BACTERIAN AGENTS IMPLICATED IN NECROTISING ENTEROCOLITIS

Surd A[1,2], Mironescu A[3], Gocan H[1,2]

Abstract

Introduction: Necrotisingenterocolitis (NEC) is the most common gastrointestinal emergency in the preterm infant [1].NEC affects 5-15% of all infants born at less than 30 weeks gestational age or <1500g birth weight. However, up to 10% of all neonates who develop NEC are born at term [2]. The main objective of this retrospective study is to describe antimicrobial utilization for NEC and identify organisms most frequently isolated from patients with NEC at our institution. **Material and Methods**: A retrospective study of all infants with a confirmed diagnosis of NEC and a positive culture (from the peritoneal cavity) collected within 72hours in the Pediatric Surgery Departement, Emergency Childrens Hospital, Cluj-Napoca Romania between January 2010 and december 2015, was performed. A total of 61 medical charts were reviewed;26 patients with suspected NEC and no microbiological data available were excluded.From the 35 patients included, 28 underwent laparotomy and 7 had peritoneal drainage. **Results:** An associated bacteremia/fungemia was found in 7(20%) of the cases.Candidemia was present in 2 cases, Enterobacteriaceae bacteriemia in 4 cases and CONS bacteriemia in 1 case.Polymicrobial sepsis was present in 1 case.The results of peritoneal fluid cultures changed antibiotic selection in 10 (28%) of 35 cases. These changes were attributable to the growth of candida or CONS in all but 1 case, in which methicillinresistant Staphylococcus aureus was identified. ***Discussion:*** The first line choice of antibiotics for babies with suspected NEC consisting of Ampicillin, Gentamicin and Metronidazole failed to adequately cover the 4 coagulase negative Staphylococci, the Staphylococcus aureus and Candida species.Also, this combination of broad spectrum antibiotics (Ampicillin, Gentamicin and Metronidazole) only adequately treated 20 of the 35 cases of NEC and 3 positive blood cultures patients. From our limited data it would appear that only the combination of Meropenem and Vancomycin would have adequately covered all the isolated organisms.While it is often presumed that the infectious agent associated with NEC is bacteria, a number of other organisms, particularly viral have been implicated. ***Conclusions:*** Due to the limitations of this study we are unable to make general recommendations on the first line antibiotic choice for babies with suspected or confirmed NEC. Our current regime of Ampicillin, Gentamicin and Metronidazole failed to adequately treat 5 of the 8 organisms subsequently isolated in blood cultures.

The only combination of antibiotics that would have adequately treated all the bacteria identified was Vancomycin and Meropenem. The concern with this approach is the possible emergence of multidrug resistant bacteria. Further research is required to determine the best antibiotic regime for babies with suspected or confirmed NEC**.**

Key words: newborn, necrotising enterocolitis, antibacterian agents.

Introduction

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in the preterm infant [1].NEC affects 5-15% of all infants born at less than 30 weeks gestational age or <1500g birth weight. However, up to 10% of all neonates who develop NEC are born at term [2].

The initial clinical presentation is variable but may include general deterioration in the patients condition,lethargy, temperature instability, apnoea, shock, peritonitis, pallor, skin mottling, jaundice, bleeding and mild feed intolerance [3]. The classic presentation of NEC is a triad of abdominal distension, bloody mucous stools and bile stained aspirates [3].

The exact aetiology of NEC is unknown, however multiple risk factors have been identified including prematurity, hypoxia, exchange transfusion, intrauterine growth restriction, loss of mucosal integrity, patent ductus arteriosus, indomethacin, enteral feeds and microbial infection [1, 4]. A large number of organisms have been isolated from babies with NEC in both epidemics and sporadic cases [3,4-7].

More recently, Gram-negative bacteria that form part of the normal flora are now speculated as important factors in triggering the injury process in a setting where there is a severe paucity of bacterial species and possible lack of protective Gram-positive organisms [9].

The current clinical practice for infants with suspected or confirmed necrotising enterocolitis is to: cease enteral feeds; commence intravenous fluids; aspirate the nasogastric tube regularly; collect a blood culture; commence antibiotics (Ampicillin, Gentamicin and Metronidazole); perform an abdominal radiograph and arrange paediatric surgical evaluation [8]. Antibiotic regimes are adjusted according to organism culture sensitivities once available.

[1] "Iuliu Hatieganu" University of medicine and Pharmacy Cluj Napoca, Romania
[2] Emergency Children's Hospital, Department of Pediatric Surgery, Cluj-Napoca, Romania
[3] Transilvania University of Brasov, Romania
E-mail: adisurd@yahoo.com, horatiugocan@yahoo.com, aurel.mironescu@gmail.com

The main objective of this retrospective study is to describe antimicrobial utilization for NEC and identify organisms most frequently isolated from patients with NEC at our institution.

Material and methods

A retrospective study of all infants with a confirmed diagnosis of NEC and a positive culture (from the peritoneal cavity) collected within 72 hours in the Pediatric Surgery Departement, Emergency Childrens Hospital, Cluj-Napoca Romania between January 2010 and december 2015, was performed. Confirmed NEC is defined as symptoms of NEC with abdominal radiograph changes including any of the following: bowel wall oedema; pneumatosis intestinalis; portal vein gas and pneumoperitoneum (includes all Bell[10] stage 3 and some stage 2).A total of 61 medical charts were reviewed;26 patients with suspected NEC and no microbiological data available were excluded.From the 35 patients included, 28 underwent laparotomy and 7 had peritoneal drainage.Data recorded included: demographic data, surgical data,microbiological data (peritoneal fluid specimens and susceptibility to antibiotics), antibiotic management (initial therapy, changes in therapy, and duration of treatment) and outcomes. Blood culture bottles were placed in the BacT/ Alert® microbial detection system (bioMérieux Inc.) Swabs and catheter tips are directly plated on enrichment broth and then incubated at 35 degrees. They are examined for growth at 24 hours, 38 hours and 7 days. Positive cultures are then inoculated onto Horse Blood agar, Chocolate agar, MacConkey agar and Brain Heart Yeast agar. Antibiotic sensitivity testing was done using the Vitex®2 (bioMérieux Inc,Hazelwood, USA) method. Disc sensitivity or resistance was determined using CLSI(Clinical and Laboratory Standards Institute) standards.

Results

From a total of 35 patients included in this study, 21(60%) were male and 14 female(40%).The birth weight of patients with NEC ranged between 528g and 3410 g(median=1282) and the gestational age ranged between 24 and 40 weeks(median=27 weeks).Clinical characteristics are ilustrated in Table.1

Total number of NEC patients	n=35
Birth weight, g, median (range)	1282(528-3410)
Gestational age, wk,median (range)	27(24-40)
Age at perforation, d, median (range)	15(3-40)
Male gender, *n* (%)	21(60%)
Case fatality, *n* (%)	12(34%)
Laparotomy	28(80%)

Table 1. Clinical Characteristics of Neonates With Peritonitis Associated With NEC

Pathogens	n (%) (N=35)
Gram-positive	
CONS*	4 (12)
S aureus	1 (1)
S epidirmidis	2(5)
Enterococcus species	8 (23)
Diphtheroids	1(3)
Gram-negative	
Enterobacteriaceae	21 (60)
E Coli	7 (20)
Klebsiella species	7 (20)
Enterobacter species	6 (17)
Citrobacter species	1(3)
Anaerobes	4 (12)
Bacteroides species	4 (12)

Table 2. Peritoneal Isolates Recovered From Neonates With NEC

Discussion

The first line choice of antibiotics for babies with suspected NEC consisting of Ampicillin, Gentamicin and Metronidazole failed to adequately cover the 4 coagulase negative Staphylococci, the Staphylococcus aureus and Candida species.Also, this combination of broad spectrum antibiotics (Ampicillin, Gentamicin and Metronidazole) only adequately treated 20 of the 35 cases of NEC and 3 positive blood cultures patients.

First, the large distribution of pathogens when dealing with NEC supports the need to obtain peritoneal fluid cultures in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient.Second, it sheds light on which organisms should be targeted by antimicrobials when empirically treating neonates with documented NEC.

From our limited data it would appear that only the combination of Meropenem and Vancomycin would have adequately covered all the isolated organisms.While it is often presumed that the infectious agent associated with NEC is bacteria, a number of other organisms, particularly viral have been implicated (3,5,11). The retrospective nature of this study has limited the search for other possible infecting organisms as viral cultures and rectal swabs are not routinely collected.The small number of babies with a positive blood culture is also a concern however a long time period was examined to identify these cases. Another limitation is that the study is confined to one centre and the external validity of the results is therefore poor.

The standard of care for patients with documented NEC continues to include broad-spectrum antimicrobial coverage; however, the agents of choice vary between centers. Lee and Polin(12) recommended ampicillin, gentamicin, and clindamycin, with the possible substitution of vancomycin for ampicillin as a result of the increasing prevalence of CONS. Others have proposed ticarcillin and an aminoglycoside,usually gentamicin(13). Foglia(14) endorsed amikacin and Flagyl in place of gentamicin and clindamycin.Neu(15) advocated starting ampicillin and gentamicin after a blood culture is obtained, substituting vancomycin for ampicillin when CONS is suspected and then adding either clindamycin or metronidazole, for anaerobic coverage, when perforation is suspected or has occurred. This lack of agreement within the medical literature confirms that peritoneal fluid cultures should be obtained in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient.

In neonates with culture-positive peritonitis, 14% with NEC showed evidence of Candida species peritonitis, emphasizing the need to address the use of antifungal agents in cases of bowel perforation in the NICU. We identified associated candidemia in only 2 (40%) of the 5 cases of culture-proven candidal peritonitis; therefore, it is imperative that the clinician be aware of patients who are at risk for fungal disease.

Bond et al(16) described 3 cases of fatal candidal enteritis seen on pathologic evaluation and therefore recommended "review of pathologic specimens for invasive fungal enteritis with institution of aggressive combination therapy in confirmed cases."

In a previous publication, Karlowicz (17) proposed that amphotericin B be considered in neonates who weigh <1000 g and have stage IIIB NEC, "especially in those with a history of prolonged umbilical vessel catheterization, prolonged antibiotic therapy, and prolonged intubation." In a report on neonates with NEC, Smith et al(18) recommend amphotericin B for patients who remain symptomatic despite negative bacterial cul-tures. The most current recommendations from Benjamin et al,(19) based on a study of neonates with birth weight <1250 g, encourage consideration of empiric antifungal therapy pending culture results on the basis of noted risk factors: <25 weeks' estimated gestational age, thrombocytopenia at the time of blood culture, or 25 to 27 weeks without thrombocytopenia but with a history of third-generation cephalosporin or carbapenem exposure in the preceding 7 days. It has been suggested that earlier institution of antifungal therapy may alter outcome in infants with Candida peritonitis(17,15).We conclude that a peritoneal culture obtained at the time of surgical intervention is reasonable, as it may allow more rapid identification of fungal peritonitis and allow initiation of antifungal therapy as promptly as possible.

Importantly there were 28 infants who had no organism identified on blood culture. A large number of babies would therefore need to be treated with Vancomycin and Meropenem to adequately cover the few with positive blood culture. The use of such broad spectrum antibiotics may lead to the emergence of multi resistant bacteria and the initial choice of narrow spectrum antibiotics has been recommended (21, 22).

It has been shown that coagulase negative Staphylococci have a relatively long incubation time (median 28.9 hours) and thereby continuing with our current antibiotic choice for NEC may significantly delay the commencement of an appropriate antibiotic (23).Due to the limitations of this study we are unable to make general recommendations on the first line antibiotic choice for babies with suspected or confirmed NEC. Our current regime of Ampicillin, Gentamicin and Metronidazole failed to adequately treat 5 of the 8 organisms subsequently isolated in blood cultures. The only combination of antibiotics that would have adequately treated all the bacteria identified was Vancomycin and Meropenem. The concern with this approach is the possible emergence of multi drug resistant bacteria. Further research is required to determine the best antibiotic regime for babies with suspected or confirmed NEC.

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Correspondence to:
Adrian Surd
Str. Moților, nr. 68
Cluj Napoca
Romania
E-mail: adisurd@yahoo.com