Essential Title Page Information

Title: Neonatal Listeriosis in the UK 2004-2014

Author names and affiliations:

Dr Shari Sapuan
Paediatric Infectious Diseases Research Group, St George’s, University of London.

Christina Kortsalioudaki
Paediatric Infectious Diseases Research Group, St George’s, University of London.

Dr Mark Anthony
Newborn Care Unit, John Radcliffe Hospital, Headington, Oxford, UK OX3 9DU. anthony.mark@ouh.nhs.uk

Dr John Chang
Croydon University Hospital, 530 London Rd, Croydon, Surrey, UK CR7 7YE. john.chang@crobyonhealth.nhs.uk

Dr Nicholas D Embleton
Royal Victoria Infirmary, Newcastle upon Tyne, UK NE1 4LP. nicholas.embleton@newcastle.ac.uk

Dr Ruppa M Geethanath
Sunderland Royal Hospital, Kayll Road, Sunderland UK SR4 7TP. ruppa.geethanath@chsft.nhs.uk

Dr Jim Gray
Birmingham Children’s Hospital NHSFST.

Professor Anne Greenough
King’s College London. King’s Health Partners. Royal College of Paediatrics and Child Health.

Dr Mithilesh K Lal
The James Cook University Hospital, Marton Road, Middlesbrough, UK TS4 3BW. mithilesh.lal@stees.nhs.uk

Dr Suzanne Luck
Kingston Hospital NHS Trust.

Dr Santosh Pattnayak
Kent Neonatal Transport Service. Medway NHSFST.

Dr Peter Reynolds
Department of Paediatrics, St. Peter’s Hospital, Ashford and St. Peter’s Hospitals NHSFST. Royal Holloway University of London. Surrey & Sussex Neonatal ODN

Dr Allison B Russell
Birmingham Women’s NHSFST. West Midlands Maternity and Children’s Strategic Clinical Network.

Dr Timothy Scorrer
Portsmouth Hospitals NHS Trust.

Dr Mark Turner
Women’s and Children’s Health, University of Liverpool. Liverpool Women’s NHSFST.

Professor Paul T Heath
Paediatric Infectious Diseases Research Group, St George’s, University of London.

Dr Stefania Vergnano
Paediatric Infectious Diseases Research Group, St George’s, University of London.

Corresponding author:

Name: Dr Shari Sapuan
Email address: sharisapuan@doctors.org.uk
Affiliation Address: Paediatric Infectious Diseases Research Group, St George’s, University of London, Jenner Wing, Level 2, Room 2.215E, Mail Point J2C, London, UK SW17 0RE.
Summary

Objective
To define the clinical features and outcomes of neonatal listeriosis, and identify the maternal risk factors to seek scope for improvement.

Methods
Neonatal listeriosis was identified prospectively from a United Kingdom neonatal infection surveillance network (neonIN) between 2004 and 2014. The participating neonatal units completed a study-specific proforma.

Results
The incidence of neonatal listeriosis was 3.4 per 100,000 live births. Of the 21 cases identified, 19 were confirmed with a median gestational age of 33 weeks and a median birth weight of 1960g. The majority had clinical features (95%, 18/19), presented within the first 24 hours (95%, 18/19), and received penicillin empirically (94%, 18/19). The neonatal case-fatality rate was 21% (24% if probable cases were included). A proportion of mothers were investigated (60%, 12/18) and diagnosed with listeriosis (58%, 7/12); 32% (6/19) were treated with antibiotics but only 33% (6/12) included penicillin.

Discussion
Despite its rarity and the prompt and appropriate use of antibiotics neonatal listeriosis has a high case-fatality rate. There is room for improvement in the adherence to the national guidance in the choice of empiric antibiotics for puerperal sepsis, which would target listeriosis. Strategies should be in place to prevent pregnancy-associated listeriosis in higher risk population.
Introduction

Listeria monocytogenes is a Gram-positive bacillus. L. monocytogenes causes listeriosis, an infection predominantly transmitted through the consumption of contaminated food. Recent estimates suggest that listeriosis is the most common cause of food-related deaths in the UK (130 deaths in 2005) [1]. The incidence of listeriosis in pregnancy is 12 per 100,000, compared with a rate of 0.7 per 100,000 in the general population [14].

For an antibiotic to be effective against L. monocytogenes, the antibiotic must penetrate into the host cell, maintain a high concentration and bind to the penicillin-binding protein (PBP), which causes cell death. Penicillin, amoxicillin and ampicillin have been used most extensively in the treatment of listeriosis as these drugs block several PBPs and do penetrate intracellularly. Some in-vitro studies also suggest a synergistic effect when gentamycin is added to the treatment regimen [9]. Studies in Denmark and Northern Italy found L. monocytogenes human isolates to be susceptible to ampicillin, amoxicillin, benzylpenicillin, meropenem, erythromycin and gentamicin [12,13]. L. monocytogenes is intrinsically resistant to broad-spectrum cephalosporin antibiotics, which are commonly used in treatment of bacterial infections [6].

Neonatal listeriosis occurs via congenital infection. In the UK, it is the third most common cause of early-onset neonatal infection [3] and the fourth most common cause of early-onset neonatal meningitis [7]. It manifests commonly in the first 24 to 72 hours of life (62% of cases) [3]. Early-onset neonatal listeriosis can manifest as bacteraemia, meningitis and less commonly pneumonia. Late-onset neonatal listeriosis is most commonly associated with meningitis [2].

Neonatal listeriosis is associated with high case fatality rates. In the UK between 1967 and 1985, 248 out of 722 cases of human listeriosis (34%) were associated with pregnancy of which 42 cases resulted in intrauterine deaths (19%) and 47 in neonatal deaths (35%), with an overall case fatality rate of 50% [4].

This study aims to define the clinical features, risk factors and outcomes of neonatal listeriosis in a UK neonatal infection network over a period of 11 years.

Materials and Methods
Cases of neonatal listeriosis were prospectively identified between January 2004 and December 2014 through neonIN, a neonatal infection surveillance network (www.neonin.org.uk). The contributing centres voluntarily collect data on culture-positive neonatal infections onto the web-based research database, which is also crosschecked with laboratory records to ensure validity and quality.

All neonIN centres in the UK contributing data within the study period were contacted and requested to complete a study-specific proforma for additional information (maternal and neonatal demographics, risk factors, clinical features, antimicrobial treatments and outcomes) on all cases of neonatal listeriosis. Cases were categorised as confirmed (defined as a case when *L. monocytogenes* was isolated from a normally sterile culture site of the neonate) and probable (defined as a case when *L. monocytogenes* was isolated from a normally sterile culture site of the mother, but no bacteria is isolated from a normally sterile culture site of the neonate who is clinically felt to be septic), and were analysed separately.

The data was analysed on Microsoft Excel 2010. Comparisons were made with chi-square test for the data on ethnic distribution. The incidence of neonatal listeriosis was calculated using the cumulative hospital life births as a denominator.

NeonIN received ethics approval from the London-Surrey Borders Research Ethics Committee in 2005 (05/Q0806/34) and in 2010. Each participating centre received separate approval from their local ethics committees prior to joining the network.

**Results**

Over the 11-year period, 18 neonatal units reported 21 cases of neonatal listeriosis. The overall incidence was 3.4 per 100,000 live births. Of the 21 cases identified, 19 were confirmed and 2 were probable. An overview of the maternal and neonatal results can be seen in Table 1 and Table 2 respectively.

**Maternal Results**
The median maternal age was 29 years (range 21-42, IQR 9). Of the 14 cases recorded (13 in England and 1 in Scotland), 50% were Caucasians, 29% Afro-Caribbeans and 21% Asians (Table 1). When comparing the data on ethnic distribution from the neonIN-participating centres in England against the Office for National Statistics population data in England, we identified a disproportionally high representation of Asian and Afro-Caribbean women in our sample (p <0.001) [5].

Clinical features were present in 95% (20/21) of mothers antenatally with onset of preterm labour being the most common. Complications during labour occurred in 62% (13/21). Of the 20 cases recorded, 60% (12/20) had blood cultures performed of which 58% (7/12) were positive for *L. monocytogenes*. Overall, 55% (11 out of 20 recorded cases) were not diagnosed with maternal infection. Of the 19 cases recorded, 32% (6/19) received antibiotics pre-delivery; one-third (2/6) included penicillin and two-thirds (4/6) included cephalosporins (Table 1).

**Neonatal Results – Confirmed Cases**

Of the 19 confirmed cases of neonatal listeriosis, the median gestational age was 33 weeks (27-38 weeks, IQR 5 weeks), the median birth weight was 1960g (1070-3210g, IQR 1002g), 90% (17/19) were born at less than 37 gestation weeks, 63% (12/19) had a birth weight of less than 2500g and 21% (4/19) had a birth weight of less than 1500g (Table 2).

Clinical features were present in 95% (18/19) of neonates with respiratory distress being the most common, and 95% (18/19) of the neonates presented within the first 24 hours. Meconium stained liquor was present in 62% (13/19). Cardio-respiratory support was required in 84% (16/19). In terms of diagnosis, 90% (17/19) were diagnosed with septicaemia, 21% (4/19) with meningitis and 5% (1/19) with pneumonia. The one (5%) neonate who presented after the first 24 hours did so at 10 days of age with pyrexia and was diagnosed with meningitis (Table 2).

In terms of treatment, 94% (17/18) of neonates with early-onset infection received penicillin empirically and 1 (6%) received a cephalosporin. Antibiotics were administered within 1 hour of birth in 67% (8/12), between 1 to 2 hours after birth in 17% (2/12) and more than 2 hours after birth in 17% (2/12). The neonate with late-onset listerial meningitis also received a penicillin as part of the empiric treatment (Table 2). The duration of penicillin treatment was variable (Table 2); of the 3
neonates with meningitis, 2 completed a 21-day course and 1 a 50-day course, and of the 10 with septicaemia, 7 completed a 21-day and 3 a 14-day course.

Looking at outcome, 21% (4/19) died in the neonatal period (all 4 within 7 days of disease onset). Of those that survived the neonatal period, 40% (6/15) had neurological and/or neurodevelopmental impairment at follow-up; 2 had developmental delay, 1 had hypertonia and a divergent squint, 1 had epilepsy, 1 had hydrocephalus requiring shunting and 1 had severe cerebral palsy who died at age 7 years.

**Neonatal Results - Probable Cases**

There were 2 reported probable cases of neonatal listeriosis.

One was born at 27 gestation weeks via emergency caesarean-section following maternal pyrexia and pathological fetal cardiotocography, and presented with respiratory distress, lethargy, bradycardia and raised inflammatory markers. The empiric treatment included a penicillin but the neonate died on day 6. *Listeria monocytogenes* was isolated from the maternal blood culture.

The other was born at 30 weeks gestation via emergency caesarean-section following maternal pyrexia, preterm rupture of membrane and pathological fetal cardiotocography, and presented with a rash, respiratory distress and raised inflammatory markers. This neonate was treated with a 21-day course of penicillin and survived the neonatal period with no neurological impairment at follow up. *L. monocytogenes* was cultured from the maternal vaginal swab.

**Discussion**

The study has highlighted some important lessons for clinicians and public health specialists.

The overall incidence of neonatal listeriosis in our study population was 3.4 per 100,000 live births. This is lower when compared to other countries; for example in the United States of America the incidence of neonatal listeriosis is 8.6 per 100,000 live births [15] and in Israel it is up to 25.5 per 100,000 live births [16]. Neonatal listeriosis is also rarer when compared to the more common cause
of neonatal infection, such as Group B streptococcal infection, with an incidence of 72 per 100,000 live births [17]. Therefore, neonatal listeriosis remains to be a rare disease. However, the case-fatality rate of neonatal listeriosis remains high; in our case series this was 21% (24% if probable cases were included) whereas the more common Group B streptococcal infection has a lower fatality rate (9.7%) [17]. Therefore, despite its rarity, improvements in the recognition and prevention of listeriosis need to be identified.

There is little scope for improvement in the choice or speed of therapy for neonates, as the vast majority with early-onset infection received penicillin empirically (95%, 18/19) within the first 2 hours (83%, 10/12). This may reflect the targeted use of antibiotics to prevent early-onset group B streptococcal infections, which has also been suggested in a recent study to have a possible role in the reduction of neonatal listeriosis [11]. Of the 4 neonates who died from listerial infection, all received a penicillin and gentamicin empirically, of which 2/3 of those who received benzylpenicillin were switched onto amoxicillin within 24 hours of life following the culture of *L. monocytogenes*. Of the 6 neonates with neurological and/or neurodevelopmental impairment at follow-up, only 1 received a cephalosporin empirically.

Of the 4 mothers of the neonates who died of listerial infection, 2 (50%) did not receive antepartum antibiotics and 2 (50%) received cephalosporins. This might suggest that there is a worse outcome in neonatal listeriosis with mothers who were not treated or inadequately treated.

We found that the majority (95%) of mothers presented with non-specific clinical features. This may be the reason why a significant proportion were not investigated and subsequently not treated as puerperal infection. The most common feature in mothers who were not investigated and treated (no culture performed on any sterile site and no antibiotics commenced) is reduce foetal movement (63%, 5/8), which is not a feature recognised to be associated with puerperal infection [10]. Therefore a lower threshold for screening of puerperal sepsis may not be the solution. However, the choice of empiric treatment for puerperal sepsis can be improved to follow the national guidance, which is designed to treat listeria along with more common bacterial causes in puerperal sepsis. The Royal College of Obstetricians and Gynaecologists (RCOG) has published a guideline on the management of sepsis in the puerperium (accredited by NICE guidelines) which includes guidance on empiric antimicrobials; cephalosporins were not part of the suggested regimens and a combination of clindamycin with either piperacillin/tazobactam or a carbapenem was recommended to provide a broad cover for severe sepsis [10].
The study suggests a disproportionally high representation of Asian and Afro-Caribbean women with listeriosis in England, as highlighted in the literature [5]. Studies into better understanding of the ethnicities and dietary characteristics may point towards those at high risk of the disease to implement strategies at preventing pregnancy-associated listeriosis. This will also provide further valuable information on how to effectively tailor communication strategies, with the help of public health specialists.

There are limitations in this study. Although the data collection in the neonIN database is prospective, participants also gathered additional information retrospectively which resulted in some data being incomplete such as maternal ethnicity. This acknowledged, Afro-Caribbean women remained over-represented in our sample when compared to the national average in England. As a consequence of the data being derived from an on-going survey, the follow-up period of the children was not homogenous. In addition, this study is limited to the units participating in the neonIN surveillance database. However, we believe that the neonIN data are representative of the national neonatal listeriosis as is the case for group B streptococcus in a previous study [3]. A prospective national epidemiological study, such as a British Paediatric Surveillance Unit (BPSU) study could offer a more complete and unbiased perspective.

### Tables

**Table 1: Maternal Results**

<table>
<thead>
<tr>
<th>Case</th>
<th>Maternal Age</th>
<th>Ethnicity</th>
<th>Symptom/Sign(s)</th>
<th>Labour Complications</th>
<th>Mec.-stained Liquor</th>
<th>Initial WCC (10^9/L)</th>
<th>Initial CRP (mg/L)</th>
<th>Source of +ve Culture</th>
<th>Diagnosis</th>
<th>Pre-delivery Antibiotic(s)</th>
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<tbody>
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<td>APH, suboptimal CTG</td>
<td>Yes</td>
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<td>94</td>
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<td>NP</td>
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<td>None</td>
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<td>30</td>
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<td>5</td>
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<td>8.1</td>
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<td>None</td>
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<td>6</td>
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<td>NP</td>
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<td>8.1</td>
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<td>21.3</td>
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</table>

NR, not recorded; ↓, reduced; abdo., abdominal; vag., vaginal; ROM, rupture of membrane; APH, antepartum haemorrhage; CTG, cardiotocography; Em. CS, emergency caesarean section; SVD, spontaneous vaginal delivery; Mc, meconium; NP, not performed; NI, not isolated; WCC, white cell count; CRP, C-reactive protein; +ve, positive;
<table>
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<tr>
<th>Case</th>
<th>Birth Weight (g)</th>
<th>Gestation (weeks)</th>
<th>5 min Apgar</th>
<th>Symptom/Sign(s)</th>
<th>Maximum Respiratory Support</th>
<th>Inotropic Support</th>
<th>Peak CRP (mg/L)</th>
<th>Diagnosis</th>
<th>Source of culture</th>
<th>Empirical Antibiotic(s)</th>
<th>Antibiotics Onset (hours post birth)</th>
<th>Length of Antibiotic(s) (days)</th>
<th>Neurological Outcome at Follow-up</th>
<th>Death within Neonatal Period</th>
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<td>IV</td>
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<td>Blood</td>
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<td>Resp. distress, lethargy, bradycardia, seizure</td>
<td>IV</td>
<td>Yes</td>
<td>87</td>
<td>Septicaemia, meningitis</td>
<td>Blood</td>
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<td>3 (until death)</td>
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<td>Resp. distress</td>
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<td>No</td>
<td>71</td>
<td>Septicaemia, Blood, bloody tap</td>
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<td>Benzylicillin, gentamicin</td>
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<td>Resp. distress, rash, bradycardia, hepatomegaly</td>
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<td>No</td>
<td>40</td>
<td>Septicaemia, Blood, superficial swab</td>
<td>*WCC505, 100% lymphocytes, no growth</td>
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<td>8</td>
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<td>NIV</td>
<td>No</td>
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<td>Septicaemia</td>
<td>NI</td>
<td>NP</td>
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<td>NR</td>
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<td>Pyrexia</td>
<td>None</td>
<td>No</td>
<td>13</td>
<td>Meningitis</td>
<td>CSF</td>
<td>*WCC768, 80% monocytes</td>
<td>Amoxicillin, cefotaxime</td>
<td>10 days</td>
<td>21</td>
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<td>6</td>
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<td>IV+HFOV</td>
<td>Yes</td>
<td>31</td>
<td>Septicaemia, pneumonia</td>
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<td>6 (until death)</td>
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<td>Stool</td>
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<td>Blood</td>
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<td>100</td>
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<td>Blood</td>
<td>NP</td>
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<td>21</td>
<td>NR</td>
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<td>Resp. distress &amp; rash</td>
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<td>Yes</td>
<td>208</td>
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<td>Blood</td>
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<td>301</td>
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</table>

Resp. distress, respiratory distress; IV, invasive ventilation; NIV, non-invasive ventilation; HFOV, high-frequency oscillatory ventilation; NO, nitric oxide; NR, not recorded; CRP, C-reactive protein; CSF, cerebrospinal fluid; NI, not isolated; LP, lumbar puncture; NP, not performed; NAD, no abnormality detected; *WCC, white cell count per mm³. # cases 10 and 12 are probable cases of neonatal listeriosis; NA, not applicable; Dev., developmental.
Contributors Statement

Dr Stefania Vergnano designed and conducted the study, including patient recruitment. Dr Shari Sapuan conducted the data analysis and prepared the manuscript draft with important intellectual input from Dr Stefania Vergnano and Dr Paul Heath. All authors approved the final manuscript. Most authors were involved in the data collection. NeonIN provided statistical support in analysing the data with input from Dr Stefania Vergnano and Dr Christina Kortsalioudaki. Dr Shari Sapuan and Dr Stefania Vergnano had complete access to the study data.

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Conflict of interest

None

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References


Neonatal Listeriosis in the UK: A 10-year Review

Highlights

• Despite its rarity and the prompt and appropriate use of antibiotics neonatal listeriosis has a high case-fatality rate

• There is room for improvement in the adherence to the national guidance in the choice of empiric antibiotics for puerperal sepsis, which also targets listeriosis

• A better understanding of dietary characteristics based on maternal ethnicities may point towards those at higher risk to implement strategies into preventing pregnancy-associated listeriosis suggested by the disproportionally high representation of Asian and Afro-Caribbean women with listeriosis