

# **Management of suspected paediatric meningitis: a multicentre prospective cohort study**

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## **ABSTRACT**

**Objective:** To quantify delays during management of children with suspected meningitis.

**Design:** Multicentre prospective cohort study

**Setting:** Three UK tertiary paediatric centres; June 2011-June 2012

**Patients:** 388 children aged <16 years hospitalised with suspected meningitis or undergoing lumbar puncture (LP) during sepsis evaluation.

**Main outcome measures:** Time of pre-hospital and in-hospital assessments, LP, antibiotic treatment and discharge; types of pre-hospital medical assessment and microbiological results. Data collected from hospital records and parental interview.

**Results:** 220/388 (57%) children were seen by a medical professional pre-hospitalisation (143 by a GP). Median times from initial hospital assessment to LP and antibiotic administration were 4.8 hours and 3.1 hours respectively; 62% of children had their LP after antibiotic treatment. Median time to LP was shorter for children aged <3 months (3.0 hours) than those aged 3-23 months (6.2 hours,  $p<0.001$ ) or age  $\geq 2$  years (20.3 hours,  $p<0.001$ ). In meningitis of unknown cause, CSF PCR was performed for meningococcus in 7%, pneumococcus in 10% and enterovirus in 76%. When no pathogen was identified, hospital stay was longer if LP was performed after antibiotics (median 12.5 days vs. 5.0 days,  $p=0.037$ ).

**Conclusions:** Most children had LP after antibiotics were administered, reducing yield from CSF culture, and PCRs were under-used despite national recommendations. These deficiencies reduce the ability to exclude bacterial meningitis, increasing unnecessary hospital stay and antibiotic treatment.

## **WHAT THIS PAPER ADDS**

### **What is already known on this subject**

- Since the widespread introduction of conjugate vaccines, most childhood meningitis in the UK is caused by viruses.
- Delayed antibiotic treatment is associated with increased mortality and morbidity from bacterial meningitis.
- Inadequate investigation causes difficulty in excluding bacterial meningitis, which may lead to unnecessary admission and antibiotic treatment.

### **What this study adds**

- Median time from assessment to antibiotic treatment exceeded 3 hours, and most children had their LP after antibiotics were given.
- There was significant under-utilisation of blood and cerebrospinal fluid PCRs, likely because of inadequate laboratory infrastructure to deliver rapid results.
- Delayed or incomplete investigation of children with meningitis was associated with increased duration of hospital stay.

## **INTRODUCTION**

The incidence of bacterial meningitis in children has significantly decreased in developed countries with the widespread use of conjugate vaccines against the major bacterial pathogens.[1] Acute bacterial meningitis causes 4-19% of childhood meningitis in this setting,[2–5] with high risk of death and neurological sequelae.[6–9] Most meningitis is due to viral pathogens, for which long-term outcomes are less well described.

In large European studies of adults with bacterial meningitis, risk of death or lasting disability increases by 10-30% per hour of treatment delay.[6,10,11] Data on mortality is limited in children, but one US study in paediatric intensive care unit (PICU) patients with sepsis reported four-fold increased odds of mortality for antibiotic delay greater than 3 hours from sepsis recognition.[12] In children who survive bacterial meningitis, delaying antibiotic treatment over 24 hours from symptom onset is associated with persistent neurological sequelae.[8] UK guidelines therefore recommend administering parenteral antibiotics without delay for children with suspected bacterial meningitis,[13] and within one hour for children with high risk of sepsis.[14]

Incomplete microbiological investigation of children with meningitis decreases the likelihood of identifying a pathogen. Although most childhood meningitis in the UK is now caused by viruses, failure to confidently exclude bacterial disease may lead to unnecessary hospitalisation and antibiotic treatment.[5] When lumbar puncture (LP) is delayed until after antibiotic initiation, diagnostic yield from cerebrospinal fluid (CSF) culture rapidly decreases, increasing the uncertainty of aetiology.[15,16]

Polymerase chain reaction (PCR) tests have significantly improved identification of pathogens in meningitis, and remain positive for longer after antibiotic administration than culture.[17–19] In the UK, whole blood meningococcal PCR is recommended in children with suspected meningococcal disease, and CSF PCR for *N. meningitidis* and *S. pneumoniae* if bacterial cultures and other initial investigations are negative.[13] Routine CSF PCR testing for enterovirus (EV), the commonest viral cause of meningitis, reduces antibiotic usage and hospital stay.[20–22] However, it is unknown how often these tests are used in routine management of suspected meningitis in different UK hospitals.

In this prospective cohort study, we quantified delays occurring throughout the management of children with suspected meningitis, before and during hospitalisation.

## **MATERIALS AND METHODS**

Children were included if they were <16 years of age and admitted to hospital with suspected meningitis or having an LP as part of a septic screen. Each child was followed up until discharge, and data collected during hospital admission. The study population, data collection and definition of meningitis have been described previously.[5] Pre-admission review was defined as face-to-face or telephone assessment by a healthcare professional pre-hospitalisation. An emergency department (ED) visit was regarded as a pre-admission review if the child was discharged, but not if it was part of the visit resulting in admission. Where time of LP was not documented, time of CSF receipt in the laboratory was used. Time to hospital was the interval between pre-admission review and initial hospital assessment. Times

to LP and time to antibiotic initiation were the intervals from initial assessment to these events.

Non-normally distributed continuous variables were compared with the Mann-Whitney U test (two-tailed). Categorical variables were compared with Pearson's  $\chi^2$  test (two-tailed), with Fisher's exact test if any expected values were  $<5$ . Linear regression was used to investigate relationships between continuous variables. A *p*-value of  $<0.05$  was defined as statistically significant. Where times of events were not documented in hours, analyses of time intervals were done in days. Where dates and times were unknown, participants were excluded from that analysis. Analyses were repeated excluding cases where time of LP and CSF processing were the same to account for cases where CSF receipt time was documented instead of LP time, to confirm validity of findings. Analyses were performed using Stata (v11.0).

Patients were not involved in study design. This study was approved by the Oxfordshire B Research Ethics Committee (Ref: 11/H0605/11) and informed consent obtained from all parents/caregivers.

## **RESULTS**

### **Study population**

A total of 388 children were included (Figure 1), of which 70 (18%) had meningitis. Median age was 2 months (range 0 days to 15.7 years). Aetiology and clinical features have been described.[5] Mean follow up was 6.8 days ( $n=386/388$ ).

### **Pre-admission review**

Pre-admission reviews occurred for 220/388 (57%) children. Of these, 144/220 (65%) were seen by one healthcare professional, and 76/220 (35%) by two or more. General practitioners (GPs) performed most pre-admission reviews (Figure 2); 142/388 (37%) of all children were reviewed by a GP at least once. Median time between pre-admission review and hospital assessment was 1.8 hours (interquartile range [IQR] 1.1-3.0). Children first reviewed by GPs were more likely to have meningitis than those initially presenting to other healthcare professionals ( $p=0.006$ ), and less likely to be hospitalised on the same day ( $p=0.029$ ) (Supplementary Table 1). There was no association between number of preadmission reviews and diagnosis of meningitis (Mann-Whitney  $p=0.724$ ), length of stay ( $p=0.459$ ) or duration of antibiotics ( $p=0.485$ ).

## **Investigations**

The median interval between initial assessment and LP was 4.8 hours (IQR 2.1-14.5,  $n=219$ ). Excluding cases where CSF processing time was a proxy for LP time, this interval was 3.3 hours (IQR 2.0-9.7). There were 83/388 children who were recorded as having an LP intentionally postponed (Table), the majority (57/83, 69%) for contraindications specified by UK guidelines.[13] Median time to LP for children who did not have their LP intentionally deferred was 3.0 hours (IQR 1.9-6.5 hours).

**Table: Reasons given for intentionally deferring lumbar puncture**

<b>Indication*</b>	<b>Number of children (%)</b>
<b>Indication specified by UK National Institute for Health and Care Excellence (NICE) guideline [13]</b>	
After convulsions until stabilised	15 (18)
Cardiorespiratory instability (including shock)	14 (17)
Signs suggesting raised intracranial pressure	13 (16)
Respiratory insufficiency	12 (14)
Abnormal coagulation and/or platelet count	7 (8)
Abnormal CT scan**	2 (2)
<b>Other Indications</b>	
No indication at admission	9 (11)
Failed initially	6 (7)
Parental refusal	2 (2)
High fever	1 (1)
Reason not given	8

\*Some children had >1 indication for deferring LP. In total, 89 indications were cited for 83 children in whom LP was intentionally deferred; \*\*CT: computerised tomography

Median time from initial assessment to LP was significantly shorter for children aged <3 months, compared with age 3-23 months ( $p<0.001$ ) and age  $\geq 2$  years ( $p<0.001$ ) (Supplementary Table 2). This remained true when considering all children with time to LP recorded in days, or excluding those where LP time and CSF processing time was identical (for  $\geq 2$  years), or excluding children who had their LP intentionally deferred. Time to LP did not differ between children with and without meningitis ( $p=0.942$  in hours,  $p=0.905$  in days). Children initially admitted to PICU experienced longer times to LP than children initially admitted to the ward (median 20.5 hours vs. 3.5 hours,  $p<0.001$ ). LP was intentionally deferred for 34/47 (72%) of children initially admitted to PICU, compared with 42/252 (17%) children initially admitted to the ward ( $p<0.001$ ). Excluding children initially admitted to PICU, delays to LP remained longer for older children (2.8 hours aged <3 months vs. 4.2 hours aged 3-23 months [ $p<0.001$ ] vs. 15.2 hours aged  $\geq 2$  years [ $p<0.001$  compared with <3 months]).



There were 23/388 (6%) children with fever and petechial/purpuric rash, all aged  $\geq 1$  month. Where data were available, 19/22 (86%) did not have blood meningococcal PCR. Six had meningitis (including 1 child with blood culture positive for *N. meningitidis*), 6 were diagnosed with other specific diseases, and 7 as non-specific infections. In 29 children with meningitis of unknown cause, CSF PCR was performed for meningococcus in 2 (7%), pneumococcus in 3 (10%), enterovirus in 22 (76%), and parechovirus in 2 (7%) (Supplementary Table 3).

### **Antibiotic Administration**

Median time from initial assessment to antibiotics was 3.1 hours (IQR 1.8-5.5) (n=221). In cases of bacterial meningitis, median time to antibiotics was 4.5 hours (IQR 2.9-12.4, n=5). Mean time to antibiotic treatment was 6.4 hours for cases of meningitis (n=38), and 10.1 hours in bacterial meningitis (n=5). Children initially admitted to PICU experienced shorter time to antibiotic administration than children initially admitted to the ward (median 1.4 hours vs. 3.2 hours,  $p=0.046$ ). This remained true when analysing all children with time to antibiotics recorded in days ( $p<0.001$ ). Time from initial assessment to antibiotics was not significantly different between age groups, or for children with meningitis compared to those without (Supplementary Table 4). Seventy-seven children aged  $<3$  months had fever  $\geq 38^{\circ}\text{C}$ , and 16 (21%) received antibiotics within 1 hour of assessment as recommended by NICE guidelines for febrile children in this age group (median time 2.8 hours).[14]

Among 250 children who had times to both LP and antibiotics documented, 154 (62%) had their LP after antibiotic administration, with a median interval of 6.0 hours (IQR 1.0-15.2, n=87). LP was more likely to be performed before antibiotic

administration for children age <3 months compared with age 3-23 months (69/132 [52%] vs. 18/57 [32%],  $p=0.009$ ), or age  $\geq 2$  years (69/132 [52%] vs. 3/29 [10%],  $p<0.001$ ). Excluding cases where LP and CSF processing times were identical, 53% still had their LP after first dose of antibiotics and the median time from antibiotics to LP was 5.2 hours (IQR 1.3-10.3). In this additional analysis 56% of children <3 months had LP before antibiotics, compared with 50% aged 3-23 months ( $p=0.672$ ) and 17% aged  $\geq 2$  years ( $p=0.015$ ). All children admitted to PICU had their LP after antibiotics were started. Children with meningitis of unknown cause who received antibiotics before their LP had a longer length of stay (median 5.0 days if having LP before antibiotics vs. 12.5 days if having LP after antibiotics,  $p=0.037$ ,  $n=17$ ), and a longer duration of antibiotics (median 8.5 days vs 15.5 days,  $p=0.103$ ) than those who underwent LP before receiving antibiotics. Analyses excluding children with identical LP and CSF processing times were similar (5.0 vs. 26.0 days for length of stay,  $p=0.033$  and 39.0 vs. 13.0 days for antibiotic duration,  $p=0.118$ ).

Of 13 children with bacterial meningitis, 12 were treated with empiric antibiotics including those recommended by NICE guidelines. Empiric antibiotics recommended by NICE were appropriate for isolated pathogens in all children. Where initial antibiotic choice was recorded, this included ceftriaxone/cefotaxime and amoxicillin for 84/107 (79%) of children aged <1 month, and ceftriaxone/cefotaxime for 227/281 (81%) of children aged  $\geq 1$  month (Supplementary Table 5).

## **DISCUSSION**

Improvement is needed throughout the management of children with suspected meningitis. The median time to antibiotic administration was 3.1 hours, and

adherence to UK guidelines on empirical antibiotics was suboptimal. There are no current data on the effect of delayed treatment on mortality in paediatric bacterial meningitis, but studies in adults report increased mortality with each hour until antibiotic administration,[6,10,11] while in children treatment delay correlates with increased risk of long term sequelae.[8] The time to antibiotics observed in this study is therefore concerning. Also, 62% of children had their LP after antibiotic initiation, reducing yield from bacterial culture.[15,16] Excluding children for whom LP was initially contraindicated, median time to LP was 3.0 hours, and longer for children  $\geq 3$  months of age. When no pathogen was identified (41% of the cohort), delaying LP until after antibiotics was associated with significantly increased hospital stay. This was likely due to failure to confidently exclude bacterial pathogens, even though most of these children probably had viral meningitis. There was also notable under-utilisation of routinely available bacterial and viral PCRs, which remain positive for longer after antibiotic administration than culture, and may support earlier discontinuation of treatment and discharge from hospital.[17–21] These deficiencies increase healthcare costs, patient morbidity, and contribute to increased risk of antimicrobial resistance.

This is the first UK study to quantify delays throughout the care pathway of children of all ages with suspected meningitis. Parent interview was used to corroborate data from medical records. In terms of limitations, our sample included 70 cases of meningitis, so lacked the power to detect small differences between different meningitis aetiologies. Some children had incomplete data recorded, so wherever possible delays were analysed in both hours and days – with the same conclusions in all cases. Where time to LP was not documented in the medical notes, it was

determined from CSF processing time, which would have been shortly after the procedure. Analyses were repeated after removing these cases, with the same conclusions. Our study occurred in three large, urban teaching hospitals in southern England, and may not reflect smaller hospitals or other parts of the UK. All centres had a PICU, skewing the study population towards more severe disease, although only a minority of patients (16%) required PICU.[5]

Our findings are consistent with existing meningitis literature. Before hospital admission, 37% of children were seen by a GP, similar to 32% in a study of infants aged <90 days with bacterial meningitis.[23] Median time to LP was 4.8 hours, compared with 5.5-5.9 hours reported in British and French adults with bacterial meningitis.[24,25] LP was performed after antibiotic initiation in 62% of children, similar to the 59-77% described in other British paediatric studies,[22,23] and 61% in Swedish adults with suspected meningitis.[10] Median time to antibiotics (3.1 hours) was similar to 3.0 hours reported in US children and adults with suspected meningitis.[26] Median time to antibiotics for children admitted to PICU (1.4 hours) was similar to 1.9 hours reported for sepsis in a Canadian PICU.[27] Mean time to antibiotics for cases of meningitis was 6.4 hours, compared to 4.0 hours in another British study of paediatric meningitis.[22] In studies of paediatric bacterial meningitis, reported mean times to antibiotics are 1.2-2.0 hours,[6,23,28] compared to 10.1 hours for this subgroup in our study, though our figure was based on few cases (n=5).

Paediatric meningitis is difficult to distinguish from other childhood infections, particularly early in the illness.[29–33] Less than half of GPs trainees undertake a

paediatric placement, and initiatives to address this should increase exposure to children with meningitis.[34] Irrespective of paediatric placements, all GPs should receive training to recognise serious bacterial disease in children in primary care, using guidelines from NICE and the Meningitis Research Foundation.[14,35] Our study also highlights the need to improve recognition and investigation of meningitis in children aged  $\geq 3$  months. UK guidelines recommend LP for all febrile infants aged  $< 1$  month, and all febrile infants aged 1-3 months who appear unwell or have abnormal WBC count,[14] whereas in older children the decision is based on clinical assessment.[13] In our study, the rate of meningitis in infants aged  $< 3$  months undergoing LP (16%) was similar to the rate in children aged  $\geq 3$  months undergoing LP (19%).[5] However, the older group experienced significantly longer time to LP, probably because of time taken for evaluation. Delays may also occur due to diagnostic difficulty given the relatively rarity of meningitis in older children, and poor cooperation with LP, which may result in the child needing sedation.

There was significant under-utilisation of bacterial and viral PCRs, which are recommended in UK guidelines.[13] When no pathogen was identified, delaying LP until after antibiotics resulted in increased hospital stay. Although most of these children probably had viral meningitis, failure to confidently exclude bacterial pathogens likely led to unnecessary prolonged hospitalisation and treatment. Negative bacterial PCR does not rule out bacterial meningitis, but such tests are highly sensitive and specific, so useful for ruling in this disease.[17–19] For viral meningitis there is strong evidence that detection of enterovirus supports appropriate discontinuation of antibiotics and earlier discharge.[20–22] Human parechovirus is also increasingly recognised as an important CNS pathogen, but testing is

uncommon.[36] PCR is likely under-utilised because of time taken to obtain results, by which time treatment decisions have been made. More rapidly available PCR would require investment in laboratory infrastructure, but would support earlier hospital discharge and discontinuation of unnecessary treatment.[20,21] Under-estimation of true disease rates also makes it difficult to assess the impact and cost-effectiveness of interventions such as vaccine programmes.

This study highlights the importance of appropriate investigation, early LP (in absence of contraindications), and urgent antibiotic treatment for children with suspected meningitis. Our findings regarding time to antibiotic therapy and LP are similar to a number of other studies, suggesting that this is a common difficulty in managing paediatric meningitis.[22–27] However, there is good evidence from other patient groups that packages of targeted interventions can reduce time to antibiotic treatment. Strategies successfully used in suspected paediatric febrile neutropenia could apply to febrile children aged <3 months, including pre-application of topical anaesthetic at triage, and allocation of trolleys containing LP equipment and antibiotics.[37] Referral by GPs as suspected meningitis could similarly prompt interventions at triage. Investment in staffing and training would support early and effective clinical assessment. There is also a need to identify novel clinical and laboratory parameters, such as CSF cytokine arrays,[38] that distinguish serious bacterial infections, especially in those children treated with antibiotics prior to LP. Development of new techniques, such as those involving host gene expression,[39] into cheap and rapid tests, might be an adjunct to clinical assessment.

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## **Competing interests**

All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). SK has received support to attend scientific meetings from GlaxoSmithKline. DFK has received research funding from GlaxoSmithKline and received support from GlaxoSmithKline and Sanofi-Pasteur to attend scientific meetings. PTH received a grant from Pfizer towards the submitted work. He is also an investigator for clinical trials done on behalf of St George's, University of London, UK, sponsored by vaccine manufacturers, and has been a consultant to Novartis and Pfizer on Group B Streptococcus vaccines, but received no payments for this. SN has acted as a consultant to Novartis Vaccines on serogroup B meningococcal vaccine and has received honoraria from Novartis and Pfizer for consultancy work paid into an educational and administrative fund. MS has received grants from Pfizer outside of the submitted work. AJP has received grants from Novartis, Pfizer, and Okairos, outside of the submitted work. His department received unrestricted educational

grants from Pfizer, GSK and Astra Zeneca in July 2016 for a course on Infection and Immunity in Children. AJP has previously conducted clinical trials of meningococcal meningitis vaccines on behalf of the University of Oxford, funded by vaccine manufacturers, but no longer does so and he received no personal payments from them. AJP is chair of the UK Department of Health's Joint Committee on Vaccines and Immunisation, chair of the European Medicine Agency's Scientific Advisory Group on Vaccines, and a member of the World Health Organization's SAGE. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health, the EMA, or the World Health Organisation. Other authors have no conflicts of interest to declare.

### **Contributorship Statement**

RR analysed the data, and wrote the initial draft of the manuscript. LW was responsible for study design and data collection. SK was responsible for data collection. DKF, PTH, SN, AJP and MS conceived and designed the study. All authors critically appraised the manuscript and approved the final version.

### **Transparency declaration**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.



**Data sharing statement**

Full dataset is available on request from the corresponding author. Consent was not obtained for data sharing but the presented data are anonymised and the risk of identification is low.

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