Early Human Development 123 (2018) 6–10

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Does antibiotic choice for the treatment of suspected late-onset sepsis in premature infants determine the risk of developing necrotising enterocolitis? A systematic review

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A B S T R A C T

Background: Necrotising enterocolitis (NEC) is a significant cause of infant morbidity and mortality, disproportionately affecting those of extreme prematurity and/or very low birth weight. A number of risk factors have been identified, including an association between the use of antibiotics, and the subsequent development of NEC.

Aim: This review sought to address whether the choice of antibiotic(s) used to treat infants with suspected late-onset sepsis (LOS) influences the risk of developing NEC.

Methods: A systematic review was performed across Web of Knowledge, Cochrane Library, Ovid Medline, EMBASE and CINAHL databases, up to February 2018, assessing the primary outcome of NEC occurrence, as extracted directly from the published articles. Studies were included if they were randomised control trials (or featured adequate adjustment for confounders); included clear criteria for defining LOS/NEC; and assessed occurrence of NEC in premature infants treated for LOS with intravenous antibiotics. Studies were excluded if non-original, not exclusively featuring premature infants, or where treatment was given for early-onset sepsis only.

Findings: 2291 titles and abstracts were identified, of which one study (81 subjects) was suitable for analysis, following screening against eligibility criteria. This suggested a decreased risk of developing definite NEC following treatment with a vancomycin/aztreonam combination, *versus* a vancomycin/gentamicin regimen (OR = 0·08, 95%CI = 0·00–1·45).

Conclusion: This systematic review identified one study where the occurrence of NEC was reported in the context of comparing different antibiotic regimens for late onset sepsis and highlights that the type of antibiotic used to treat LOS in preterm infants might be a determinant of the risk of developing NEC. Although it is known that different antibiotic combinations impact the enteric microbiome and that antibiotic exposure is a risk factor for NEC, there is a paucity of well-designed studies that look at the relationship between NEC risk and specific antibiotic exposures.

1. Introduction

1.1. Current knowledge

Necrotising enterocolitis (NEC) is an inflammatory bowel condition affecting the health of newborn infants, often with severe adverse consequences. It is associated with both a significant mortality [1], primarily during the acute phase of the illness; and morbidity, with long-term outcomes including bowel dysfunction [2, 3] and adverse neurodevelopment [4].

NEC is known to disproportionately affect extremely premature and/or very low birth weight infants, with an estimated incidence of ~7% in very low birth weight (VLBW; < 1500 g) babies [5], and a further increased incidence in those infants born at the margins of viability [6]. However, an *inverse* relationship is seen between gestational age at birth, and chronological age at onset of symptoms of NEC

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https://doi.org/10.1016/j.earlhumdev.2018.06.009
Received 29 March 2018; Received in revised form 11 June 2018; Accepted 12 June 2018

(*i.e.* infants born at more extremely premature gestations tend to develop NEC at a later chronological age, relative to their comparatively less premature peers). This has the effect of producing a convergence of NEC diagnoses, from babies of differing gestational ages at birth, at ~28–33 weeks post-menstrual age [7].

The burden of NEC cannot be overstated. Recently published data from the United Kingdom confirms that severe or fatal NEC (confirmed at laparotomy and/or leading to death) affects 3.2% of babies born before a gestational age of 32 weeks. Almost half (48.1%) of babies included in this study died as a result of developing this devastating disease [8].

Despite much research, a consensual agreement on the aetiology of NEC remains elusive, although a number of risk factors associated with its development have been identified [6, 9, 10]. By far the most influential of these risk factors is preterm birth, which is theorised to promote a pathophysiological process based upon immaturity of the perfusion and barrier function of the preterm intestine; abnormal patterns of microbial colonisation of the preterm intestine in the presence of enteral feeding; and a dysregulated response from the preterm immune system to this process [11].

Indeed, there is now mounting evidence to support the role of abnormal microbial colonisation as a contributor to the pathophysiological model of NEC development. Recent studies utilising molecular biological techniques (*i.e.* high-throughput 16S RNA sequencing) to profile bacterial communities around the time of NEC development have shown distinct shifts in the microbiome prior to the onset of disease [12–15], although between studies there is inconsistency and conflict regarding the nature of these changes [16]. However, it is unclear whether these shifts in microbial community profile represent the cause or effect of the underlying pathophysiology; and, if they do drive the process, by what means.

The use of postnatal antibiotics has been implicated as a risk factor for the development of NEC [17, 18]; it may be hypothesised that this association stems from the impact of these antibiotics on the developing intestinal microbiome. Antibiotics have been demonstrated to be potent modulators of the intestinal microbiome in neonatal, paediatric and adult studies, with distinct effects seen for differing antibiotic types [19]. The influence of antibiotics upon the neonatal intestinal microbiome propounds potential mechanisms by which the development of NEC may be influenced. For example, antibiotic administration may directly impact upon the microbiome of the individual neonate, resulting in suppression of protective commensal organisms, and development of more pathogenic colonisation, either through loss of competitive inhibition, insensitivity to the antibiotic, or a combination thereof. Increased levels of potentially pathogenic *Enterobacteriaceae*, coupled with reduced endogenous anaerobes and reduced microbial diversity prior to onset of NEC, support this proposal [13–15, 20]. Additionally, antibiotic use may indirectly influence the intestinal microbiome, through alteration of the general microbial ecology of the neonatal unit within which individual babies reside [13].

This hypothesised role of antibiotics in the development of NEC is of particular relevance in premature babies, in whom antibiotics are frequently commenced, either prophylactically, or for the treatment of suspected sepsis [21]. It has been shown that prolonged antibiotic therapy ($\geq$5 days), for the treatment of suspected or confirmed early onset sepsis (EOS), is associated with an increased risk of the development of NEC in both extremely low birth weight [17] and premature infants [18], and an exposure-response relationship has been demonstrated for the combined burden of antibiotics for the treatment of EOS and LOS [22]. Additionally, an increase in rates of NEC (albeit to a non-statistically significant degree) is seen following the 'routine' administration of antibiotics to preterm infants in the first 12 h of life (who were asymptomatic and without risk factors for infection), compared to an untreated control group [23].

1.2. What is not known

In contrast, there is a paucity of research assessing the risk of development of NEC following the initiation of antibiotics for the treatment of suspected LOS; despite a clear converse association (*i.e.* development of NEC is strongly associated with prior treatment for LOS [24]). A Cochrane review [25] comparing different antibiotic regimes for the treatment of suspected LOS was not able to assess the development of complications such as NEC, acknowledging that there is a lack of robust studies focusing on antibiotic treatment for LOS and subsequent outcomes. This systematic review sought to characterise this gap in the literature, by attempting to answer the question of whether the choice of antibiotic(s) used to treat infants with suspected LOS influences the risk of developing NEC.

2. Search strategy and selection criteria

A systematic literature search was performed, based on a PICO framework, to answer the question "In premature infants (P), is the choice of antibiotic for the treatment of late-onset sepsis (I/C) associated with a difference in the risk of the subsequent development of necrotising enterocolitis (O)?"

The Web of Knowledge, Cochrane Library, Ovid Medline, EMBASE and CINAHL databases were interrogated using the NICE NHS evidence HDAS (Healthcare Databases Advanced Search) platform across the search fields of "Abstract", "MeSH subject heading", "Exploded subject heading", "Subject heading word", "Text word" and "Title". The following key words and search strategy were employed, linked with Boolean operators as appropriate: ["infan*" OR "newborn*" OR "neonat*"] AND ["sepsis" OR "infection" OR "septicaemia" OR "late onset sepsis" OR "late onset infection"] AND ["antibiotic*" OR "antimicrobial*"] AND ["NEC" OR "necroti?ing enterocolitis"(n.b. "text word" field only)]. The US trials database was also examined for any current trials regarding antibiotics and LOS in the context of NEC risk. The searches were performed up to February 2018 with no restrictions placed upon study design, language or year of publication, in order to enable a thorough review of the literature and to reduce the risk of bias.

Articles were initially screened by examination of their titles and abstracts by four reviewers (JS, AKS, SH and PF). Screening criteria were that the studies should include neonates, and that subjects were allocated to antibiotics in a randomised or quasi-randomised manner.

For any prospectively eligible study which included all studies of antibiotic treatment for neonatal sepsis regardless of whether NEC was mentioned in the abstract, the full text was obtained and re-screened to confirm the presence of information regarding the development of NEC. Eligible studies were then reviewed for inclusion in the final stage of the review. Additionally, the references of these articles were examined, in order to uncover any previously unidentified studies: a further iteration of assessment of eligibility was performed on this subset.

All prospectively eligible studies were analysed separately by five members of the reviewing team (AKS, MM, PF, SH, STK) against an agreed protocol. Data were extracted within the following fields:

- Study design and randomisation status.
- The occurrence of intravenous antibiotic therapy for the treatment of LOS, separate from that for EOS (either as a primary or secondary analysis, or an extrapolatable sub-group).
- Criteria employed for the definition of LOS.
- Type of comparative antibiotic regimens.
- Sample (and sub-group) size.
- Numbers of NEC cases.
- Criteria employed for the definition of NEC.

Any discrepancies between reviewers were resolved by an independent assessor.

Eligibility criteria for inclusion in the final stage of the systematic