National Audit of Meningitis Management (NAMM) based on the 2016 Joint specialist UK guidelines on the management of meningitis in adults.

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BIA British Infection Association

NITCAR National Infection Trainee Collaborative for Audit and Research

Meningitis Research Foundation

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Abbreviations

BIA	British Infection Association
CRF	Case Record Form
CSF	Cerebrospinal fluid
ICD10	10th International Classification of Diseases
PCR	Polymerase Chain Reaction
SMI	Standards for microbiology investigations
WCC	White cell count

Background

Despite a reduction in the incidence of bacterial meningitis it continues to be a devastating disease with a mortality of up to 30%[1,2]. The decreasing incidence means clinicians may not see many cases and will have to be increasingly vigilant to recognise and treat promptly. To that end an updated, user friendly, national guideline was published in April 2016[3].

Previous publications have highlighted that former meningitis guidelines have not necessarily been well adhered to in the UK. In particular investigations including use of polymerase chain reaction and HIV testing were poorly performed[4,5]. However, other publications from outside the UK have shown improvements in outcomes following guideline publication/implementation[1,6,7].

Inappropriate neuroimaging and delays in lumbar puncture have been highlighted as issues in the management of patients with suspected meningitis in the UK[8,9]. Inappropriate neuroimaging, with subsequent delays in antibiotics, has been associated with worse outcomes[10].

Pilot audits of the management of meningitis in adults were carried out in the Northwest of England (Royal Liverpool University hospital, Aintree University hospital, Liverpool, Arrowe Park hospital, Wirral and at St Helens and Knowsley NHS trust, Whiston) and at University College Hospital, London. These audits aimed to test the audit tool that was published with the national UK meningitis guidelines as well as possible inclusion criteria and search strategies to identify potential participants. The data from these audits were presented at local audit meetings and national conferences (British Infection Association Spring Conference 2018).

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All local audits had common themes and identified a need to define the study population and hone the audit tool. The study population for this audit will be all patients with meningitis as defined in the definitions of this protocol.

In addition to the 2016 joint specialties guidelines, there have been changes in the way laboratories are managed in the UK with increased centralisation. This has the possibility of impacting on turnaround times and prompt management of patients with meningitis. The UK Standards for Microbiological Investigations (SMI) B27 – Investigation of cerebrospinal fluid (CSF) – states that the microscopy of a CSF should be done within 2 hours of lumbar puncture in order to prevent cell degradation[11].

Aims and objectives

The aims of this audit are:

1) To assess clinical adherence to the new, current guidelines
    a. To assess if non-adherence to guidelines has any impact on clinical outcome
2) To evaluate if laboratories are meeting the turnarounds times as stated in the Standards for Microbiological investigations

The audit will primarily look at all patients with meningitis, but sub-group analyses will be performed on those with proven bacterial meningitis.

The objectives are:

1) To identify areas of poor performance with regard to the standards identified in the national guidelines and SMI
2) To suggest ways in which the performance might be improved
3) To feedback to individual sites regarding their (and national) performance
4) To re-audit after feedback to see if any improvement
5) To provide data to input to revisions of the guidelines in due course

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6) To publish national data on the clinical and laboratory management of meningitis in the UK

Sample size calculation

Pilot data shows approximately 20 cases of meningitis a year in a district general hospital. 25-30% were bacterial. Previous studies have shown bacterial meningitis to be approximately 20% of all meningitis cases[9]. We will ask each site to collect data on all patients with meningitis seen in 2017. This will allow for seasonal variation and give the full spectrum of disease. If 40 sites contribute this should give c. 800 patients and 160-240 with bacterial disease.

Audit Design and methods

Audit subjects

All patients diagnosed with meningitis (see definitions) in 2017, should be recruited from every site[1]. Patients should be identified by using either coding data or laboratory data or a combination of both.

Inclusion criteria:

Adult patients (>= 16 years) with meningitis.

Meningitis is defined as:

Symptoms and signs of meningitis (as determined by the clinical team) with a CSF WCC >4 $x10^6$ cells/L (regardless of whether a pathogen is identified or not)

OR

in the case of bacterial meningitis symptoms and signs of meningitis with a significant pathogen in the CSF (culture or PCR) or blood regardless of CSF leukocyte count.

[1] If this number proves to be prohibitively large for any site this may be reduced to 2 cases a month for the year 2017 in discussion with the NAMM investigators

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Suspected bacterial meningitis is defined as:

Any patient who fulfils the criteria for meningitis and is being treated with a course of antibiotics (5 or more days) for bacterial meningitis.

Methods of patient identification that can be used:

1) ICD10 codes that can be used are:

A32.1+ Listeria meningitis/meningoencephalitis
A39.0+ Meningococcal Meningitis
A87 Viral Meningitis
A87.0+ Enteroviral meningitis
A87.8 Other viral meningitis
A87.9 Viral meningitis, unspecified
B00.3+ Herpesviral meningitis
B01.0+ Varicella meningitis
B02.1+ Zoster meningitis
G02.0 Meningitis in viral diseases classified elsewhere
B26.1+ Mumps meningitis
G00 Bacterial meningitis, not elsewhere classified
G00.0 Haemophilus meningitis
G00.1 Pneumococcal meningitis
G00.2 Streptococcal meningitis
G00.8 Other bacterial meningitis
G00.9 Bacterial Meningitis, unspecified
G01 Meningitis in bacterial diseases classified elsewhere
G02 Meningitis in other infectious and parasitic diseases classified elsewhere
G03 Meningitis due to other and unspecified causes

2) Additionally/alternatively laboratory information management systems (LIMS) can be interrogated for CSF samples with leukocyte count >4 $x10^6$ cells/L received in 2017.
3) LIMS can also be interrogated for target organisms in CSF/blood cultures/PCR (e.g. *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* and *Listeria monocytogenes, Enteroviruses, Herpes simplex virus, Varicella zoster virus*)

Exclusion criteria

- Fungal meningitis
- Tuberculous meningitis
- Nosocomial meningitis (device related or within 30 days of neurosurgery).
- Patients 15 years or less

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- Encephalitis[2][3]

For pragmatic reasons pre-hospital management and follow up will not be assessed.

Audit Sites

Participating sites will be identified through the NITCAR network, the UK Meningitis network, the BIA and through personal networking. Additionally, as the guidelines are a joint initiative between acute care, intensive care and neurologists – co-authors of the guidelines will be encouraged to distribute amongst their own networks as well.

Each site will have a nominated consultant lead. Each site can also have a trainee and medical student investigator as well. If none of the investigators have access to the laboratory information system to assess the timing of the CSF microscopy there should also be a microbiology lead. All contributing investigators, which will include a named consultant and trainee at each site plus a medical student if relevant, will be acknowledged in any reports or publications arising from the audit.

Data collection and analysis

All data will be collected on e-CRF. Each site will have a site code and participants analysed will be numbered according to this code followed by sequential numbers e.g. LIV001, LIV002. CRFs will be anonymised with each centre holding a copy of an identification sheet to correspond each patient to their hospital identifiers. This data will not leave the hospital site. Central data checking of the whole anonymised database will take place at University of Liverpool. The data will be analysed by the co-ordinating team.

[2] Altered consciousness for >24 h (including lethargy, irritability, or a change in personality) with **no other cause found** and two or more of the following signs: fever or history of fever (≥38°C) during the current illness; seizures or focal neurological signs (with evidence of brain parenchyma involvement); CSF pleocytosis (>4 × 10^6 cells per L); EEG suggesting encephalitis; and neuroimaging suggestive of encephalitis

[3] Often encephalitis and bacterial meningitis can be difficult to distinguish clinically initially. Any uncertainty should be referred to the lead investigator and if there is any doubt it will be discussed within the lead investigating team to determine what the diagnostic category should be.

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Electronic CRFs will be completed onsite by inputting data into a password protected central web-based database (REDcap™). This will be hosted on a secure server at the University of Liverpool. The CRF will be based on a modified version of the audit tool that comes with the guidelines.

Descriptive statistics will be used to summarize data. Categorical data will be analysed using Chi squared or Fisher's exact test. Continuous data will be analysed using t-tests or Mann Whitney U depending on the distribution of the data. Regression analysis will be used to identify any potential risk factors associated with poor outcomes.

Standards

The standards used in this audit will be taken from the 'UK Joint Specialists Societies guideline on the diagnosis and management of meningitis and meningococcal sepsis in immunocompetent adults'[3], and the UK National Standards in microbiological investigations on the processing of cerebrospinal fluid (B27)[11]. The case record form (CRF) will be adapted from the existing audit tool that comes with the guidelines. The audit tool is being piloted in a number of sites in the Northwest of England in order to create the CRF for the national audit. The standards to be addressed are as follows:

Immediate management

1. A decision regarding the need for senior review and/or intensive care admission should be made within the first hour (AR).
2. The patient's conscious level should be documented using the Glasgow coma scale (2C).
3. Blood cultures should be taken as soon as possible and within 1 h of arrival at hospital (AR)
4. LP should be performed within 1 h of arrival at hospital provided that it is safe to do so (1D)
5. Antibiotic treatment should be commenced immediately after the LP has been performed, and within the first hour (1B)
6. If the LP cannot be performed within 1 h antibiotic treatment should be commenced immediately after blood cultures have been taken and LP performed as soon as possible after that (1B)
7. Patients with meningitis and meningococcal sepsis should be cared for with the input of an infection specialist such as a microbiologist or a physician with training in infectious diseases and/or microbiology (AR)
8. Patients should not have neuroimaging before their LP unless there is a clinical indication suggestive of brain shift

Investigations

9. Blood culture should be sent
10. Pneumococcal and Meningococcal PCR should be sent
11. CSF opening pressure should be documented
12. CSF glucose with concurrent plasma glucose should be sent
13. CSF protein should be sent
14. Microscopy of the CSF should take place within 2 hours of the lumbar puncture (SMI)
15. CSF for pneumococcal and meningococcal PCR should be sent in all cases of suspected bacterial meningitis
16. A swab of the posterior nasopharyngeal wall should be obtained as soon as possible, and sent for meningococcal culture, in all cases of suspected meningococcal meningitis/sepsis

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17. All patients with meningitis should have an HIV test (1C)

Treatment

18. All patients with suspected meningitis or meningococcal sepsis should be given 2 g ceftriaxone intravenously (IV) every 12-h or 2 g cefotaxime IV every 6-8h [1B]
19. If the patient has, within the last 6 months, been to a country where penicillin resistant pneumococci are prevalent, IV vancomycin 15e20 mg/kg should be added 12-hourly (or 600 mg rifampicin 12-hourly IV or orally) [1C]
20. Those aged 60 or over should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].
21. Immunocompromised patients (including diabetics and those with a history of alcohol misuse) should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].
22. If there is a clear history of anaphylaxis to penicillins or cephalosporins give IV chloramphenicol 25 mg/kg 6-hourly [1C]
23. If Streptococcus pneumoniae is identified continue with IV benzylpenicillin 2.4 g 4 hourly, 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
24. If the pneumococcus is penicillin resistant (MIC > 0.06) but cephalosporin sensitive then cefotaxime or ceftriaxone should be continued (AR)
25. If the pneumococcus is both penicillin and cephalosporin resistant, continue using 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly plus vancomycin 15-20 mg/kg IV 12-hourly plus 600 mg rifampicin IV/orally 12-hourly (AR).
26. For patients with confirmed pneumococcal meningitis who have recovered by day 10 treatment should be stopped (1C).
27. For patients with confirmed pneumococcal meningitis who have not recovered by day 10, 14 days treatment should be given (1C)
28. For patients with penicillin or cephalosporin resistant pneumococcal meningitis treatment should be continued for 14 days
29. If N. meningitidis is identified 2 g ceftriaxone IV 12 hourly, 2 g cefotaxime IV 6-hourly or 2.4 benzylpenicillin IV 4-hourly may be given as an alternative (AR)
30. If the patient is not treated with ceftriaxone, a single dose of 500 mg ciprofloxacin orally should also be given (1C)
31. For patients with confirmed meningococcal meningitis who have recovered by day 5 treatment can be stopped
32. If Listeria monocytogenes is identified Give 2 g ampicillin/amoxicillin IV 4-hourly (stop Ceftriaxone/ Cefotaxime) and continue for at least 21days (AR). Co-trimoxazole 10-20 mg/kg in four divided doses (of the trimethoprim component) or chloramphenicol 25 mg/kg 6 hourly are alternatives in cases of anaphylaxis to beta lactams (AR).
33. If H. influenzae is identified Continue 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly for 10 days (1D)
34. In patients with no identified pathogen who have recovered by day 10 treatment can be discontinued
35. 10 mg dexamethasone IV 6 hourly should be started on admission, either shortly before or simultaneously with antibiotics [1A].
36. If antibiotics have already been commenced 10 mg IV dexamethasone every 6 h should still be initiated, up until 12 h after the first dose of antibiotics (AR).
37. If pneumococcal meningitis is confirmed dexamethasone should be continued for 4 days [1C].

Critical Care

38. The following patients should be transferred to critical care (1B): a)Those with a rapidly evolving rash, b. Those with a GCS of 12 or less (or a drop of >2 points), c. Those requiring monitoring or specific organ support and d. Those with uncontrolled seizures

Notification

39. All cases of meningitis (regardless of aetiology) should be notified to the relevant public health authority (AR)

Patient outcome in terms of mortality will also be recorded.

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Audit timeline

Activity	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020
CRF and protocol development											
Hospital recruitment											
Data collection and local submission											
Data collated centrally, missing data chased and data analysis											
Result feedback and dissemination											
Individual sites to feedback locally and implement any quality improvement measures											
Re-audit - 2021											

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Patient consent

This audit does not require patient consent as we will be auditing against standards and all patient data will be anonymised before being centrally compiled.

Feedback, dissemination and publication

Feedback is an integral part of audit and as such various forms of feedback will be employed. The lead investigating team will feedback to all sites involved and provide the national data as benchmarking data. Each individual site will then be encouraged to feedback to their own sites in whichever way they deem useful. Examples of feedback would be:

- Grand Rounds
- Teaching sessions for medical staff
- Teaching sessions for nursing staff
- One to one feedback to clinical leads of key departments
- Development of local guidelines
- Use of technology assisted patient management e.g. incorporating prompts to electronic test ordering
- Use of a departmental 'champion'

Each site will be asked to document how they fed back the findings of their local data and the national data along with any changes made as a result of the audit. A re-audit will then be carried out and the different forms of feedback can then be assessed to see which might have been most successful in improving management.

Pooled results from the audit will be fed back to all participating hospitals. They will then be submitted for presentation at national and international conferences and for publication. Individual hospital details will remain anonymised when results are presented and they will not be identifiable.

Results of the audit will also be used to guide any revisions of the national guidelines.

Project management

This audit will be overseen by Dr Fiona McGill (trainee lead) and Prof. Rob Heyderman (consultant lead). It will be co-ordinated, analysed and written up by investigators in the named investigator section.

Investigators

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