A systematic review of the role of penicillin vs penicillin plus metronidazole in the management of peritonsillar abscess.

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Abstract

Background Peritonsillar abscess is a common clinical problem. Management involves drainage of the abscess and administration of antibiotics. The choice of antibiotic is related to the polymicrobial growth of aspirate cultures, leading to prescriptions of co-amoxiclav, or metronidazole in addition to phenoxymethylpenicillin. However there is little evidence to support this. Objectives The aim of this review was to assess clinical effectiveness of phenoxymethylpenicillin vs phenoxymethylpenicillin plus anaerobic cover in the management of peritonsillar abscess. Design/Setting A systematic review of literature and clinical trial databases in accordance with the PRISMA 2020 statement. Studies were screened for eligibility by two independent reviewers. Main outcome measure Three studies were included, two comparing oral penicillin to oral penicillin plus metronidazole, one comparing IM/oral penicillin to IM/oral sulbactam-ampicillin. Clinical outcomes were assessed in all, including recurrence rate, symptom improvement and duration of pyrexia. Results There was no significant difference in any clinical outcome across all studies between the two groups. One study found a significant increase in diarrhoea and vomiting as a side effect in the group receiving metronidazole plus penicillin compared to penicillin alone (p=0.01). Conclusion On reviewing the literature, no significant clinical benefit has been demonstrated in the addition of either metronidazole or more broad-spectrum antibiotic cover compared to oral penicillin monotherapy for peritonsillar abscess when combined with incision and drainage protocols. Moreover, unnecessary broad-spectrum antibiotics contribute to increased side effects, costs, and antimicrobial resistance.

Abstract

Background

Peritonsillar abscess is a common clinical problem. Management involves drainage of the abscess and administration of antibiotics. The choice of antibiotic is related to the polymicrobial growth of aspirate cultures, leading to prescriptions of co-amoxiclav, or metronidazole in addition to phenoxymethylpenicillin. However there is little evidence to support this.

Objectives

The aim of this review was to assess clinical effectiveness of phenoxymethylpenicillin vs phenoxymethylpenicillin plus anaerobic cover in the management of peritonsillar abscess.

Design/Setting

A systematic review of literature and clinical trial databases in accordance with the PRISMA 2020 statement. Studies were screened for eligibility by two independent reviewers.

Main outcome measure

Three studies were included, two comparing oral penicillin to oral penicillin plus metronidazole, one comparing IM/oral penicillin to IM/oral sulbactam-ampicillin. Clinical outcomes were assessed in all, including recurrence rate, symptom improvement and duration of pyrexia.

Results

There was no significant difference in any clinical outcome across all studies between the two groups. One study found a significant increase in diarrhoea and vomiting as a side effect in the group receiving metronidazole plus penicillin compared to penicillin alone (p=0.01).

Conclusion

On reviewing the literature, no significant clinical benefit has been demonstrated in the addition of either metronidazole or more broad-spectrum antibiotic cover compared to oral penicillin monotherapy for peritonsillar abscess when combined with incision and drainage protocols. Moreover, unnecessary broad-spectrum antibiotics contribute to increased side effects, costs, and antimicrobial resistance.

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Introduction

Peritonsillar abscess, commonly called a quinsy, is a collection of pus between capsule of the palatine tonsil and the superior constrictor muscle. It's anterior and posterior boundaries are formed by the palatoglossus, and palatopharyngeus, respectively. It is the most common deep neck space infection, with previous studies showing an estimated incidence of 37/100,000.[1] Peritonsillar abscess primarily affects young adults during the months of April to May and November to December, when exudative tonsillitis and streptococcal pharyngitis are at their peak.[2] Symptoms of this condition include sore throat and otalgia on the affected side, trismus, malaise, halitosis and fever.[3] Clinical signs on examination include swelling and erythema of the soft palate on the affected side with deviation of the uvula to the contralateral side, trismus and cervical lymphadenopathy. Management of a quinsy involves aspiration of the abscess and administration of antibiotics.[4] Cultures of the aspirated pus commonly produce polymicrobial growth of gram positive and gram negative bacteria, including aerobes (e.g. *Streptococcus pyogenes)* and anaerobes (e.g *Fusobacterium spp*).[5–7] As a result many institutions prescribe antibiotics such co-amoxiclav, or metronidazole in addition to the traditional narrower spectrum antibiotics like phenoxymethylpenicillin for fear of under-treating.[8–12] The proposed rationale for prescribing these broader spectrum antibiotics is primarily to prevent complications secondary to the gram negative anaerobe,*Fusobacterium necrophorum* such as Lemierre's syndrome.[7,13] First described in 1936, Lemierre's syndrome consists of a bacteraemia with thrombophlebitis of the internal jugular vein, which can also result in septic emboli.[14] However little evidence exists to support the use of penicillin plus additional anaerobic cover in the management of peritonsillar abscess.[15,16] Furthermore, their prescription is not without potential complication. Agents with a broader spectrum of activity are known to have increased side effects plus their use increases the incidence and prevalence of antibiotic resistant organisms.[17,18]

The aim of this systematic review is to assess penicillin (or allergy alternative) vs penicillin (or allergy alternative) plus anaerobic cover in the management of peritonsillar abscess.

Material and methods

Data sources and literature search

A systematic review was done in accordance with the PRISMA 2020 statement.[19] The search was conducted in Ovid MEDLINE, Ovid Embase, PubMed, Web of Science, Cochrane library and ClinicalTrials.gov databases from inception until before the 26th of March 2021. The following search terms and strategy was used:" (Peritonsillar Abscess OR quinsy) AND (Penicillin OR Penicillin V OR Phenoxymethylpenicillin OR Clarithromycin OR Clindamycin OR Erythromycin OR Azithromycin OR Monotherapy OR Dual therapy

OR Amoxicillin-Potassium Clavulanate Combination OR Co-amoxiclav OR Augmentin OR Metronidazole OR Anti-Bacterial Agents OR Antibiotics OR Anti-Infective Agents OR Antimicrobial OR Anaerobic Bacteria OR Anaerobic OR Macrolide)". The titles and abstracts from the initial search results were screened independently by two authors (KP and CMM).

Study selection

The inclusion criteria were a) studies that evaluate the role of penicillin alone (or equivalent penicillin allergic) versus penicillin plus additional anaerobic cover in the management of peritonsillar abscess, b)Randomized control trials, c)published in English language only. Studies that did not compare a penicillin alone (or equivalent penicillin allergic) versus penicillin plus additional anaerobic cover were excluded. Duplicate studies, reviews, comments, animal studies, letters to the editor and studies demonstrating high risk of bias on analysis were also excluded. Data extraction was performed by two authors (KP and CMM) independently.

Type of participants

Adults or children with a clinical diagnosis of peritonsillar abscess.

Type of interventions

Any RCT which involved the administration of antibiotics, specifically where one group was prescribed Penicillin (or allergy alternative) and the other group was prescribed Penicillin (or allergy alternative) plus additional anaerobic cover.

Outcomes

Measured outcomes were rate of recurrence, and resolution of clinical symptoms.

Data extraction and analysis

After the generation of the list of studies meeting the inclusion criteria, KP and CMM each performed an in depth review of studies and extracted all relevant data for comparison.

Results

Figure 1: PRISMA process.

Table 1: Included studies.

Table 2: Table showing content of studies analysed.

Search Results

Three studies were included in the review as set by the inclusion criteria, described in **table 1** . All studies included were randomised control trials (RCTs). Whilst two RCTs compared penicillin alone to penicillin plus metronidazole, the third looked at penicillin in comparison with a broader spectrum penicllin (ampicillin) combined with a beta-lactamase inhibitor (Sulbactam). All studies assessed the clinical outcomes of these treatments on peritonsillar abscess, including recurrence rate, symptom improvement and the duration of pyrexia. The outcomes will be grouped and assessed across the evidence. **Table 2** shows the full findings of each study.

Outcomes assessed

Recurrence

Wiksten et al 2016 conducted a double-blind, adequately powered RCT involving 200 patients.[15] With the primary outcome measured being recurrence within 56 days of follow up, they found that there was no significant difference in the recurrence rates between the two groups (penicillin and placebo vs penicillin and metronidazole). Furthermore, no significant difference was found in the time to recurrence or the baseline characteristics of these patients including age, gender, smoking status or prior antibiotic use. Similar findings were identified by Tuner et al 1986 in which all patients in both the penicillin and placebo and the penicillin

and metronidazole group were deemed fully recovered after 10 days of treatment.[20] Every patient was treated with needle aspiration or incision and drainage daily for the 10 days or until no pus was drained, and the main conclusion drawn was that daily incision and debridement along with antibiotics is the treatment of choice.

Symptoms

Wiksten et al 2016 assessed symptom duration with patient questionnaires. The follow up of the questionnaires fell well below the number required for statistical power, however intention to treat analysis was used. The mean duration of throat-related symptoms (difficult mouth opening, sore throat, painful swallowing) was 5.3 days in the penicillin and metronidazole group and 5.6 days in the penicillin and placebo group; this was not statistically significant. The patients also reported on their general physical condition and presence of pyrexia, and these findings were not statistically different between the two groups.

Yilmaz et al 1998 conducted a double blind RCT comparing a 10-day course procaine-penicillin alone vs sulbactam-ampicillin.[21] There were 42 patients in total, randomly assigned however the co-morbidities or initial clinical symptoms on presentation were not described. Both treatments were given intramuscularly on an outpatient basis. The main resistance mechanism of some anaerobic bacteria to beta-lactams is beta-lactamase production. Therefore the addition of a beta-lactamase inhibitor, sulbactam, to the ampicillin group in this instance broadens the spectrum of antibiotic activity.[22] The duration of throat pain and the time to resumption of normal eating in both groups as measured by patient report of symptoms was not significantly different. Axillary temperature did also not differ significantly between the groups. Turner et al 1986 broadly described the clinical outcomes of the penicillin and placebo vs penicillin and metronidazole as very similar between groups.

Wiksten et al 2016 also asked patients to report on symptoms associated with adverse antibiotic effects. The study found a significant increase in the association of nausea and diarrhoea with the penicillin and metronidazole group compared with the penicillin and placebo group, advocating the use of penicillin alone for the desired clinical outcome with minimal treatment harm. Although many of the other papers included discuss the harms of unnecessary additional treatment Wiksten et al 2016 were the only group to formally assess the increased risk of side effects.

Risk of Bias

Risk of bias was assessed for each study included in this systematic review. For randomised trials the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used, as seen in **table 3** .[23,24]

Table 3: Table showing risk of bias in randomised trials.

Discussion

In the review of the literature to date, no significant clinical harm has been reported using oral formulations of phenoxymethyl penicillin alone as part of peritonsillar abscess incision and drainage interventions in the treatment of peritonsillar abscess. Specifically, here, the studies focussed on the clinical outcomes rather than the microbiology findings. We have not focussed the polymicrobial nature of pus samples from quinsy and antibiotic administration. This is because ultimately resolution of symptoms and clinical cure is the priority in these patients.

All studies advocated the use of either needle aspiration or incision and drainage as the source control measure in addition to the appropriate administration of antibiotics, and this is a well-documented treatment in the literature.[25] It is the general consensus that antibiotics alone are not appropriate for the treatment of peritonsillar abscess, and the literature has shown no difference in effectiveness between needle aspiration vs incision.[4]What differed between the studies reviewed, was the use of aspiration or incision and drainage. Turner et al 1986 performed daily aspiration or incision and drainage for up to 10 days or until no more pus was drained. At the end of the 10 days, patients in both groups were deemed completely

treated, and no recurrence was demonstrated. In contrast Wiksten et al 2016 performed needle aspiration on day one and then monitored for signs of recurrence within a 56-day window. One could argue daily drainage is eliminating the risk of any potential recurrence from sub-therapeutic antibiotic therapy, and therefore it is hard to assess accurately the effect of the antibiotic.

This systematic review is a useful addition to the literature in the context of rationalising antimicrobial choice that provides effective clinical cure without unnecessarily broadening the antimicrobial spectrum of activity. In the context of increasing burden of antimicrobial resistance[26], the current evidence (such as it is) suggests that addition of a second agent specifically targeting anaerobes (Metronidazole) and other pathogens (Sulbactam-Ampicillin) does not provide additional clinical benefit. Further optimisation of therapy to improve clinical efficacy and lessen impact on resident flora from single agent oral phenoxymethyl penicillin may be considered in context of optimising dose, frequency and duration. Furthermore all three studies used a 10 day treatment duration for which evidence is lacking. In line with other specialties reviewing the use of shorter duration of antimicrobials whilst maintain clinical efficacy, it would be appropriate to consider shorter courses in the light of improvements in clinical signs and symptoms and effective surgical drainage.

When analysing potential benefit of the addition of metronidazole to penicillin for the treatment of peritonsillar abscess, another important factor to consider is cost. A typical course of oral metronidazole is 400mg three times a day for seven days, with a cost of around £2.17 in the NHS.[28] The current evidence does not support the routine use of metronidazole (or second agent) in the routine management of quinsy, therefore there is the potential for cost saving if only single therapy penicillin is prescribed.

Strengths, limitations and potential bias of evidence

This systematic review to the best of our knowledge is the first of its kind to collate the evidence surrounding penicillin vs metronidazole (or broad spectrum penicillin) for the treatment of peritonsillar abscess, looking specifically at clinical response. Despite the high frequency of presentations with peritonsillar abscess, the optimum antibiotic(s) treatment of choice is still unclear and no consensus has been reached. Given this uncertainty, it is unsurprising only three studies have been found that assess the clinical effectiveness of penicillin against combination with metronidazole (or broad-spectrum counterparts), and therefore the main limitation of this review is the small amount of evidence available to present. The potential for concerns over bias in these studies has been identified from the screening tools. Of the three randomised control trials, all were judged to have some risk of bias. The differing pencillin agents used, route, dose and frequency also limit direct extrapolation to clinical practice.

A confounding and limiting factor affecting interpretation was the use of different penicillin agent used, route, dose and frequency. Similar for metronidazole with dosages varying between 400mg TID for 7 days and 800mg BID for 10 days. These schedules will not be applicable to many current practices and understandings of the pharmacokinetics and pharmacodynamics of oral phenoxymethyl penicillin and metronidazole.

Implications for future clinical practice and research

The reviewed evidence suggests that in the presence of effective drainage of the peritonsillar abscess single agent oral phenoxymethyl penicillin is not associated with adverse clinical outcomes. There is no evidence to suggest benefit of administration of metronidazole in the management of quinsy. As such, clinicians should avoid prescribing additional metronidazole in this clinical setting. Some studies have suggested the addition of metronidazole if no clinical improvement after 24 hours.[29]Only three studies were included in this systematic review. Further research into penicillin alone (or equivalent pen allergic) versus penicillin plus additional anaerobic cover using updated dosing schedules is needed.

Conclusions

Peritonsillar abscess is an extremely common ENT condition, and as such appropriate safe and effective management is critical. Current evidence suggests no clinical benefit for the routine administration of additional anaerobic cover (Metronidazole) to oral phenoxymethyl penicillin as part of the treatment of peritonsillar abscess. The use of single agent oral phenoxymethyl pencillin is effective and avoids the use of additional

anaerobic cover reducing costs in healthcare systems, as well as reduced pressure to develop antimicrobial resistance.

Key Points

- Peritonsillar abscess is a common deep neck space infection.
- Pus from the abscess is often polymicrobial, and usually contain anaerobes.
- Single agent oral Phenoxymethyl pencillin provides a safe and effective clinical outcome in the outpatient setting and as part of surgical management of the peritonsillar abscess
- Many clinicians prescribe metronidazole as well as a penicillin or an allergy alternative. There is no evidence to suggest additional benefit by adding metronidazole, with some studies suggesting increased side effects
- More work is required to strengthen the evidence base on single narrow spectrum agent prescribing for optimum dose, frequency and duration of treatment

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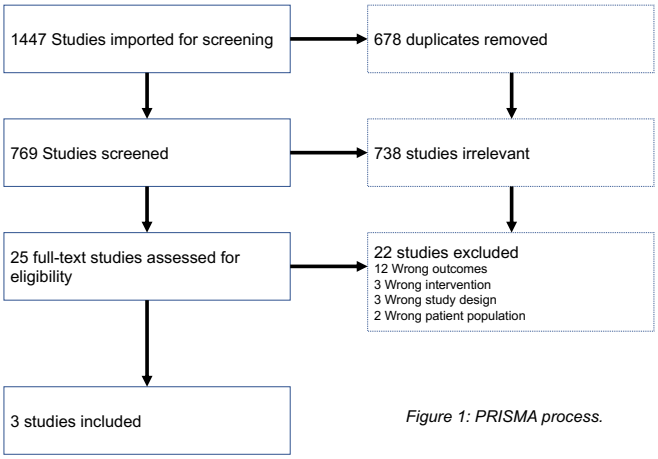

Figure 1: PRISMA process.