NATIONAL MASTOIDITIS AUDIT

Lead organisations:	**British Association of Otology** (BSO) **British Association for Paediatric Otolaryngology** (BAPO)
In association with:	**INTEGRATE**, the UK ENT Trainee Research Network
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Local Principal Investigators:	INTEGRATE members BAPO and BSO Committee members (who manage acute mastoiditis in children as part of their routine practice)

Background

What is acute mastoiditis?

Acute mastoiditis (AM) in children is a serious and potentially life-threatening complication of acute otitis media (middle ear infection) caused by the spread of infection to the bone of the mastoid air-cell system. Its incidence is estimated to be between 1.2-4.2 per 100,000 per year (Claudia Balsamo et al Italian Journal of Pediatrics. 2008, 44, 71)**.** A tertiary referral NHS hospital in the UK covering a population of 1,000,000 would expect to admit approximately 12-42 such cases per year using this data. Acute mastoiditis is a disease of childhood. A large multicentre study found 28% to be in children less than 1 year of age, 38% 1-4, 21% 4-8, 8% 8-18, and 4% over 18 years old. This higher incidence in younger children reflects the peak ages for AOM.

Acute mastoiditis presents with otalgia and irritability in most children. Pyrexia is less common in those treated with antibiotics. Otorrhoea is present in only about 30%. Clinically a red or bulging tympanic membrane will often be seen. A normal drum is reported in a very variable proportion of cases, but certainly does not exclude the diagnosis, and is believed to result from resolution of the meso-tympanic infection following antibiotic treatment while the osteitis in the mastoid progresses ('masked mastoiditis'). Retro-auricular swelling is seen in about 80%, and retro-auricular erythema in 50-84% (less in previously treated children). Tenderness is typically sited over MacEwen's triangle (on palpation through the conchal bowl). Pinna protrusion is present in 2/3 of cases. Sagging of the posterior wall of the external auditory canal may result from sub-periosteal abscess formation.

How is acute mastoiditis managed and why is it important?

The standard management of uncomplicated AM that does not improve following 24 hours of intravenous antibiotic is to perform a cortical mastoidectomy (CM), with or without ventilation tube (grommet) insertion. A subperiosteal abscess presenting as a 'boggy' swelling behind a protruding ear is a relatively common intra-temporal complication of AM. The traditional management of subperiosteal abscess is to proceed directly to a CM with drainage of the abscess overlying the bone of the mastoid cortex. However, the evidence in support of more 'conservative' approaches is expanding, including incision & drainage (under general anaesthesia) and needle aspiration without CM. Postauricular needle aspiration (PANA) or incision & drainage (I&D) have been shown to be an effective treatment for subperiosteal abscess (SPA), avoiding the complications of CM (CSF leak, sigmoid sinus bleeding, and facial nerve injury, which is considered a particular risk in younger children) (Bakhos 2011, Bartov 2019). However, in most published studies PANA and I&D are combined with myringotomy or ventilation tube insertion to drain the middle ear, which would still necessitate a GA (Loh 2018). Notwithstanding this, the avoidance of CM has been shown to lead to reduced hospital stay in conservatively treated children (Bakhos 2011).

Published studies tend to be limited by a retrospective study design and lack of clarity regarding the exact nature of 'conservative' management of AM (antibiotics alone, antibiotics + myringotomy or ventilation tube) or AM with SPA (PANA alone, PANA + myringotomy or ventilation tube, I&D + myringotomy or ventilation tube). In addition, lack of detail about the rationale for the *selection* and *choice of 'type'* of conservative surgery make the results difficult to interrogate effectively, other than a broad comparison to management involving CM. In part, these difficulties are addressed by the current concerns about aerosol generating procedures (AGP) during the COVID-19 pandemic, where surgeons are being urged and professional bodies are providing guidance, to follow conservative management strategies.

Intracranial complications from AM develop in 6 to 17% of cases, and these may develop during hospitalisation *(Rea P, Ronan N. Acute otitis media. Scott Brown Otolaryngology 2018. Paediatric Volume 2. CRC Press)*. The classical intracranial complications of AM are meningitis, extradural abscess, subdural empyema, sigmoid sinus thrombosis, focal otitic encephalitis (cerebritis), brain abscess, and otitis hydrocephalus. Intracranial complications may require a craniotomy to drain an abscess. Significant focal neurological sequelae may be permanent and can be life-threatening.

Acute mastoiditis and COVID-19

Given that acute mastoiditis has been shown to result from viral infections of the upper respiratory tract, of which COVID-19 infection is a severe example, it is both plausible and likely that COVID-19 infection will lead to an increase in acute otitis media and subsequent acute mastoiditis. Early in the response of the medical community to the COVID-19 pandemic, CM was identified as an AGP. In light of this, guidance has been produced by relevant professional bodies [https://www.entuk.org/] and from individual experts aimed at shielding the surgeon from virus exposure, by either performing more conservative management (e.g. needle aspiration of subperiosteal abscess) or reducing the potential for the generation of aerosolised virus (e.g. incision & drainage of subperiosteal abscess with curettage of cortical mastoid bone under general anaesthesia, or the use of additional surgical drapes to 'capture' aerosolised virus during CM under general anaesthesia). Both approaches have merits and their existence reflects the lack of strong evidence of efficacy.

Why do children get acute mastoiditis?

Acute otitis media (AOM), the precursor to acute mastoiditis, is a common paediatric infection, with 75% of children estimated to suffer at least one episode. Microbiological, anatomical, and environmental factors combine with altered host defence mechanisms to predispose to infection. Genetic predisposition to recurrent AOM is being increasingly cited in the literature. AOM results from infection of the middle ear cleft. Both bacterial and viral infections are implicated. These infections may occur in isolation or combination.

What is the role of viruses in acute mastoiditis?

Clinically it is apparent that AOM is commonly associated with viral upper respiratory tract infections. As our ability to identify these improves, the role of viruses in the aetiology of AOM is becoming clearer. Increasing use of polymerase chain reaction assays for respiratory viruses suggests 60-90% of cases of AOM may be associated with viral infection *(Heikkinen T. The role of respiratory viruses in otitis media. Vaccine 2001; 19: S51-S55).* In one study a specific viral cause of upper respiratory tract infection was shown in 41% of children with AOM. The viruses most commonly associated with AOM vary between studies, but in decreasing frequency include*: respiratory syncytial virus (RSV), influenza A virus, parainfluenza viruses, human rhinovirus*, and *adenoviruses*. This heterogeneity is important when considering vaccination against viruses as a prophylactic measure. The mechanism by which they give rise to AOM is likely to vary between viruses. Viral material has been demonstrated in the middle ear aspirates of children with AOM in 48-71% of cases. The viral material may arrive either passively along the Eustachian tube along with other nasopharyngeal secretions, or may actively invade the middle ear cleft possibly by haematogenous spread. These alternative routes of entry are suggested by the wide variation in rates of isolation of specific viral strains in the middle ear during systemic infection, ranging from 4% to 74% of cases dependent upon the specific virus. If all arrived passively, similar rates of isolation would be expected. This implies some viruses may be actively invading the middle ear cleft, and may be contributing directly to mucosal inflammation. *Respiratory syncytial virus* invaded the middle ear most frequently. In contrast those arriving passively appear to cause AOM by virtue of their action on the Eustachian tube, on bacterial adherence, and on host immunity.

There is good clinical and animal evidence viral infection affects Eustachian tube function. At a cellular level there is release of multiple inflammatory mediators from cells within the nasopharynx. Ciliated epithelial cells numbers decline, mucus production increases in the Eustachian tube, and negative middle ear pressure results. This is likely to predispose to AOM. Alteration of host immunity has been documented after viral infections, increasing susceptibility to bacterial infections. Cell mediated immunity has been shown to be affected by *RSV* infection, and neutrophil function altered by influenza viruses. In a study of children with bronchiolitis caused by *RSV*, 62% developed AOM. *Bacteria* were isolated from the middle ear in all these children. The ability of bacteria to colonise and adhere to the nasopharyngeal epithelium appears to be increased by certain viral infections. Increased colonisation by pathogenic bacteria may predispose to AOM.

Viral and bacterial infection co-exist in the middle ear cleft in AOM in as many as two-thirds of cases where viruses have been identified. This is important as clinical studies show that children who have both viruses and bacteria in their middle ear are very much more likely to have a poor response to antibiotics when compared to those with bacteria only (33% versus 3% failure respectively, in one study). Why this should be is unclear, but may be related to the greater concentrations of inflammatory mediators in ears in which both bacteria and viruses are present. *(Rea P, Ronan N. Acute otitis media. Scott Brown Otolaryngology 2018. Paediatric Volume 2. CRC Press).*

Are some children more likely to get acute mastoiditis?

Genetic Factors: There is growing evidence that recurrent AOM is largely genetically determined. It is likely many genes are involved. There are numerous studies suggesting a familial association. A meta-analysis of risk factors has shown that when one family member had had AOM the risk increased for other family members (relative risk 2.63) *(Uhari M, Mantysarri K, Niemela M. A meta-analysis of the risk factors for acute otitis media. Clin Infect Dis 1996; 22(6): 1079-1083)*

Racial differences are well described with increases in American Indians, Eskimos, and Australian Aboriginals. However environmental factors, such as poor economic status, may contribute to the increased risks in these groups. The most powerful evidence comes from twin studies, in particular comparison of monozygotic and dizygotic twins in whom the occurrence of AOM was compared *(Casselbrant ML, Mandel EM. The genetics of otitis media. Current Allergy and Astma Reports 2001; 1: 353-357).*

Many immune related mechanisms, which are likely to have a genetic basis, have been proposed. Certain HLA classes have been shown to be significantly associated with increased risk of AOM. Maternal blood group A is reported to an independent risk factor (relative risk 2.82). Atopy has also been associated with increased risk of developing AOM.

Immune Factors: Our understanding of the immune response to AOM remains incomplete. However, a number of specific associations have been identified which suggest that certain defective or immature pathways may predispose to infection. Low levels of IgG2 subclasses have been reported in several studies to be more common in otitis prone children. Those with IgG2 deficiency were shown to be three times more likely to develop post ventilation tube insertion otorrhoea for example. Delayed maturation of anti-pneumococcal antibodies (IgG1 and IgG2 were studied) does appear to predispose to AOM. This may explain in part why children grow out of AOM as immunity matures. Defective complement-dependant opsonisation has been associated with recurrent AOM and diarrhoea in infancy. This is caused in some examples by low concentrations of mannose binding protein which acts as an opsonin. This appears to be a common defect with over 20% of children with recurrent AOM affected in some studies. This may be particularly important in infancy when the antibody repertoire is limited. Aberrant expression of critical cytokines such as tumour necrosis factor and interleukins, resulting in sub-optimal host defence, has been postulated as a cause for persistent infection. Expression of mucin genes, at least nine of which have been identified, may differ in those predisposed to AOM. Middle ear mucosa expresses specifically the MUC5B gene. Mucin genes regulate the production of mucin. Limited evidence is beginning to emerge that over-expression may alter the mucociliary transport system. A number of studies on children with HIV infection have yielded conflicting results. Advanced disease associated with low CD4 counts does seem to be associated with an increased incidence of AOM. *(Rea P, Ronan N. Acute otitis media. Scott Brown Otolaryngology 2018. Paediatric Volume 2. CRC Press).*

Audit standard

Has the UK management of acute mastoiditis changed in line with March 2020 BSO / ENTUK guidance on limiting the use of aerosol generating procedures during the COVID-19 pandemic?

Secondary questions:

1. What is the relative effectiveness of conservative and surgical management of acute mastoiditis?
2. Is COVID-19 infection identified in children undergoing treatment for acute mastoiditis (AM) above the population prevalence?
3. What are the disease and individual characteristics of children found to be COVID-19 positive at the time of receiving treatment for acute mastoiditis?
4. What are the long-term outcomes (>14 days, e.g. hearing) of acute mastoiditis in children, and does COVID-19 status affect these?

Methods

Design:
Multisite mixed retrospective and prospective audit

Study group:
All children admitted to participating centres during the audit period for the treatment of acute mastoiditis

Audit duration:
10 months: Approximately 7 months data collection, 3 months analysis. Audit start date November 1st 2020.

Eligibility criteria:
Children aged 0-18 years at date of admission.

Participating centres:
All UK secondary/tertiary care ENT centres would be eligible to enter patients. Sites will be approached via BSO, BAPO and INTEGRATE the UK ENT trainee research network, and at each site a consultant ± a trainee lead will be identified. Site leads will obtain local approval from the audit department, clinical audit lead and Caldicott guardian.

Data collection:
Only routinely collected clinical data will be captured. Cases will be identified by the site leads and routine clinical care teams both retrospectively and prospectively. The primary method for retrospective case identification will be a search of admission ICD-10 coding using the codes derived

from the H70 - 'mastoiditis and related conditions'. In addition, it is recommended that sites able to review daily inpatient handover sheets search these to identify any additional cases improperly coded. This will have the dual benefit of assessing the validity of the coding search method.

For prospective case identification it is hoped that awareness of clinicians within the department will facilitate contemporary recording of case details. In addition, the coding search will be repeated following the end of the 6 month prospective period.

An 18 month period will be studied:

- Retrospective data collection period 1st November 2019 - 31st October 2020 (12m)
- Prospective data collection period 1st November 2020 – 30th April 2021 (6m)

Data collection will be via online electronic case report forms (eCRF) utilising REDCap, a secure web application for building and managing databases that has been used in several NHS projects. Quality of the data entered into the eCRF data fields will be controlled by limited data entry, drop down options and predefined data formats. Range checks for chosen fields will automatically appear where data points are outside of a pre-specified range. The data will be stored on the AIMES Health Cloud which is only connected to the Secure NHS Network (N3/HSCN), allowing protection of sensitive patient data (ISO 27001 certified).

Dataset:
Local site information will be collected at the point of registration. The individual case dataset has been designed to collect only essential data relating to the patient, the condition, management and outcomes following discharge. The eCRF can be found in the appendix.

NHS numbers will be anonymised before data submission using the provided Excel spreadsheet, used offline on a Trust computer. The spreadsheet will: 1) subject the NHS number to a MD5 cryptogenic hash function to generate a unique 32 character hexidecimal code; 2) trim the resulting code to 20 characters by removing the initial 12 characters. The same NHS number will always produce the same code, allowing tracking of NHS numbers between sites, but without the need to share identifiable data. This is a one-way anonymisation process that will ensure the resulting code is impossible to decrypt, with a negligible chance of duplication (16^20).

To include:

- Demographics
- Details of the patient's presentation
- Available blood test results (Full Blood Count, C-Reactive Protein, Liver Function Tests, Glucose, Urea & Electrolytes
- Pre-operative COVID-19 test result, if available
- CT and MR reports (if imaging performed)
- Initial management
- Clinical outcome- including need for formal cortical mastoidectomy or further surgical procedures, development of intracranial complications and sequalae
- Age-appropriate hearing test at scheduled follow up

Data analysis:

Individuals treated at more than one Trust will have records linked though identification of a common code from the anonymised NHS number. Descriptive statistics will be used to

assess the relative proportions and nature of conservative and surgical management of mastoiditis before and after March 2020 guidelines.

Secondary analyses

1. Outcomes from conservative and invasive treatment methods will be compared in terms of rate of complications, length of hospital stay, need for further intervention, and hearing outcome. If possible, cases in each treatment group will be stratified by severity on the basis of presenting features and/or imaging/laboratory results to ensure valid comparison can be made between treatment modalities.

2. The percentage of patients with acute mastoiditis who are found to be positive for COVID-19 will be compared to Office for National Statistics UK population prevalence, grouping cases by month.

3. Regression analysis will explore the relationship between 3 groups (test positive, test negative/pre-COVID, and no test) and a panel of variables to include: clinical presentation, blood tests, age, ethnicity, co-morbidity, imaging findings and disease severity.

4. Comparison of data between confirmed positive and negative groups.

Dissemination of findings

Findings will be presented at national and international meetings, and published in a peer reviewed journal. Results will also be shared via BAPO and INTEGRATE newsletters and social media. Findings may be used to develop new consensus management guidelines with key stakeholders. All site leads will be included as authors in all publications and presentations.

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Appendix

The expanded eCRF is attached to this document. The forms use branching logic and cases will not require every section to be completed, however this view provides a comprehensive list of the data that may be collected.