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

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Contributions

CMM & KP did equal amounts of work and are **joint first author**. They were involved in Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing, Original draft Writing, Review & editing.

XL: Conceptualization, Methodology, Writing.

AW: Conceptualization, Writing, Original draft Writing.

HC: Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing, Original draft Writing

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All authors approved the final draft of the paper.

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MeSH Key words : Palatine Tonsil, Abscess, Anti-Bacterial Agents, Drug Resistance, Bacterial

Abstract

Introduction

Peritonsillar abscess is a localised infection in the peritonsillar space. Pus from the abscess can contain anaerobes. Many clinicians prescribe metronidazole in addition to penicillin, however evidence to support this is limited. We assessed the evidence of benefit of metronidazole for treatment of peritonsillar abscess.

Methods

Systematic review of literature and databases including Ovid MEDLINE, Ovid Embase, PubMed and Cochrane library. Search terms included all variations of peritonsillar abscess, penicillin and metronidazole.

Results

Three Randomized Control Trials were included. All studies assessed the clinical outcomes after treatment for peritonsillar abscess, including recurrence rate, length of hospital stay and symptom improvement. There was no evidence to suggest additional benefit with metronidazole, with studies suggesting increased side effects.

Conclusions

Evidence does not support the addition of metronidazole in first line management of peritonsillar abscess. Further trials to establish optimum dose and duration schedules of oral phenoxymethyl-penicillin would benefit clinical practice.

Key Words: Otolaryngology, Anti-Bacterial Agents

Word count 150

Introduction

Peritonsillar abscess, commonly called a quinsy, is a collection of pus between the capsule of the palatine tonsil and the superior constrictor muscle. Its 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]

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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.

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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 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.

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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.

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Results

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 penicillin (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

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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

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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]

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Discussion

In the review of the literature to date, no significant clinical harm has been reported using oral formulations of phenoxymethylpenicillin 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 on 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

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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 phenoxymethylpenicillin 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 maintaining clinical efficacy, it would be appropriate to consider shorter courses in the light of improvements in clinical signs and symptoms and effective surgical drainage.

Antimicrobial resistance (AMR) is a global challenge. The World Health Organisation has endorsed a global action plan on AMR, and studies have predicted that by 2050 AMR will result in 10 million deaths.[27] To this end, antibiotic stewardship is a key policy within the NHS. In the context of the systematic review findings, ENT surgeons treating patients with peritonsillar abscess must ensure prudent use of the correct antibiotic and not prescribe an unnecessary second agent.

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

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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 penicillin agents used, route, dose and frequency also limit direct extrapolation to clinical practice. 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 phenoxymethylpenicillin 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 phenoxymethylpenicillin 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.[28]Only three studies were included in this systematic review. We would welcome a well powered, high quality RCT to establish the optimum dose and duration schedule of oral phenoxymethylpenicillin to better inform clinical practice. Further more this would ensure that ENT surgeons are contributing to high quality research in the global fight against anti-microbial resistance. With the increasing burden of antimicrobial resistance it would also be prudent to undertake routine microbiological surveillance for susceptibility to penicillin in bacteria isolated from peritonsillar infections.

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Surveillance data generated will be invaluable in informing rational empiric antimicrobial choices.

Summary

- Peritonsillar abscess is the most common deep neck space infection.
- Pus from the abscess is often polymicrobial, and can contain anaerobes.
- Many clinicians prescribe metronidazole as well as a penicillin or an allergy alternative.
- However there is no evidence to suggest additional benefit by adding metronidazole, with some studies suggesting increased side effects.
- Clinicians must be mindful of their own impact on the incidence of antibiotic resistant organisms.
- We would welcome a well powered, high quality RCT to establish the optimum dose and duration schedule of oral phenoxymethylpenicillin to better inform clinical practice.

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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 phenoxymethylpenicillin as part of the treatment of peritonsillar abscess. The use of single agent oral phenoxymethylpencillin is effective and avoids the use of additional anaerobic cover. Further trials to establish optimum dose and duration schedules of oral phenoxymethylpenicillin would be the next step to better inform clinical practice.

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Research ethics committee approval is not required for access to the data.

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Conflicts of interest None of the authors have any conflict of interest.

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Figure 1: PRISMA process.

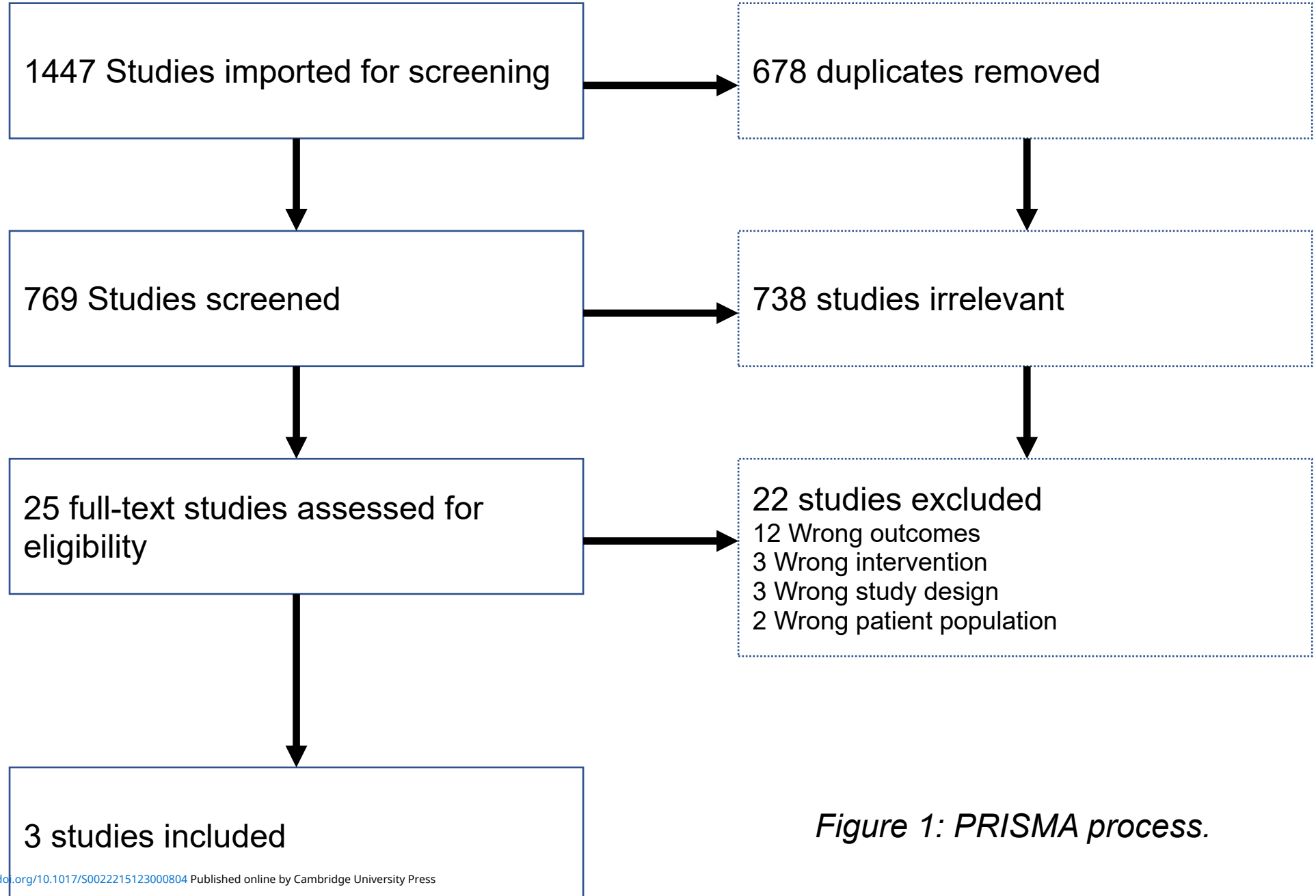

Figure 1: PRISMA process.

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Table 1: Included studies.

Author	**Study design**	**Question**	**Outcomes**	**Results**
Turner et al 1986	Double blind RCT	Penicillin + placebo vs penicillin + metronidazole	-Clinical findings -Laboratory findings -Microbial findings	No significant difference in clinical outcomes at day 10
Wiksten et al 2016	Double blind RCT	Penicillin +placebo vs Penicillin + metronidazole	-Recurrence rates -Throat related symptoms, fever, overall physical condition	No significant difference in recurrence rate or symptom duration Metronidazole associated with significant increase in nausea and diarrhoea (p=0.01)
Yilmaz et al 1998	RCT	Procaine-penicillin vs ampicillin-sulbactam	-Axillary temp -Throat pain -Eating and drinking as normal	No significant difference in any outcome measured

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Table 2: Table showing content of studies analysed.

Author	**Study design**	**Setting**	**Antimicrobial comparison**	**Surgical intervention**	**Numbers treated and Outcomes**	**Results**
Tuner et al 1986	Double blind RCT	In-patient	2g (oral) Phenoxymethylpenicillin & placebo BID for 10 days vs 2g (oral) Phenoxymethylpenicillin & 0.8g (oral) metronidazole BID for 10 days	Mucosal incision and daily drainage by debridation until no further pus was found.	N= 20 patients assigned to each group. Total N= 40 -Clinical findings -Laboratory findings -Microbial findings	No significant difference in clinical outcomes at day 10
Yilmaz et al 1998	RCT	Out-patient	25,000 U $kg^{-1}day^{-1}$ Procaine-penicillin (IM) switch to oral penicillin (dose/frequency/formula not specified) for 10 days total duration vs 50mg $kg^{-1}day^{-1}$ Sulbactam-Ampicillin (IM)	Peroral incision and drainage. Daily outpatient follow-up with aspiration of the abscess cavity	N= 21 patients assigned to each group. Total N= 42 -Axillary temp -Throat pain -Eating and drinking as normal	No significant difference in any outcome measured

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			switch to oral Sulbactam-Ampicillin (dose/frequency/formula not specified) for 10 days total duration	until no drainage was encountered.		
Wiksten et al 2016	Double blind RCT	Out-patient	1000,000 IU (Oral) Penicillin (formula not specified) & placebo TID for 10 days vs 1000,000 IU (Oral) Penicillin (formula not specified) & Metronidazole 400mg TID for 7 days	Incision and drainage at presentation	N=100 patients assigned to each group. Total N=200 -Recurrence rates -Throat related symptoms, fever, overall physical condition	No significant difference in recurrence rate or symptom duration Metronidazole associated with significant increase in nausea and diarrhoea (p=0.01)

Note 1000,000 IU = 625mg Phenoxymethylpenicillin

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

Study	Randomisation process	Deviations from intended outcomes	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Wiksten	Low	Low	Some concerns	Low	Low	Some concerns
Yilmaz	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Tuner	Some concerns	Low	Low	Low	Some concerns	Some concerns

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