Original Article

Exploring *Streptococcus Milleri* in superficial suppurative lymphadenitis: a retrospective review

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Background: *Streptococcus Milleri* is commonly found in the oral cavity, oropharynx and gastrointestinal tract and has been linked to pyogenic infections. Reports on the incidence of head and neck abscesses caused by *Streptococcus Milleri* have increased in the last few decades; however, literature remains scarce. Furthermore, Therapeutic Guidelines recommend cefalexin or flucloxacillin as first line antibiotic therapy for cervical lymphadenopathy. However, *Streptococcus Milleri* is most sensitive to *Penicillin G*. This study aims to examine the incidence of *Streptococcus Milleri* in superficial suppurative lymphadenitis and the implications of this on recommended antibiotic therapy.

Methods: This is a retrospective review of patients with superficial suppurative lymphadenitis in a tertiary hospital in Queensland, Australia from February 2019 to June 2024. Patient data was collected from electronic medical records on cultured microorganism, antibiotic choice, duration of therapy and complications. Inclusion criteria comprised of patients with intra-operative samples sent for microscopy, culture, and sensitivity.

Results: A total of 30 patients underwent incision and drainage of a superficial suppurative lymphadenitis between February 2019 to June 2024. This study found that *Streptococcus Milleri* was the most common microorganism cultured. This was cultured in nearly a quarter of patients (23.3%). *Streptococcus Milleri* was more common in male patients (57.1%) and patients aged 18 years old and older (71.4%). Patients with *Streptococcus Milleri* cultures experienced longer inpatient stays, total antibiotic durations and a higher incidence of changes to their initial intravenous (IV) antibiotic regimen based on intraoperative culture results. The odds ratio for hospital representation for *Streptococcus Milleri* patients was 1.1 (95% confidence interval: 0.1–12.8) with a p value of 1, suggesting no significant difference between the groups. Similarly, the odds ratios for gender (male/female) and changes in IV antibiotics were greater than 1, indicating a higher likelihood of these outcomes. However, none of these relationships were statistically significant (P>0.05).

Conclusions: The findings of this study demonstrate a need for increased awareness of *Streptococcus Milleri* in patients presenting with superficial suppurative lymphadenitis and provides foundational insights for future research in this area.

Keywords: *Streptococcus Milleri*; neck abscess; antibiotics

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Introduction

Streptococcus Milleri constitutes a group of microorganisms consisting of *Streptococcus Anginosus*, *Streptococcus Constellatus* and *Streptococcus Intermedius* (1). *Streptococcus Milleri* was initially identified by Guthof in 1956 (1). This commensal bacterium is commonly found in the oral cavity, oropharynx and gastrointestinal tract and has been linked to pyogenic infections (1,2). The incidence of abscesses from *Streptococcus Milleri* has increased in the last few decades, rising from 0.93 per 100,000 to 3.7 per 100,000 from 2000 to 2017 (3,4).

Given its abundance in the oral cavity, this has been linked to deep neck space and peritonsillar abscesses (5,6). Despite this, literature on *Streptococcus Milleri* in head and neck infections remains scarce (6). This can be attributed to several factors. Several complex laboratory tests were previously required to culture *Streptococcus Milleri* (7). This limited the capacity of facilities culture to this microorganism and restricted it to those equipped with the necessary equipment (2). *Streptococcus Milleri* was also considered a commensal organism for many years (7). Given the recent advances in detection, literature on this bacterium remains scarce. Most existing studies on *Streptococcus Milleri* in head and neck infections are case series or case reports (8-10).

Existing literature on head and neck abscesses has noted an increase in the incidence of head and neck abscesses secondary to *Streptococcus Milleri*. A 2022 study by Kawar *et al.* found a significant increase in *Streptococcus Milleri* neck abscesses in patients aged 16 and under (11) over the last few decades. A 2024 case series by Ulu *et al.* noted an increase in the frequency of severe head and neck infections caused by *Streptococcus Milleri* (8) during the coronavirus disease 2019 (COVID-19) pandemic.

Therapeutic Guidelines are an Australian evidence-based resource for healthcare practitioners, developed by an independent not-for-profit organization, Therapeutic Guidelines Limited (12). Therapeutic Guidelines advise that the most common causes for acute unilateral cervical lymphadenitis are *Staphylococcus Aureus* and *Streptococcus Pyogenes*. The guidelines recommend cefalexin, dicloxacillin or flucloxacillin as first line antibiotic therapy (13). However, *Streptococcus Milleri* is most sensitive to Penicillin G (14).

This is a retrospective review of superficial suppurative lymphadenitis patients at a tertiary hospital in Queensland, Australia from February 2019 to June 2024. This study aims to examine the incidence of *Streptococcus Milleri* and the implications of this on recommended antibiotic therapy.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was granted an ethics exemption by the Gold Coast Health Service Ethics Committee (HREC Reference HREC/2024/QGC/110022) due to its classification as a clinical audit. The requirement for individual consent was waived as this was a retrospective study. The study is reported according to the STROBE reporting guidelines (available at https://www.theajo.com/article/view/10.21037/ajo-24-46/rc).

Inclusion and exclusion criteria

A retrospective review was conducted of patients who underwent an incision and drainage of a neck abscess at Sunshine Coast University Hospital from February 2019 to June 2024. Patients were coded by surgical coders and subsequently sourced from a hospital electronic database. Inclusion criteria consisted of all patients who had an intra-operative sample sent for microscopy, culture and sensitivity. Exclusion criteria included patients who had a deep neck space abscess (retropharyngeal, parapharyngeal, submandibular), peritonsillar abscess, and neck abscess secondary to a postoperative infection. Patients who had non-operative abscess drainage, such as an ultrasound-guided drainage, were also excluded.

Data collection and analysis

Information was collected on patient age, cultured microorganism, area of abscess (left, right or submental), cultured microorganism, initial intravenous (IV) antibiotic choice, duration of IV antibiotics (days), duration of inpatient stay (days), duration of oral antibiotics (days) and rate of representation post discharge. Cases with missing data pertaining to the inclusion and/or exclusion criteria were excluded. All relevant data points were available for analysis, resulting in no instances of incomplete data.

Fisher exact testing was conducted to assess for statistical significance between independent categorical variables. A Mann-Whitney *U* test was conducted to assess for statistical significance between independent categorical and continuous variables. Descriptive statistics were calculated

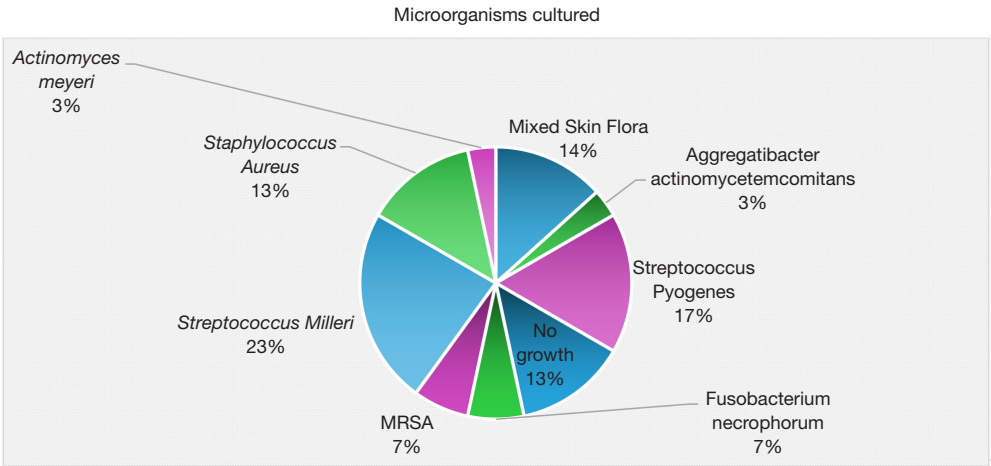

Figure 1 Proportions of culture results. MRSA, methicillin resistant *Staphylococcus Aureus*.

for the dataset, including the mean, median, standard deviation (SD), and interquartile range (IQR). Odds ratio (OR) and 95% confidence intervals (CI) were calculated. The P value for statistical significance was set to <0.05. Data analysis was conducted on IBM SPSS version 29.0.2.0 and Microsoft Excel version 16.86.

Results

Demographics

A total of 30 patients who met our inclusion and exclusion criteria underwent incision and drainage of a neck abscess between February 2019 to June 2024. Of these, 11 were under 18 years old and 19 were 18 years old and above. Twelve of these patients were female and 18 were male. The mean and median ages were 23±19.4 and 20 (IQR, 5–38) years old, respectively. The patients' ages ranged from 14 months to 68 years. The locations of the neck abscesses were approximately symmetrical, with 14 on the right side of the neck, 13 on the left side, and 3 in the submental region.

Microbiology

Nine different culture results were identified in microscopy, culture, and sensitivity. This can be seen in *Figure 1*. These consisted of 6 different microorganisms (*Streptococcus Milleri*, *Streptococcus Pyogenes*, *Fusobacterium Necrophorum*, Actinomyces Meyeri, *Aggregatibacter Actinomycetemcomitans*), 2 strains of 1 microorganism [methicillin resistant *Staphylococcus Aureus* (MRSA) and methicillin sensitive *Staphylococcus Aureus* (MSSA)], mixed skin flora, and some samples showed no growth.

The most common culture result was *Streptococcus Milleri*—found in 7 patient samples (23.3%). The second most common culture result was *Streptococcus Pyogenes*, identified in five patient samples (16.7%). The least common culture results were *Aggregatibacter Actinomycetemcomitans* and *Actinomyces Meyeri*, each detected in only 1 sample (3.3%). These were exclusively found in patients aged 18 years and older.

In the year 2019, the most common culture results were mixed skin flora, *Streptococcus Pyogenes* and no sample growth. These were all identified twice in sample results. This can be seen in *Figure 2*. From the years 2020 to 2022, *Streptococcus Milleri* was the most common microorganism cultured, occurring 1, 3 and 2 times, respectively.

The most common culture result in patients aged 18 years old and over was *Streptococcus Milleri* with 5 cases (26.3%). The most common culture result in patients under 18 years old was *Streptococcus Pyogenes* and no sample growth, both occurring in 4 samples (36.4%).

Treatment

The mean and median duration of oral antibiotic course was 9.7±5.0 and 10 (IQR, 7–10) days, respectively. The minimum course of oral antibiotics was 5 days, and the maximum course of oral antibiotics was 1 month. The mean and median duration of total antibiotic course was 15±8.5 and 13 (IQR, 11–15) days, respectively. The total shortest antibiotic course of 8 days occurred in a patient whose

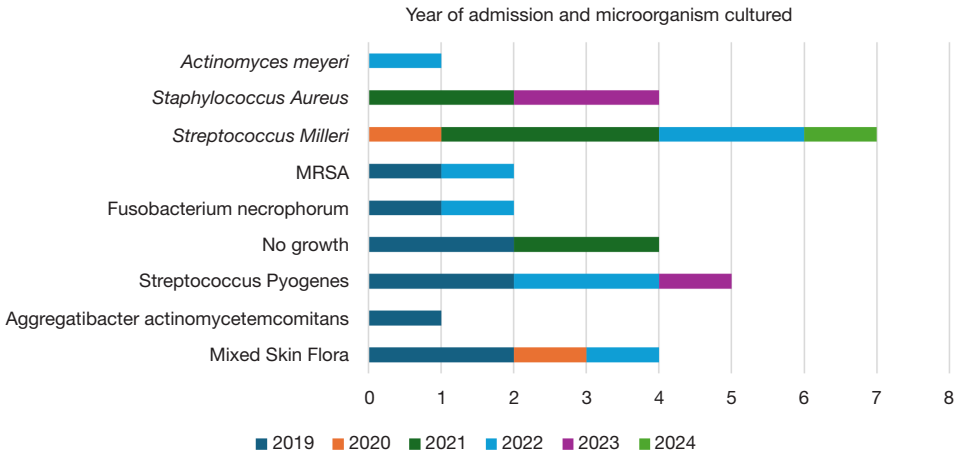

Figure 2 Year of admission and microorganism cultured. MRSA, methicillin resistant *Staphylococcus Aureus*.

Table 1 Total duration of antibiotics and culture results

Culture result	Mean (days)	Median (days)	Standard deviation (days)	Interquartile range (days)	Range (days)	Minimum (days)	Maximum (days)	Number of patients
Streptococcus Milleri	17	12	14.2	11–14	40	11	51	7
Staphylococcus Aureus	15.8	14	8.1	10.5–21	19	8	27	4
Streptococcus Pyogenes	14.6	15	3.5	11.5–17.5	9	11	20	5
Methicillin resistant *Staphylococcus Aureus*	9.5	9.5	0.7	9–10	1	9	10	2
Fusobacterium Necrophorum	12	12	2.8	10–14	4	10	14	2
Aggregatibacter Actinomycetemcomitans	18	18	N/A	N/A	0	18	18	1
Actinomyces meyeri	14	14	N/A	N/A	0	17	17	1
Mixed skin flora	13	13	1.8	11.5–14.5	3	11	15	4
No growth	13.5	12.5	3.1	11.5–15.5	7	11	18	4

N/A, not available.

sample cultured *Staphylococcus Aureus*. This can be seen in *Table 1*. The longest total antibiotic course occurred in a patient whose sample cultured *Streptococcus Milleri*. This patient had a 51-day course of antibiotics.

Outcomes

Mean and median duration of inpatient stay was 4.9±1.9 and 5 (IQR, 4–6) days, respectively. The minimum duration of inpatient stay was 1 day and occurred in 2 patients who each cultured *Staphylococcus Aureus* and mixed skin flora. The longest inpatient stay of 9 days occurred in a patient who grew *Streptococcus Milleri*.

Twelve patients (40%) had their IV antibiotics changed based on culture results from their samples. Of these, the most common culture result was *Streptococcus Milleri*—accounting for 5 patients. The most common IV antibiotic to which patients were switched to overall was amoxicillin-clavulanic acid. This occurred in 5 patients.

Four patients (13.3%) represented post-discharge. Of these, 3 had a repeat incision and drainage intra-operatively. 2 of these patients grew mixed skin flora on their swab, 1 grew *Streptococcus Milleri*, and one grew *Streptococcus Pyogenes*.

Table 2 Association of *Streptococcus Milleri* with demographic factors

Variables	*Streptococcus Milleri* (%) (n=7)	No *Streptococcus Milleri* (%) (n=23)	P value	Odds ratio	95% confidence interval
Gender			1.0	1.9	0.3–12.1
Male	57.1	60.9			
Female	42.9	39.1			
Age (years)			0.4	0.4	0.1–2.7
≥18	71.4	60.9			
<18	28.6	39.1			
Change in intravenous antibiotics	71.4	30.4	0.08	5.7	0.9–36.9
Representation	14.3	13.0	1.0	1.1	0.1–12.8

Streptococcus Milleri

Of patients with *Streptococcus Milleri* culture results, 5 (71.4%) were aged 18 years and over, and 2 (28.6%) were aged younger than 18 years old. The mean and median ages were 33±24.2 and 38 (IQR, 2–60) years old, respectively. The youngest patient was 17 months old, and the oldest patient was 68 years old.

In terms of gender distribution, 4 (57.1%) of these patients were male and 3 (42.9%) were female. 5 (71.4%) of these neck abscesses were located on the right neck, 1 (14.3%) was on the left neck, and 1 (14.3%) was in the submental region. The initial choice of IV antibiotics was changed in 5 (71.4%) of these patients based on intra-operative culture results. The most common antibiotic patients were switched to was benzylpenicillin—occurring in 2 patients. Other antibiotics patients were switched to were amoxicillin, cefotaxime and lincomycin, and piperacillin-tazobactam and amoxicillin-clavulanic acid. The mean and median total antibiotic duration were 17±14.2 and 11 (IQR, 11–14) days, respectively. The mean and median total inpatient stay was 6±1.8 and 6 (IQR, 4–8) days. The total duration of antibiotic treatment for patients who cultured *Streptococcus Milleri* ranged 40 days, ranging from 11 to 51 days.

OR was calculated for patients who cultured *Streptococcus Milleri* to evaluate the effects of gender, age, representation rates, and changes in initial IV antibiotics. These results are summarized in *Table 2*. The OR for gender (male/female), changes in IV antibiotics, and representation were greater than 1, indicating a higher likelihood of these outcomes; however, none of these relationships were statistically significant (P>0.05). Additionally, there was no significant relationship between total antibiotic duration and patients who cultured *Streptococcus Milleri* (P=1.0). Notably, 71.4% of patients with *Streptococcus Milleri* experienced changes in their IV antibiotics compared to 30.4% in the non-*Streptococcus Milleri* group, with a P value of 0.08 suggesting a trend toward significance. Furthermore, the OR of 5.7 (95% CI: 0.9–36.9) suggests that patients with *Streptococcus Milleri* were over five times more likely to have their antibiotic regimen modified. However, the confidence interval includes 1, indicating that this association may not be statistically significant and warrants cautious interpretation.

Discussion

To our knowledge, this study is the first of its kind to review the incidence of *Streptococcus Milleri* in patients with superficial suppurative lymphadenitis. *Streptococcus Milleri* is a commensal bacterium commonly found in the oral cavity. This has been linked to pyogenic infections and exhibits several pathogenic features that contribute to its ability to cause infection. These include a fibronectin-binding protein that facilitates adherence to host tissues (15), a bacterial capsule that enables evasion of host immune response (16), and the production of extracellular enzymes such as hyaluronidase, which degrade the extracellular matrix (17). A 2002 study by Wanahita *et al.* found that *Streptococcus Milleri* is also killed more slowly by and inhibits chemotaxis by white blood cells. This delayed immune response may contribute to the pyogenic nature of *Streptococcus Milleri* as bacteria have more time to proliferate before the host's immune defences respond (18).

This study found that *Streptococcus Milleri* was the most common microorganism cultured in patients with superficial suppurative lymphadenitis from February 2019 to June 2024 in our institution. This was cultured in nearly a quarter of patients (23.3%) (15-18).

Streptococcus Milleri was more common in male patients (57.1%) and patients aged 18 years old and older (71.4%) in this study. Male patients were nearly twice (OR 1.9; 95% CI: 0.3–12.1) as likely to present with *Streptococcus Milleri* as female patients. There was, however, no statistically significant relationship (P>0.05) between gender and *Streptococcus Milleri* infections. Patients under 18 years old had an OR of 0.4 (95% CI: 0.1–2.7) of presenting with *Streptococcus Milleri* than patients aged 18 years and older. The mean age of patients with *Streptococcus Milleri* infections in our study was 33±24.2 years old. These align with findings in existing literature (19,20). A 2020 study by Jiang *et al.* found that the highest incidence of oral and maxillofacial *Streptococcus Milleri* infections occurred in males and patients aged 35–54 years old, followed by patients aged over 65 years old (20). This study also found no statistical difference between gender and *Streptococcus Milleri* infections.

This study found that the most common cultured microorganism in patients under 18 years old was *Streptococcus Pyogenes*—accounting for 28.6% of patients in this age group. This aligns with findings in the literature indicating that *Streptococcus Milleri* is less common in younger patients (1,21). However, the rate of *Streptococcus Milleri* infections in children, as reported in literature, has been increasing (11,22). For example, a 1979 study by Poole *et al.* reported no cases of *Streptococcus Milleri* in patients under 5 years old (1). A 2022 study by Kawar *et al.* reported a 300% increase in the incidence of *Streptococcus Milleri* neck abscesses in children over a 25-year period (11). Kawar *et al.* also found that the most common culture result in paediatric neck abscesses was *Staphylococcus Aureus* followed by *Streptococcus Pyogenes*, which aligns with the results of our study.

In this study, patients with *Streptococcus Milleri* cultures experienced longer inpatient stays, total antibiotic durations and a higher incidence of changes to their initial IV antibiotic regimen based on intraoperative culture results. The mean inpatient stay for *Streptococcus Milleri* patients was 6±1.8 days compared to the overall mean of 4.9±1.9 days. The mean total antibiotic duration was 17±14.2 days for *Streptococcus Milleri* patients, compared to the overall mean of 15±8.5 days. Similarly, a 2001 study by Han *et al.* also found that patients with *Streptococcus Milleri* infections of the head and neck had an average antibiotic duration of 18.9 days (21).

In this study, patients with *Streptococcus Milleri* cultures also exhibited a higher incidence of changes to their initial IV antibiotic regimen based on culture results, accounting for 41.7% of these patients. Patients who cultured *Streptococcus Milleri* exhibited an OR of 5.7 (95% CI: 0.9–36.9) for changes in their initial IV antibiotics based on intra-operative sample results. The most common antibiotic *Streptococcus Milleri* patients were switched to was benzylpenicillin (40%). These findings are corroborated by a 2020 literature review by Issa *et al.*, who found that over 40% of patients with *Streptococcus Milleri* infections were exposed to three or more antibiotics during their duration of treatment (23). This bears concerning implications for antimicrobial resistance.

Currently, there are no specific guidelines available for the antibiotic management of superficial suppurative lymphadenitis. The closest guideline available is on cervical lymphadenopathy, as outlined on the Therapeutic Guidelines website (13). This guideline was last updated in April 2019 and advises that the most common cause of cervical lymphadenopathy is *Staphylococcus Aureus* and *Streptococcus Pyogenes*. The guidelines recommend cefalexin or flucloxacillin as first line treatment and clindamycin for patients with hypersensitivity to penicillins.

Risk factors for *Streptococcus Milleri* infections include factors that can damage local mucosal barriers and lead to the spread of bacteria, such as smoking and poor dentition (24). Conditions associated with immunodeficiency, such as diabetes and cancer, are also risk factors (16). Based on these risk factors, the suspicion of *Streptococcus Milleri* as the cause of a neck abscess depends on the patient's clinical presentation and underlying risk factors.

Streptococcus Milleri has shown susceptibility to beta-lactams—primarily penicillin G (3,14,25) and variable susceptibility to cephalosporins (14). Resistance to macrolides has been reported to occur in up to 16.6% of *Streptococcus Milleri* cultures (26). Resistance to penicillin—albeit in low numbers—has also been reported in other literature (26,27), highlighting the importance of prudent antimicrobial stewardship. In patients with penicillin hypersensitivity, vancomycin is an appropriate alternative treatment (28). A 2012 case series by Foxton *et al.* on *Streptococcus Milleri* in neck abscesses found that all cultures were sensitive to penicillin G, cephalexin and erythromycin (10). A study by Aracil *et al.* found that first generation cephalosporins

exhibited good activity on *Streptococcus Milleri*, but ultimately recommended beta-lactams as the antibiotic of choice (14). A study by Gómez-Garcés *et al.* found that beta-lactams, vancomycin, chloramphenicol, and trimethoprim exhibited good activity against *Streptococcus Milleri* (28). Considering these findings, we recommend initiating antimicrobial treatment with penicillin G in suspected *Streptococcus Milleri* neck abscesses.

In our study, the relationship between patients who cultured *Streptococcus Milleri* and gender, age, change in IV antibiotics, representation and total duration of antibiotics was not statistically significant (P>0.05). This aligns with findings in literature where studies have not found statistically significance for these demographic factors (20,29). One reason may be that as literature on *Streptococcus Milleri* remains scarce, most studies on head and neck abscesses are case series and single-centre studies. Nevertheless, this is the first study of its kind to review the incidence of *Streptococcus Milleri* in superficial suppurative lymphadenitis patients.

Conclusions

This study found that *Streptococcus Milleri* was the most common microorganism cultured in patients with superficial suppurative lymphadenitis. *Streptococcus Milleri* was more common in male patients and patients aged 18 years old and older. In this study, patients with *Streptococcus Milleri* infections experienced longer hospitalization, required longer duration of treatment and treatment adjustment, and had a higher rate of representation. The odds ratios for gender (male/female), changes in IV antibiotics, and representation were greater than 1, indicating a higher likelihood of these outcomes; however, none of these relationships were statistically significant (P>0.05). The findings of this study demonstrate a need for increased awareness of *Streptococcus Milleri* in patients presenting with superficial suppurative lymphadenitis and provide foundational insights for future research in this area.

Limitations

As a single-centre study, a limitation of this study is the small sample size. This may impact the validity of the conclusions drawn. Other limitations are that this is a retrospective review. This study also did not include patients who had other means of neck abscess drainage, such as ultrasound-guided drainage.

Notably, 71.4% of patients with *Streptococcus Milleri* experienced changes in their IV antibiotics compared to 30.4% in the non-*Streptococcus Milleri* group, with a P value of 0.08 suggesting a trend toward significance. The results of this study raise the possibility of exploring different diagnostic methods to improve rapid diagnosis and allow earlier treatment with appropriate antibiotics. Focusing efforts on targeted antibiotic therapy will be useful in improving patient outcomes and reducing rates of antibiotic resistance. Future applications of these results could be used to inform treatment approaches and protocols with patients who present with superficial suppurative lymphadenitis. Future studies should aim to enrol larger patient populations across multiple centres to compare findings.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://www.theajo.com/article/view/10.21037/10.21037/ajo-24-46/rc

Data Sharing Statement: Available at https://www.theajo.com/article/view/10.21037/ajo-24-46/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was granted an ethics exemption by the Gold Coast Health Service Ethics Committee (HREC Reference HREC/2024/QGC/110022) due to its classification as a clinical audit. The requirement for individual consent was waived as this was a retrospective study.

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