This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124001804

The Microbiology of Acute Mastoiditis Infections Presenting to a large UK Tertiary Paediatric ENT centre in a post Pneumococcal Conjugate Vaccination era

Authors

Walker NR MRCSEd (ENT) [a], Eleftheriadou A MRes [a], Mortaja S MRCSi (ENT) [a], Sharma SD FRCS (ORL-HNS) [a]

Affiliations

[a]Department of Otolaryngology, Alder Hey Children's Hospital, Liverpool, United Kingdom

Corresponding author

Dr Nathan R Walker, Department of Otolaryngology, Alder Hey Children's Hospital, Liverpool, United Kingdom

Email: nathan.walker2@nhs.net

NW + SS devised the project and designed the study. NW, SM, AE collected and analysed the data for the project. NW wrote the manuscript with input from all authors

This work was presented at the European Society of Paediatric Otorhinolaryngology Annual 2023 meeting

Abstract

Objectives:

Mastoiditis commonly presents to ENT services. Following the UK introduction of the 13-valent conjugate pneumococcal vaccine in 2010, changes in the organisms of these infections were hypothesised. We aim to assess the microbiological profile of patients with acute mastoiditis in our centre.

Methods:

Retrospective review of patients admitted to Alder Hey Children's Hospital for mastoiditis between January 2017-September 2022. Data was collected from electronic patient records, microbiology, and biochemistry reports.

Results:

108 patients were admitted: 61 males and 47 females, median age of 2 years (range 4 months-14 years). 82 organisms were isolated from 50 (46%) children. Streptococcus spp (22 specimens; 27%) and Staphylococcus spp (13 specimens; 16%) were most common. Other organisms included Pseudomonas aeruginosa (6; 7%), anaerobes (4; 5%), Haemophilus influenzae (4; 5%), and Fusobacterium (4; 6%).

Conclusions:

Mastoiditis predominantly involves gram-positive facultative anaerobic bacteria. Empirical ceftriaxone and metronidazole provides adequate coverage. Culture and sensitivity testing is essential for antibiotic stewardship.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

Introduction

Acute mastoiditis denotes a suppurative inflammation within the mastoid air cell system of the temporal bone. The condition typically arises as a complication of acute otitis media through local propagation via the aditus ad antrum connecting the middle ear to the mastoid. Conventional teaching suggests causative organisms to be predominantly those colonising the upper respiratory tract such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Group A Streptococci*, *Haemophilus influenzae* as well as *Pseudomonas aeruginosa*. [1]

The routine infant Pneumococcal conjugate vaccine (PCV) programme was first introduced in the United Kingdom (UK) in 2006, with a 7-valent vaccine (PCV7) which was replaced with the 13-valent vaccine (PCV13) in 2010. Studies have found the introduction of the vaccine to be highly protective in reducing invasive pneumococcal infection in both children and adults by up to 50%. [2,3] In the United States, there have been reports of reducing numbers of middle ear fluid cultures growing *S. Pneumoniae* in young children with acute otitis media, since this introduction. [4] Interestingly, Attlmayr et al. previously summarised the microbiological results of patients presenting with mastoiditis at Alder Hey Children's Hospital for the years 2003 and 2012, covering a pre-vaccination period. At that time, the most common micro-organisms responsible for acute mastoiditis included Streptococcus pyogenes (group A), Streptococcus pneumoniae and Pseudomonas aeruginosa. [5]

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

In this study, we aim to assess the latest microbiological profile of patients with acute mastoiditis in a major UK paediatric tertiary centre.

Material and Methods

A retrospective observational study was undertaken at Alder Hey Children's Hospital, Liverpool, UK between January 2017 and September 2022. Inclusion criteria involved all patients with a coded diagnosis of mastoiditis requiring hospital admission. Institutional approval was granted prior to data collection.

Patient demographics, length of stay, biochemical markers including maximal C-reactive protein (CRP), culture and sensitivity analysis (obtained from pus swabs, pus cultures or blood cultures) and interventions were recorded for analysis. Data was stored securely on the hospital database. Patients were followed up for a minimum of 9 months for evidence of complications and recurrence.

The primary outcome was the identification of the type of pathogen responsible for mastoiditis infections within this cohort of children. Secondary outcomes included length of hospital stay, 30-day mortality, biochemical markers of inflammation including CRP and white blood cell count (WBC), complications, and the need for surgery. These secondary outcomes were stratified by the identified causative pathogen, when available.

Data was collected and analysed using Microsoft Excel and Statistical Package for the Social Sciences (IBM SPSS , New York USA).

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

Results and Analysis

A total of 108 patients were admitted with 112 episodes of mastoiditis; 61 males and 47 females. Recurrent presentations were recorded in 3 male patients and 1 female patient. The median age on admission was 2 years old (4 months – 14 years old), and average length of stay was 4.6 days (range 0 – 40; median 3). Study patient characteristics cross-referenced by the more common organisms isolated on microbiological analysis are summarised in table I. Mixed skin flora was not included in the summary table due to the likelihood of contamination.

In 87 cases (78%), samples (ear swabs, pus cultures or blood cultures) were obtained and sent for microbiology. Of those, 50 cases had 58 positive samples, and 82 organisms were isolated (summarised in Figure I). After excluding likely contaminant mixed skin flora (n=18, 22%), the most commonly isolated organisms from all samples were *Streptococcal spp*, isolated in 22 cases; 12 (15%) *S. pneumoniae*, 6 (7%) *Group A Streptococci*, 1 (1%) *Streptococcus intermedius*, 1 (1%) *Streptococcus oralis,* 1 (1%) *Streptococcus constellatus* and 1 (1%) *Streptococcus massiliensis*. The second most common organisms were *Staphylococcal spp*, isolated in 13 cases; 6 (7%) *S. aureus* and 7 (9%) *coagulase-negative Staphylococci*. *Pseudomonas aeruginosa* was isolated in 6 cases (7%), *Fusobacterium necrophorum* in 5 cases (6%), *anaerobes* in 4 cases (5%), *H. influenzae* in 4 cases (5%), and *Escherichia coli* in 3 cases (4%). Other organisms isolated once only were *Haemophilus parainfluenzae*, *Prevotella*

spp., Moraxella spp., *Bacillus spp.*, *Micrococcus spp.*, *Acinetobacter baumannii*, and *Mycobacterium tuberculosis* (1 each). Figure II and Figure III provide a summary of positive cultures by site of specimen.

Sensitivity data was available in 34 of the 58 positive samples. The most common antibiotic was Cefotaxime which was tested in 18/34 samples and was effective in 100% of cases tested upon. This was followed by Amoxicillin which was effective in 94% of cases and tested in 16/34 samples. Clarithromycin was tested in 13/34 samples and was effective in 93% of cases. A total of 8/34 (24%) samples were found to have antibiotic resistant strains of bacteria. This included a *S.Aureus* resistant to Clarithromycin, and two cases of *H.Influenza* resistant to Clotrimoxazole. Ciprofloxacin resistance was encountered in 4 cases, organisms included *S.Pyogenes* (which additionally was resistant to Metronidazole), *S.Pneumonia* and two cases of *P.Aeruginosa.*

Blood cultures were obtained in 56 cases and were positive in 9 (16%). The most commonly isolated organisms were *coagulase-negative Staphylococci* in 5 cases, with 1 case positive for *Acinetobacter baumannii* from the same sample; all were thought to be contaminants on consultant microbiologist review. This was followed by 2 cases of *S. pneumoniae*, which was in one case associated with positive *H. influenzae* from the same sample. There was 1 case of *group A Streptococci*, and 1 positive for *Micrococcus spp.,* which was thought to be a contaminant based on expert microbiologist opinion.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

After excluding mixed skin flora isolates, a total of 18 cases had multiple organisms isolated from specimens which were obtained during the same presentation, while 25 patients had a single organism isolated from specimens (table II). There was a significant difference between the length of stay for each group (median 7 days for multiple organisms, median 5 days for single isolated organisms, p=0.03), but no significant difference was detected across other variables (surgical intervention, subperiosteal abscess, intracranial complications or re-admission). When multiple culture samples were obtained from the same child, only 2/87 cases had positive cultures from more than one sample. In both cases the bacteria cultured from the positive samples were different. One case reported *S.Pyogenes* as positive from a blood culture whilst the ear swab from the same patient reported *S.Aureus*. The second case demonstrated *S.Pneumoniae* from pus cultured during mastoidectomy and *Bacillus.Sp* from a sample of granulation tissue sent for culture.

A total of 5 children in our study were found to have concurrent cholesteatoma. Of these, 4 had culture results available; *P.Aeruginosa* was isolated in two children , with *S.Aureus* and *Prevotella.sp* and *E.Coli* isolated in the other two children.

Intracranial complications were recorded in 18 patients (median age = 4.5 years), 15 (83%) of which had positive cultures. There were 4 cases positive for *S. pneumoniae* (27%), 4 *S. aureus (27%),* 3 *Group A Streptococci (20%)*, 3 *anaerobes (20%)*, 1 *S. intermedius (7%)*, 1 *S. oralis (7%)*, 1 *F. necrophorum (7%)*, 1 *E. coli (7%)*, 1 *H. parainfluenzae (7%)*, 1 *Prevotella spp. (7%)*, and 1

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

Bacillus spp. (7%). In most cases, cultures were positive from a combination of ear swabs and mastoid pus/intracranial source; 3 patients had ear swabs only, 2 of which were positive for *S. pneumoniae,* while 1 yielded mixed skin flora. None of these patients had positive blood cultures.

As per the local hospital guidelines, patients were treated with intravenous Cefotaxime and Metronidazole unless allergic. In the event of allergy, intravenous Clarithromycin was used as an alternative. Mortality at 30 days across all groups was zero.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124001804

Discussion

Our study confirms that, despite the introduction of the pneumococcal vaccine across the UK, the majority of acute mastoiditis is secondary to *Streptococcal spp*. Moreover, we identified that there is a high incidence of mastoiditis-related complications (subperiosteal abscess and intracranial complications) in patients with *Fusobacterium* positive cultures, followed by mixed anaerobes. Surgical intervention was required in all patients with *Fusobacterium necrophorum*, *H. influenzae* and anaerobe positive cultures.

Notably, the high incidence of abscess and intracranial complications reported in the present study is likely to be that Alder Hey Children's Hospital is a large tertiary referral centre for paediatric ENT and neurosurgery, therefore these cases are usually referred from other centres.

Our data aligns with the findings of previously published data regarding causative pathogens responsible for mastoiditis infection. Studies conducted globally consistently showed *Streptococcal spp* as the most prevalent, with many of those studies identifying *S. pneumoniae* as the most isolated bacterium. [6-10] Although the data focusing only on the post-pneumococcal vaccine era is limited, Roddy et al. identified no difference in the proportion of paediatric mastoiditis cases caused by *S. pneumoniae* before and after the introduction of the PCV7 in the US in 2000. [11] Moreover, in a prospective study conducted between 2010 and 2011, Giannakopoulos et al. identified that 81% of cases of acute mastoiditis were attributed to *S. pneumoniae*. [12] However, Tamir et al. observed an inverse relationship between the increasing rate of immunised children and

the proportion mastoiditis cases with confirmed *S. pneumoniae* positive cultures. [13]

Interestingly, our study has identified a comparable proportion of mastoiditis cases attributable to *Streptococcal spp*, when compared to the pre- and intra-pneumococcal conjugate vaccine era data from our institute. In the retrospective analysis of mastoiditis cases presenting to Alder Hey Hospital between 2003 and 2012, Attlmayr et al. identified that both *Streptococcus pyogenes* (6/32 patients) and *S. pneumoniae* (5/32 patients) were the most commonly isolated pathogens, collectively comprising 34% of all identified pathogens. [5] Paradoxically, our data demonstrated an increased number of *S. pneumoniae* infections in the post-pneumococcal conjugate vaccine era (24/85 (28%) vs 5/32 (16%)). This could be partially explained by an increase of the 19A serotype in pneumococcal mastoiditis cases, following the introduction of PCV7 which did not decline after PCV13 was introduced as previously reported by Koutouzis et al. [14] Other possible aetiologies for the continuing presence of *S. Pneumoniae* include shifting of bacterial serotypes after vaccine introduction, increasing resistance secondary to inadequate antibiotic use and also the low to late use of antibiotics in acute otitis media. [15, 16]

The findings from this study suggest that in cases of mastoiditis, empirical treatment should focus on targeting organisms frequently colonising the upper respiratory tract. However, resistance patterns are likely to differ between regions/nations, therefore, local microbiological advice should always be sought and antibiotic therapy should be guided by microbiology sampling, where possible. Importantly, antibiotic stewardship is vital to ensure prevention against

resistance and responsible prescribing of broad-spectrum antibiotics is highly encouraged. Moreover, given the high incidence of mastoiditis-related complications as demonstrated in this study in patients identified to be infected with *Fusobacterium necrophorum*, *H. influenzae* or mixed anaerobic bacteria, caution is advised when the specific pathogens are identified, and the responsible clinicians should carefully consider further investigations and aggressive treatment. However, in a majority of cases, these cultures were taken during surgery, raising the question of whether these bacteria may also be present in cases where surgery was not performed.

The study's design being both retrospective and observational lends itself susceptible to selection bias. Microbiological samples were more likely to be obtained from the more severely unwell patients and those requiring surgical intervention, therefore, the estimated incidence of these organisms could be subjected to bias. In the case of conservatively managed mastoiditis (with an intact tympanic membrane), the likelihood of being able to obtain a microbiological diagnosis is low. Some of the specimens were swabs from the ear canal, which means the bacteria grown may not be directly responsible for mastoiditis. The use of nasopharyngeal swabs as a surrogate marker for acute otitis media infections in cases with an intact tympanic membrane has been explored in the literature, with high negative predictive value rates quoted between 68-97%. [17-19] Additionally, serotyping was not performed, limiting our ability to identify specific bacterial strains. In cases where multiple pathogens were detected, determining the causative pathogen becomes challenging.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

What is Already Known on the Subject:

- The 13-valent conjugate pneumococcal vaccine was introduced in the UK in 2010, hypothesized to affect causative organisms of mastoiditis.
- Streptococcus pneumoniae, Staphylococcus aureus, Group A Streptococci, Haemophilus influenzae, and Pseudomonas aeruginosa are traditionally the most common causative organisms of mastoiditis.

What This Paper Adds to Our Understanding:

- Despite the pneumococcal vaccine introduction, Streptococcal spp remains the most prevalent pathogen in mastoiditis.
- Surgical intervention is often required in cases involving Fusobacterium necrophorum, H. influenzae, and anaerobes.
- Empirical treatment with ceftriaxone and metronidazole provides adequate coverage for the majority of mastoiditis infections.

Conclusion

Mastoiditis infections have predominantly gram-positive facultative anaerobic microbiology. Despite the introduction of the pneumococcal vaccine, *S. pneumonia* remains the most prevalent identified pathogen. From this sample of data, empirical treatment with ceftriaxone and metronidazole gives adequate antibiotic cover. Microbiology culture and sensitivity, wherever possible, is essential to ensure effective antibiotic therapy and further studies are required in order to definitively evaluate the effect of pneumococcal vaccination scheme on the bacteriology of mastoiditis.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

References

1. Cassano P, Ciprandi G, Passali D. Acute mastoiditis in children. Acta Biomed. 2020;91:54-9
2. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine. 2011;29:9127-31
3. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15:535-43
4. Tamir SO, Roth Y, Dalal I, Goldfarb A, Marom T. Acute Mastoiditis in the Pneumococcal Conjugate Vaccine Era. Clinical and Vaccine Immunology. 2014;21:1189-91
5. Attlmayr B, Zaman S, Scott J, Derbyshire SG, Clarke RW, De S. Paediatric acute mastoiditis, then and now: is it more of a problem now? The Journal of Laryngology & Otology. 2015;129:955-9
6. Laulajainen-Hongisto A, Saat R, Lempinen L, Markkola A, Aarnisalo AA, Jero J. Bacteriology in relation to clinical findings and treatment of acute mastoiditis in children. International Journal of Pediatric Otorhinolaryngology. 2014;78:2072-8
7. Bilavsky E, Yarden-Bilavsky H, Samra Z, Amir J, Nussinovitch M. Clinical, laboratory, and microbiological differences between children with simple or complicated mastoiditis. International Journal of Pediatric Otorhinolaryngology. 2009;73:1270-3
8. Stähelin-Massik J, Podvinec M, Jakscha J, Rüst ON, Greisser J, Moschopulos M, et al. Mastoiditis in children: a prospective, observational study comparing clinical presentation, microbiology, computed tomography, surgical findings and histology. Eur J Pediatr. 2008;167:541-8
9. Zevallos JP, Vrabec JT, Williamson RA, Giannoni C, Larrier D, Sulek M, et al. Advanced pediatric mastoiditis with and without intracranial complications. Laryngoscope. 2009;119:1610-5
10. Mierzwiński J, Tyra J, Haber K, Drela M, Sinkiewicz A, Puricelli MD. Pediatric recurrent acute mastoiditis: Risk factors and insights into pathogenesis. International Journal of Pediatric Otorhinolaryngology. 2018;111:142-8
11. Roddy MG, Glazier SS, Agrawal D. Pediatric mastoiditis in the pneumococcal conjugate vaccine era: symptom duration guides empiric antimicrobial therapy. Pediatr Emerg Care. 2007;23:779-84
12. Giannakopoulos P, Chrysovergis A, Xirogianni A, Nikolopoulos TP, Radiotis A, Lebessi E, et al. Microbiology of acute mastoiditis and complicated or refractory acute otitis media among hospitalized children in the postvaccination era. Pediatr Infect Dis J. 2014;33:111-3
13. Tamir SO, Roth Y, Dalal I, Goldfarb A, Marom T. Acute mastoiditis in the pneumococcal conjugate vaccine era. Clin Vaccine Immunol. 2014;21:1189-91
14. Koutouzis EI, Michos A, Koutouzi FI, Chatzichristou P, Parpounas K, Georgaki A, et al. Pneumococcal Mastoiditis in Children Before and After the Introduction of Conjugate Pneumococcal Vaccines. Pediatr Infect Dis J. 2016;35:292-6

15. Goldberg-Bockhorn E, Hurzlmeier C, Vahl JM, Stupp F, Janda A, Heike von Baum, et al. Increase in acute mastoiditis at the end of the COVID-19 pandemic. European Archives of Oto-Rhino-Laryngology. 2024.
16. Koelman DLH, Brouwer MC, van de Beek D. Resurgence of pneumococcal meningitis in Europe and Northern America. Clinical Microbiology and Infection. 2019;26:199–204.
17. van Dongen, T.M.A, van der Heijden, G.J.M.G, van Zon, A, Bogaert, D, Sanders, E.A.M, Schilder, A.G.M. Evaluation of Concordance Between the Microorganisms Detected in the Nasopharynx and Middle Ear of Children With Otitis Media. Pediatr Infect Dis J. 2013;32:549–552
18. Radzikowski A, Skórka A, Mikołajczyk W, Woźniak M, Wysocki J. Does nasopharyngeal bacterial flora predict etiology of acute otitis media in children? Pediatria Polska. 2011;86:620-623
19. Yatsyshina S, Mayanskiy N, Shipulina O, et al. Detection of respiratory pathogens in pediatric acute otitis media by PCR and comparison of findings in the middle ear and nasopharynx. Diagnostic Microbiology and Infectious Disease. 2016;85:125-130

Funding

This research did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interests

None from all authors

This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124001804

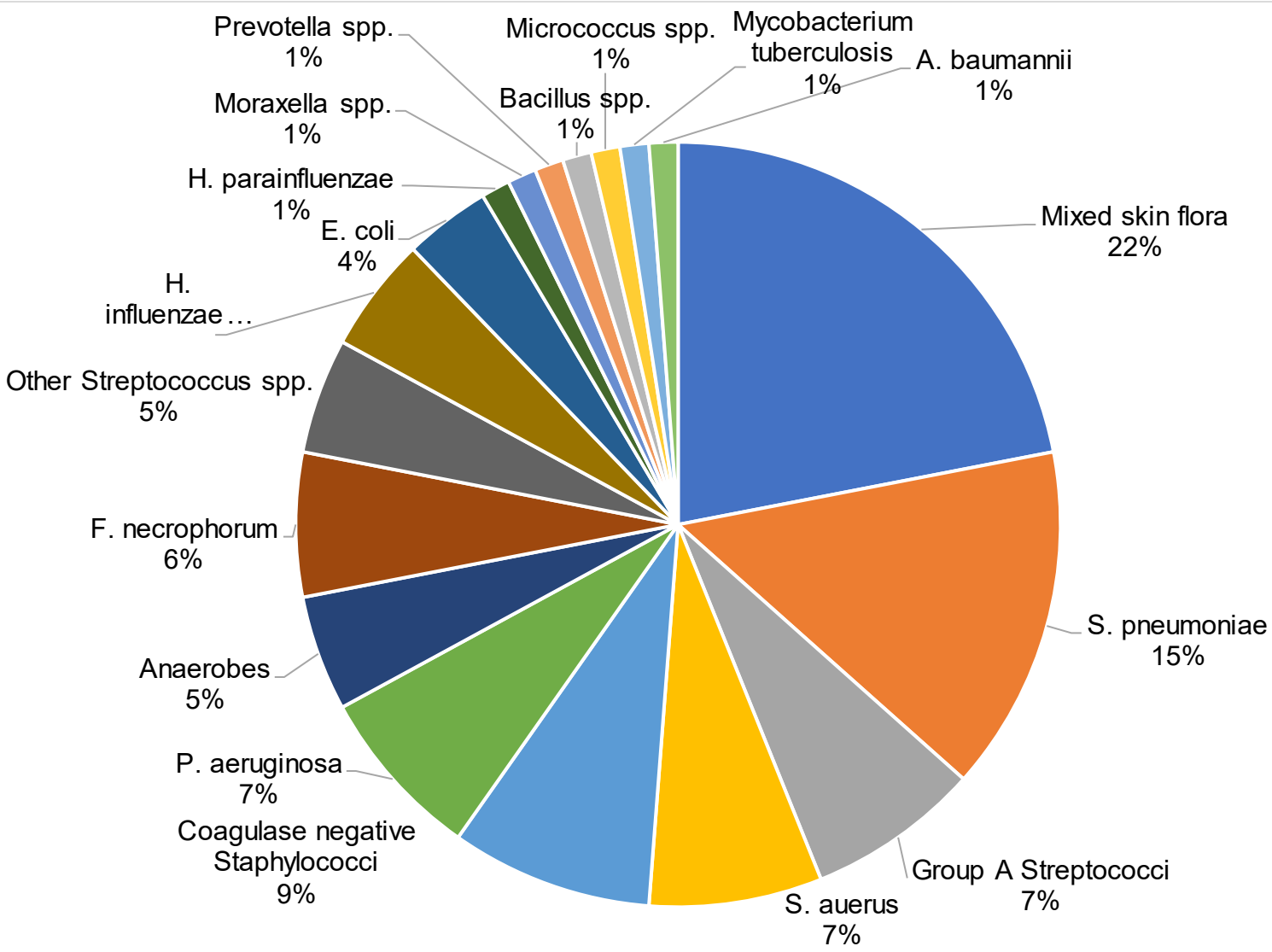

Figure I. 82 organisms isolated from 58 microbiological samples

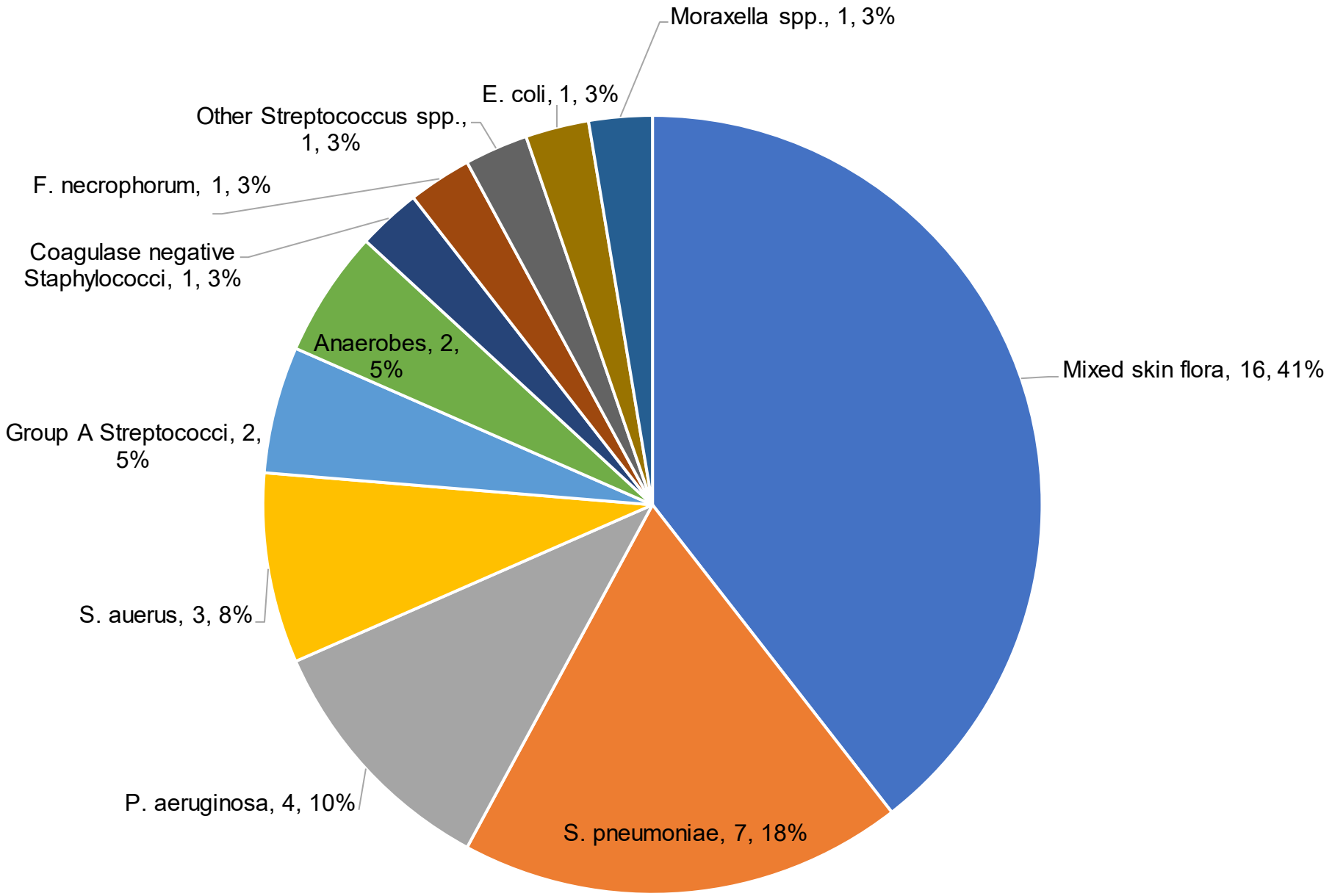

Figure II. 39 Organisms isolated from 31 ear swabs

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

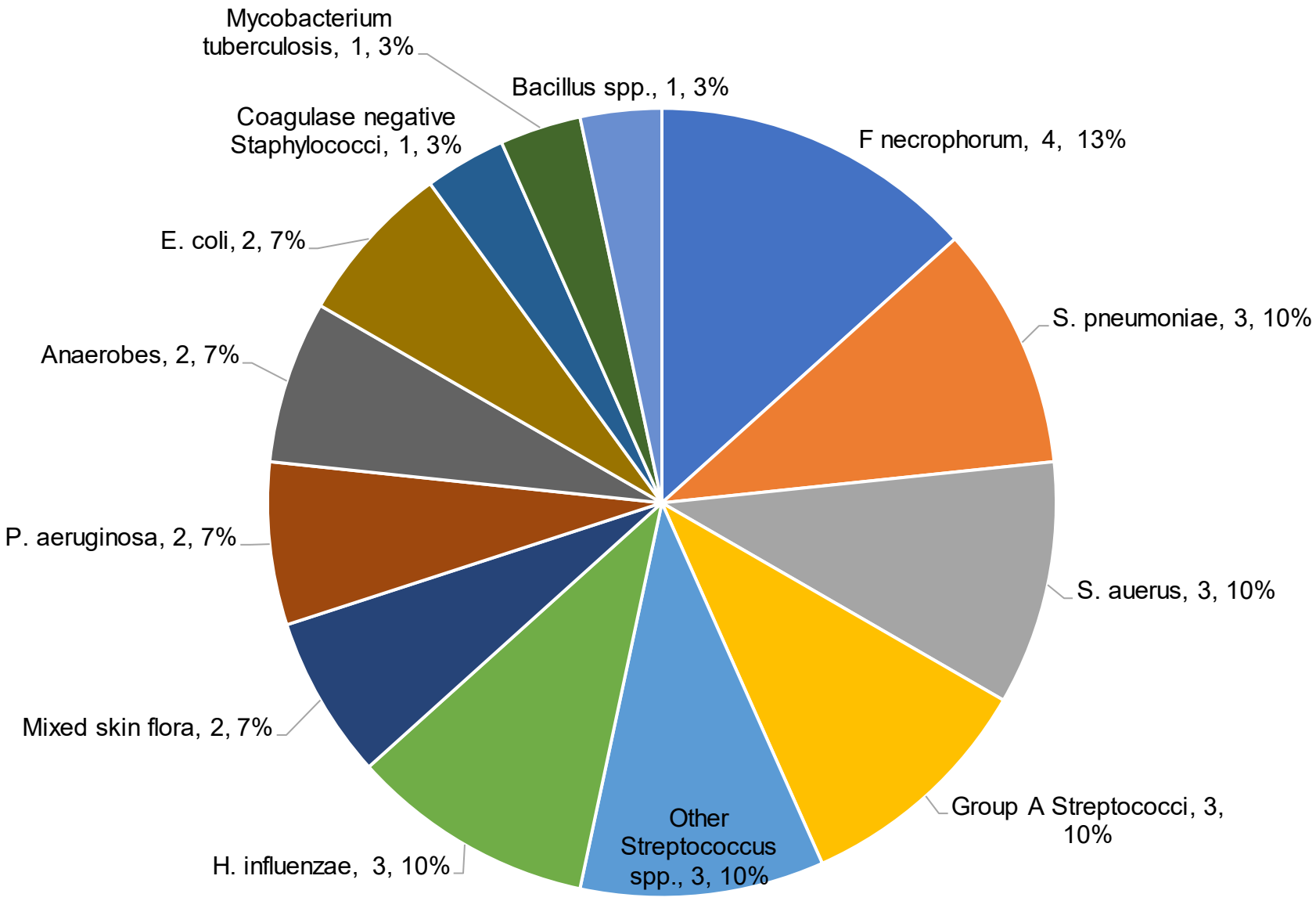

Figure III. 30 organisms isolated from 18 mastoid pus samples

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

	All (N=112)	*S. pneumoniae (n=11)*	*GAS (N=8)*	*S. aureus (n=7)*	*P. aeruginosa (n=6)*	*Anaerobes (n=5)*	*F. necrophorum (n=5)*	*H. influenzae (n=4)*	*Negative cultures (n=37)*	*No samples for analysis (n=25)*
Age (years)	2	2	3	4	6	12	1	1.5	2	4
Male gender	63 (56)	7 (64)	6 (75)	6 (86)	5 (83)	2 (40)	1 (20)	3 (75)	20 (53)	11 (44)
Surgical Intervention	49 (44)	8 (72)	6 (75)	6 (86)	3 (50)	5 (100)	4 (100)	4 (100)	10 (27)	2 (8)
Subperiosteal Abscess	38 (34)	6 (55)	3 (37.5)	3 (43)	2 (33)	2 (40)	4 (80)	3 (75)	10 (27)	1 (4)

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

Intracranial complications	18 (16)	4 (36)	3 (37.5)	4 (57)	0	3 (60)	2 (40)	0	3 (8)	0
Maximal CRP	96	120	138	83	44	150	203.5	182	86	57
LOS (days)	3	5	4.5	4	4	12	8	5.5	3	2
Re-admission	7 (6)	1 (9)	0	1 (14)	0	0	1 (20)	0	2 (5)	1 (4)

Table I. Patient characteristics with comparison between most common organisms identified on microbiological analysis

Categorical data are summarised as n (%). GAS: group A Streptococci. LOS: Length of stay. CRP represented as average. Age and LOS are represented as medians.

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press

	Single organism isolated (N = 25)	Multiple organisms isolated (N = 18)	P-value
Age	2	4.5	0.059*
Male gender	16 (64)	12 (66)	0.559†
Surgical Intervention	17 (68)	16 (89)	0.107†
Subperiosteal Abscess	14 (56)	9 (50)	0.468†
Intracranial complications	7 (28)	7 (39)	0.335†
Maximal CRP	116	140.9	0.222*
LOS, days	5	7	0.031*
Re-admission	3 (12)	2 (11)	0.657†

Table II. Patient Characteristics subdivided by single vs multliple organism isolation
Categorical data are summarised as n (%). LOS: Length of stay. CRP represented as average. Age and LOS represented as median.
*Mann-Whitney U test
†Fisher's exact test – 1-sided

https://doi.org/10.1017/S0022215124001804 Published online by Cambridge University Press