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Amoxicillin is not necessary for empirical treatment of suspected sepsis or meningitis outside the neonatal period

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Abstract

Objectives - To describe the epidemiology, time of infection, clinical characteristics and outcome of listeria infection in young infants to inform management and empiric antibiotic choice in young infants

Design – Prospective two year surveillance of *L. monocytogenes* infection in young infants detected through the British Paediatric Surveillance Unit "orange card" system and triangulated with the public health laboratories

Setting – National population study (England, Wales, Scotland and the Republic of Ireland)

Patients - All infants under 90 days with proven or probable invasive listeriosis

Main outcome measures – Incidence, mortality, age of infection, clinical characteristics and outcome

Results – During a two-year period (2017- 2019) 27 cases of listeriosis in infants <90 days of age were reported. The incidence of listeriosis was 1.8 per 100,000 livebirths with 7% mortality (2/27). Nearly all cases presented within the first 24 hours of life (26/27). The majority (20/27,74%) were born preterm and 16/24 (67%) of women were from ethnic minority background.

Conclusions – Invasive listeriosis in young infants in the UK and Ireland is rare and presents early in the neonatal period. National guidelines that recommend the use of amoxicillin as part of empiric regimes for sepsis and meningitis in infants over 1 month of age should be modified.

Manuscript

Listeria monocytogenes causes severe disease in neonates, immunocompromised individuals and the elderly and disproportionally affects pregnant women. Vertical transmission can result in miscarriages, stillbirths or premature birth in up to 80% of affected pregnancies [1]. In neonates it can cause severe sepsis and meningitis with considerable morbidity and mortality (up to 30% reported, even in high income countries) [2]. Outside the neonatal period, listeriosis is usually acquired through consumption of contaminated food [3]. Traditionally, listeriosis was associated with the ingestion of unpasteurised dairy products and ready-to-eat processed meats, but with changes in the food processing industry, more recent sporadic cases and outbreaks have resulted from other food products such as fruits, raw frozen vegetables and pre-packed sandwiches [4-7]. The use of whole genome sequencing has provided rapid detection and strain characterisation of *L. monocytogenes* in humans and food, allowing for the detection of outbreaks within the UK and internationally [7-9].

Listeria is intrinsically resistant to cephalosporins but remains largely susceptible to penicillins [10]. As a result, amoxicillin is included in the empirical guidelines for young infants with possible sepsis or meningitis, where this may be due to *L. monocytogenes.* National UK guidelines currently include infants up to 90 days of age in this group, but recent data from the UK, and internationally, suggests that including neonates only be more appropriate [11-15].

We present the result of a prospective population study of listeriosis in infants under 90 days of age in the UK and Republic of Ireland which aimed to establish the incidence of proven and possible listeria, geographical and ethnic distribution, management and outcomes and to inform national antibiotic policies for infants under 90 days.

Methods

We conducted a two-year active surveillance for cases of invasive *L. monocytogenes* in young infants using the British Paediatric Surveillant Unit orange card system [16-17]. This is a voluntary survey sent via e-mail to all paediatricians and neonatologists in the UK and Republic of Ireland[18]. All clinicians are asked to notify the BPSU if they have treated a patient with one of a list of rare conditions. Once a case is notified, a questionnaire is sent to the treating clinician and more detailed information is gathered.

We cross-referenced our data with that from the national reference laboratories in England, Scotland and the Republic of Ireland. Additionally, in England we reviewed the Hospital Episode Statistics (HES) database through Public health England. We also made contact with relevant national charities and asked for information on any cases that had been referred to them over this time period (Meningitis Now, Meningitis Research Foundation and Bliss,UK charity for babies born premature or sick)).

Infants under 90 days were included if they had a clinical diagnosis of confirmed or possible invasive listeriosis according to the definitions in Table 1.

The study received ethical approval from the South Yorkshire Ethics Committee (REC 16/YH/0491).

Table 1. Study definitions of Listeria infection

Microbiological Methods:

Isolates of *L. monocytogenes* from cases in England were referred to the Public Health England (PHE) Gastrointestinal Bacteria Reference Unit (GBRU) for confirmation and further typing using whole genome sequencing(WGS)[19] Sample preparation was performed using the NexteraXT (Illumina Inc., San Diego, USA) and sequenced using Illumina HiSeq 2500 platform with 2x100bp reads (Illumina Inc., San Diego, USA). Short reads were quality trimmed using Trimmomatic and *L. monocytogenes* identification was confirmed using kmer analysis [20] and four serotypes (1/2a, 1/2b, 1/2c, and 4) were derived from the WGS by alignment to four specific marker genes [21] using Bowtie2 [22]. Clonal complexes (CCs) were derived from WGS analysis: CCs were assigned using MOST [23] in accordance with the designation of the Institut Pasteur international MLST database for *L. monocytogenes* (http://bigsdb.pasteur.fr/listeria/listeria.html). A core single nucleotide polymorphism (SNP) alignment for each clonal complex was generated using SnapperDB [19], recombination removed using Gubbins [24] and a seven-threshold SNP sequencing address generated [19]. Pairwise comparisons of SNP distances were performed between isolates and *L. monocytogenes* linked within a 5 SNP single linkage cluster.

Results

During the two year period, 1st September 2017 to 31st August 2019, 35 cases of listeria infection were notified, of which 27 fulfilled the case definition (Table 1); an incidence of 1.8

per 100,000 livebirths. Cases were from England (n=23), Republic of Ireland, 3 and Scotland, 1. Excluded cases were asymptomatic babies of mothers with *L. monocytogenes* bacteraemia (n=7)and one still-birth. *L. monocytogenes* was isolated from 16/27 (59%) mothers and 23/27 (85%) infants.

From the obstetric perspective, 16/24 (67%) mothers were from an ethnic minority background (3 Black African, 8 Asian, 4 Other White Background, 2 Mixed background). Preterm labour was the most common presentation (20/27, 74%), followed by maternal sepsis (10/27, 37%) and chorioamnionitis (6/27; 22%). Maternal symptoms at presentation are reported in Table 2. *L. monocytogenes* was isolated in maternal specimens before delivery in six women, of whom four went on to receive a penicillin antibiotic before delivery.

From the paediatric perspective, confirmed sepsis was the most common presentation (14), with probable sepsis in 8 and confirmed meningitis in seven. Two asymptomatic infants were treated because of maternal listeria bacteraemia and are not included in the analysis. The median birthweight was 2280g (IQR 1035) and median gestational age 33 weeks (IQR 6); 20/27 (74%) were born preterm, 11/26(42%) were male.

All cases but one were identified in the first 24 hours of life, the presenting signs of infants are shown in Table 2. The one exception was a neonate with late onset meningitis who presented on day 14. The median CRP at presentation for all cases was 43 mg/L (IQR 75). 83% of infants (22/27) had a lumbar puncture (LP) performed, with a median time to LP of 37 hours. Of 18 infants for whom the CSF microscopy was available, an abnormal CSF pleocytosis was demonstrated in six.

With one exception, the empirical antibiotic treatment given was appropriate (a penicillin and aminoglycoside combination in 26 and a third-generation cephalosporin with amoxicillin in 1). Excluding the infant presenting with late onset meningitis at day 14, the median time to prescribing antibiotics, available for 25 infants, was 1 hour (IQR 1).

Of the 27 infants, two (7%) died and outcome information at discharge was available for 21 infants. Of these, one was discharged with ongoing seizures and one with a nasogastric feeding tube, all other infants did not have hearing, visual, neurological or other impairment evident at discharge.

Both of the two infants (one male) who died were born prematurely, one at 29 and the other at 30 weeks gestation. One of the infants was born to a mother who presented with fever,

'flu-like symptoms' and abnormal cardiotocography. The other was born to an asymptomatic mother with premature delivery. Both babies were delivered by emergency caesarean section. Neither of the mothers received antibiotics before delivery. Both infants were in poor condition at birth, requiring resuscitation, ventilation, inotropes and treatment for glucose intolerance; both had temperature instability and neurological signs. The CRP was high in both infants (65 and 213 mg/l at peak). They were treated with appropriate antibiotics including a penicillin within two hours of birth. *L. monocytogenes* was isolated from blood cultures. One infant died 19 hours and the second 54 hours after delivery, both had a post-mortem examination and listeriosis was confirmed to be the primary cause of death with prematurity as a contributory cause.

Table 2. Clinical presentations of *L. monocytogenes*

Microbiological investigations, typing and phylogenetic analysis using WGS: Typing results were available from strains isolated from 23 cases cases in England and Wales. The majority of isolates were characterised as serotype 4 (18, 78%) with the remaining isolates characterised as serotype 1/2a (3, 22%). Four cases from England were linked to other cases by pairwise SNP analysis using WGS and were recognised to be a part of ongoing clusters or outbreaks. Two cases of *L. monocytogenes* serotype 4 (ST32) were identified as being a part of a multinational listeriosis outbreak affecting Eastern European (predominantly Romanian) women, a specific food source has not been identified till date. Two other cases of serotype 1/2a (CC220 and CC7 respectively) belonged to two separate multinational outbreaks, a causative food has not been identified.
Of the three cases from the Republic of Ireland 2 were serotype 4 and the other 1/2b.
All isolates were reported as fully sensitive to first line antibiotics.

Discussion

We report an incidence of listeriosis of 1.8 cases per 100,000 live birth in the UK, which is lower than that reported in the ten years between 2004 and 2014 (3.4/100,000) [25]. A similar decrease has been observed in other countries and has been attributed in part to the widespread use of intrapartum antibiotic prophylaxis directed against Group B streptococcus [26]. In the UK, intrapartum antibiotic prophylaxis recommendations are not based on universal swab-based screening, but on the presence of risk factors, including (since 2017) preterm labour and fever, which may therefore include women with listeriosis.

The neonatal listeriosis case fatality in this cohort is lower (7%) than previously reported in the UK (21%) [25] and is comparable with more recent French data demonstrating a case fatality rate of 5% [1]. This may be due to the early and universal use of penicillin and gentamicin to treat presumed early onset neonatal infections.

Only 20% of mothers were treated with a penicillin based antibiotic regimen before delivery, indicating the difficulty in the clinical diagnosis of pregnancy associated listeriosis [27]. Maternal symptoms were non-specific and included premature labour, fever, reduced foetal movements and flu-like symptoms. Similar observations were made in a French study [1].

We note that the majority of cases came from ethnic minorities (67%), although no single ethnic group dominated. This is a recurrent observation in other countries as well and calls for careful consideration of listeriosis as a possible diagnosis in pregnant women from ethnic minority backgrounds presenting with flu like symptoms and premature labour.[28,29] An accurate food history is recommended and the use of a penicillin in preference to a cephalosporin as an antibiotic choice should be considered as listeriosis, although rare, has a very high rate of foetal loss and poor neonatal outcomes [1]. The current dietary guidance for pregnant women in the UK focuses on avoidance of unpasteurised dairy products and ready to eat foods, such as pate, however the causative foods, shopping and cooking practices differ in ethnic minorities and the recommendations need to be updated to include precautionary measures with foods such as fresh produce.

Listeriosis is rare, and we did not identify any cases occurring outside the neonatal period over a two-year period of national surveillance involving 1.5 million live births. This is consistent with other recent surveillance studies including a review of the 24 year period from 1990-2013 in England and Wales in which only 5 of 356 cases of listeria occurred in infants between 30 and 90 days of age and 6 in infants over 90 days [11,30-33]. Despite this, all current National Institute for Health and Care Excellence (NICE) guidelines (covering sepsis, meningitis and fever) recommend the additional use of amoxicillin in cases of possible sepsis and meningitis up until the age of 90 days (NG 51 and 143, CG 102). The potential impact of this policy on antibiotic use was modelled on data from a single centre study which concluded that it leads to “unnecessary” treatment of around 9000 infants (28000 doses) per year [34].

We propose that it is time to restrict this guidance to infants in the neonatal period only.

Our study has some potential limitations. Pregnancy associated listeriosis may be an under-reported infection. However, given the variety of sources used for data collection and the use of a broad case definition (to include maternal listeria), we believe that ascertainment is as complete as possible.

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Table 1. Study definitions for cases of *Listeria monocytogenes* in young infants in the UK and Ireland.

Listeria Meningitis		**Listeria sepsis**	
Confirmed	Probable	Confirmed	Probable
• Isolation of *Listeria* or a positive *Listeria* PCR from CSF • Isolation of *Listeria* or a positive PCR from blood) **AND** CSF pleocytosis*	• In a baby <7 days old: Isolation of *Listeria* or a positive *Listeria* PCR from maternal tissue (blood, CSF, placenta or genital tract) **AND/OR** isolation of *Listeria* from surface swabs, meconium or nasogastric aspirate from baby **PLUS** clinical signs of meningitis **AND** CSF pleocytosis	Isolation of *Listeria* from blood cultures or a positive *Listeria* PCR from blood **AND** no CSF pleocytosis **AND** *Listeria* not isolated from CSF **OR** no CSF available	In a baby < 7 days old: Isolation of *Listeria* or a positive *Listeria* PCR from maternal tissue (blood, CSF, placenta or genital tract) **AND/OR** isolation of *Listeria* from surface swabs, meconium or nasogastric aspirate from baby AND clinical signs of sepsis AND treatment of the baby with at least 5 days of appropriate antibiotics

*Cerebrospinal fluid (CSF) pleocytosis:

WCC ≥20 cells/mm^3 (0- 28 days of age); WCC ≥10cells/ mm^3 (28-90 days of age).

Table 2. Clinical presentations of cases of *Listeria monocytogenes* in young infants in the UK and Ireland.

Infants (N=27)	Total (%)	**Maternal (N=27)**	Total (%)
Increased oxygen requirement/respiratory support	2 (89)	Premature labour	20 (74))
Temperature instability	6(22)	Fever	13(48)
Apnoea/bradycardias	6 (22)	Reduced foetal movements	7 (26)
Lethargy/convulsions	5 (18	Flu-like symptoms	5 (19)
Signs of shock	5 (18)	None	6 (22)
Hypotension requiring inotropes	4 (115)	Pre-labour contractions	4 (15)
Rash	3 (11)	Back pain	3 (11)
Glucose intolerance requiring treatment	3 (11)	Vaginal bleed	2 (7)
Base deficit >=10	3 (11)	Diarrhoea	1 (4)
Jaundice	2 (7)	Unknown	1 (4)

What is already known

- Listeriosis is a rare infection in young infants but may have a high mortality and morbidity.
- National UK guidelines for empiric antibiotics in young infants (0-3 months of age) with suspected sepsis or meningitis dictate the addition of ampicillin or amoxicillin to provide cover for Listeria.

What this study adds

- Listeriosis in young infants in the UK and Ireland is confined to the neonatal period
- The addition of a penicillin for empiric treatment of sepsis and meningitis in young infants is no longer required beyond the neonatal period