and transfusions of packed red cells (alterations in volaemia) | Stool, peritoneal fluid and blood cultures; search for Cryptosporidium; electronic microscopy; immunoassay for rotavirus | No significant pathogen | Emphasis on hand washing, use of gloves and masks; isolation of cases; closure of the ward; cohorting |
| [24] | Case control study | Rotavirus infection; low birth weight; age at first feeding | Rectal swabs, serological tests, immuno-electron microscopy, EIA on cases, healthy newborns and nursing staff; enviromental cultures | Rotavirus | NM |

| Ref | | | | |
|---|---|---|---|---|
| [4] | Case description, comparison infected (symptomatic and asymptomatic) and not infected patients | Low birth weight; gestational age | Stool cultures, virus isolation; virus typing; serological tests on nursing staff | Echovirus type 22 | Emphasis on hand washing, use of gloves and masks; isolation of cases; cohorting; monitoring of staff for symptoms |
| [12] | Case description | NM | Blood cultures, full blood count, measurement of acute phase reactants, molecular fingerprinting | *Klebsiella pneumoniae, Enterobacter cloacae* | Emphasis on hand washing, reducing the number of ward admission |

chromatography became culture positive after 1 month of incubation, the other five after 4 months [16]. The techniques used to identify the virus were ELISA [8, 11, 23] and EIA [24]; some studies used electron microscopy to detect viral particles in the faeces [6, 11, 17, 24]. In many epidemics, microbiological tests (either serological or culture) were also carried out on the hospital staff [4, 6, 8, 10, 11, 16, 23, 24] who were often shown to be positive, mostly to the serological tests [4, 6, 23, 24] but also to culture [10].

The measures used for controlling the epidemics were those for epidemics of other orofaecally transmitted infections, specifically: strict adherence to basic rules of hygiene such as hand washing and the use of gloves and masks [1, 4, 6, 11, 12, 13, 17, 27], isolation of infected newborns [1, 4, 6, 13, 17, 23, 27], cohorting cases (i.e., infected newborns always cared for by the same staff members) [1, 4, 6, 17, 27], and, in some cases, closing of the ward involved [1, 11, 17].

## Discussion

This review shows that the reported epidemics greatly differed in terms of the number of cases, the spectrum of clinical presentations reported and the proportion of newborns who underwent surgery or who died. These differences, in part, can be explained by differences in the application of the case definition (i.e. whether or not only confirmed cases or also suspected cases of NEC and/or simple gastroenteritis were included) and by differences in diagnostic procedures. The reported causal agents also varied greatly. The causative role of *Clostridia* is controversial: some authors suggest that *Clostridia* may be part of the normal intestinal flora and that it is thus difficult to establish whether or not they act as pathogens [21, 30]. In one of the epidemics [16], the causal role of *Clostridia* was corroborated by their isolation from the blood of nearly all of the cases; however, as discussed in the epidemic report, the seriousness of the clinical syndrome could probably be attributed to the particularly invasive nature of the specific strain which would account for healthy newborns not normally at risk for NEC also being affected. Furthermore, the authors suggested that the failure to isolate *Clostridia* in other NEC epidemics may depend on the fact that anaerobic cultures are not always performed or, when performed, the samples are not always incubated for a sufficiently long period and more sophisticated diagnostic techniques are not used (i.e. gas-liquid chromatography) [16]. None of the investigations reported *Staphylococcus epidermidis* as the causative agent; however, Ng et al. [19] described two cases of NEC known to have been caused by *Staphylococcus epidermidis* since this microorganism was isolated from blood, peritoneal liquid and breast milk, which was the likely source of infection. Moreover, other studies [18, 25] have suggested that coagulase-negative staphylococci are commonly involved in NEC and are associated with high rates of mortality and morbidity.

Since viral agents are often the cause of epidemics of hospital-acquired gastroenteritis and are not generally associated with serious clinical syndromes such as NEC, it has been suggested that NEC may be caused by the concomitant presence of viral agents and predisposing factors in newborns or to a possible synergism among viral agents and other microorganisms. In one of the epidemic reports [23], the authors suggested that a synergism exists between rotavirus and *Klebsiella* resulting in an increased pathogenicity. In four of the eight cases reported, both microorganisms were present, and in one case, although there was no rotavirus in the faeces, a high IgM anti-rotavirus titre was detected. In 33% (6/17) of the outbreaks, the causative agent was not identified, probably as a result of incorrect or incomplete diagnostic testing. In contrast to sporadic cases of NEC which may be caused by various factors and that do not necessarily include a specific pathogen, in epidemics, the causative factor is the diffusion of a particular pathogen in a specific ward and in a certain period of time. Thus the involvement of a specific pathogen must be taken into account when conducting epidemiological investigations and diagnoses and effective control measures must be rapidly adopted to stop the infection from spreading. Of note is the finding that hospital staff appeared to be frequently involved in these epidemics, probably because they are exposed to patients, although it cannot be excluded that the staff may play a direct role in transmitting the infection.

The reason for which a relatively high proportion of newborns with gastrointestinal symptoms developed NEC is still unclear, though two hypotheses can be proposed:

1. Epidemics of NEC occur when the pathogen is transmitted orofaecally among newborns considered to be particularly susceptible (i.e. premature or with predisposing factors in the intestinal ischaemia). For healthy newborns, simply being exposed to the infective agent would only result in colonisation or, depending on the faecal flora concentration, a simple case of gastroenteritis. For premature newborns or those with predisposing clinical conditions, exposure to the infective agent would lead to intestinal necrosis and to NEC.
2. The onset of NEC depends on the level of virulence of the microorganism concerned (e.g. *Clostridium butyricum*) or on the pathogenic effect consequent to the synergic action of two microorganisms (e.g. rotavirus and *Klebsiella pneumoniae*).

Given the severity of nosocomial outbreaks of NEC, it is fundamental that healthcare workers in neonatology and neonatal intensive care wards be made aware of the potential for epidemics to occur and that all necessary preventive measures be taken. Outbreaks must be identified promptly and measures must be taken to identify and interrupt the chain of transmission. This means being prepared to cope with the epidemic before it happens. The following is a brief summary of activities to be conducted in the case of an epidemic of NEC.

1. Identification of the causal agent. In addition to routine investigations, it is necessary to perform the following: stool cultures for *Clostridia*, their toxins, and viral agents such as enterovirus and rotavirus; blood cultures for both aerobes and anaerobes; and appropriate serological investigations of cases and contacts when a direct search for the pathogen fails.
2. Exhaustive investigation of cases. Attempts must be made to identify all newborns who have been infected by the causal agent and any other newborns who have developed any form of NEC. Newborns discharged from nurseries could be monitored to verify any additional cases. A thorough identification of the cases is important not only for epidemiological reasons but also for adopting adequate cohort programmes (i.e. having a separate nursing staff care for the infected or colonised newborns).
3. Adoption of effective measures for stopping the spread of the infection. These include: (a) isolating or adopting cohort programmes for both infected and colonised newborns; if colonised newborns cannot be identified, then the isolation or cohort programmes can be organised for both exposed and non-exposed (i.e. newly admitted) asymptomatic newborns; (b) enforcing routine procedures for antisepsis (e.g. hand washing, barrier measures, adequate decontamination of equipment and protocols for the treatment of newborns exposed to an invasive procedure); (c) considering the option of closing the ward as a last resort if the epidemic cannot be contained and (d) surveillance of staff and removal of those persons with symptoms of gastroenteritis [5]. In three epidemics [5, 10, 26], the adoption of these control measures stopped the epidemic. In one of the hospitals [5], these measures continued to be strictly followed after the epidemic and the incidence of NEC decreased from 3.6% to 0.7% over a 3-year period.
4. Identification of the possible means and mechanisms of transmission. This can only be achieved by conducting a descriptive epidemiological investigation, followed by, if possible, an analytical investigation (e.g. cohort and case-control studies).
5. Search for the causal agent in the environment. This only makes sense if a causal agent has been identified and if the epidemiological investigation has led to a hypothesis on the possible source of infection.

In conclusion, epidemics of NEC are serious events that may, however, be prevented by specific measures for preventing transmission in hospitals. It is also possible to contain an epidemic provided that measures have been carefully planned in advance.

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