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The Use of Postoperative Antibiotics Following Endoscopic Sinus Surgery for Chronic Rhinosinusitis: A Systematic Review and Meta-analysis

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The use of postoperative antibiotics following endoscopic sinus surgery for chronic rhinosinusitis: a systematic review and meta-analysis

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Abstract

Background

Endoscopic sinus surgery is performed for medically recalcitrant chronic rhinosinusitis. There is no universally accepted strategy regarding post-operative antibiotics despite the high rates of usage worldwide. The aim of this study was to analyse patient-reported and objective outcomes behind antibiotic use following endoscopic sinus surgery.

Methods

A search of electronic databases was performed. Eligible randomised controlled trials (RCTs) and observational trials were included. The primary outcome was patient reported outcome measures. Secondary outcomes were local infections, endoscopy scores and adverse events. Meta-analysis was performed.

Results

Of 1045 publications identified, 7 were included in the qualitative synthesis and 5 RCTs were included in meta-analysis. Antibiotic regimens varied between studies in terms of antibiotic selection, timing commenced and duration of use. Meta-analysis suggested no significant difference between placebo and antibiotics in patient reported outcome measures (standardised mean difference (SMD) -0.215, 95% confidence interval (CI) -0.637 to 0.207) or endoscopic scores (SMD -2.86, 95% CI -0.846 to 0.273). There was no consistent definition in reporting of infection; therefore, this outcome cannot be comprehensively considered. No severe adverse events were attributable to antibiotics.

Conclusions

From the studies analysed, there is no level 1 evidence to suggest that antibiotics improved patient outcomes following sinus surgery. However, there was significant heterogeneity in outcome measures and no clear data exists regarding the effects of antibiotics on postoperative infections. The available evidence at present is not enough to make a recommendation in either direction. Further designed larger RCTs are required to investigate these questions in more detail.

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Background

Chronic rhinosinusitis (CRS) is a multifactorial disease characterised by inflammation of the sinonasal mucosa and a range of symptoms including nasal obstruction, rhinorrhoea, facial pain and olfactory dysfunction. Broadly, patients present with (CRSwNP) and without nasal polyposis (CRSsNP). The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) provides guidelines for progressive management of such patients[1]. Functional endoscopic sinus surgery (FESS) is recommended when there is no response to optimal medical treatment[1,2]. Post-operative treatment varies between clinicians including nasal irrigation, decongestants, intranasal steroids and antibiotics[3,4]. Traditionally, use of postoperative antibiotics for 7 to 10 days has been recommended to prevent bacterial infection after FESS[5,6]. A 2018 survey distributed to members of the American Rhinologic Society demonstrated that 62.3% routinely gave postoperative antibiotics, citing reasons including postoperative infection (75.6%), synechiae formation (58.3%) and shortening of postoperative sinonasal symptoms (29.9%)[4].

Surgical procedures have conventionally been classified as clean, clean-contaminated, contaminated or dirty[7]. FESS is a clean-contaminated case, due to bacterial colonization of the sinonasal cavity. Antibiotic prophylaxis is used in most surgical interventions where the surgical site is clean-contaminated or contaminated[8]. However, the use of post-operative antibiotics is a contentious issue, particularly in an environment with increasing microbial resistance. It is important to address this subject to help standardise post-operative regimens in future to help minimise patient harm and ensure appropriate antimicrobial stewardship is practiced.

Aims and Objectives

This review aims to compare the outcomes of postoperative antibiotic usage in adults undergoing endoscopic sinus surgery for chronic rhinosinusitis. The primary objective was to compare post-operative nasal symptom scores, via patient reported outcome measures. The secondary objectives were to assess objective endoscopy scores, post-operative infection rates and adverse events.

Methods

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This review utilized the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[9]. The protocol was registered with the research registry (PROSPERO CRD42019126083).

Search strategy

A search strategy was developed by a medical librarian to capture all relevant terms. The electronic database search was performed using EMBASE, MEDLINE, COCHRANE and CINAHL. There were no publication year restrictions. Only English language articles were included. The search strategies were exported to a bibliographic database (Mendeley Desktop Version 1.19.2) and duplicates were excluded. The full search strategy is shown in Supplementary Material A [Insert Supplementary Material A]. Two researchers (CS, JW) independently assessed titles, abstracts, and full texts of the retrieved articles.

Eligibility criteria

Participants

Studies in adults with chronic rhinosinusitis undergoing endoscopic sinus surgery were considered eligible for inclusion in this review. The inclusion criteria were: (1) antibiotic prophylaxis prescribed following endoscopic sinus surgery for chronic rhinosinusitis; (2) patient reported outcome measure was used. Studies were excluded for the following characteristics: sinonasal malignancy, children less than 16 comprised greater than 20% of the cohort, cystic fibrosis or primary ciliary dyskinesia, and where topical antibiotics or antibiotic-impregnated stents were used. Discrepancies between the two reviewers were discussed to reach consensus. When no consensus was met, the senior author (NT) was consulted. Reasons for study exclusion and inclusion were noted.

Intervention and comparison

Included studies had to compare post-operative antibiotic regimen with either placebo, standard of care or alternative antibiotic courses. Standard of care could consist of saline irrigation, steroid nasal spray, steroid nasal drops, nasal decongestant or alternative antibiotics e.g. topical or pre-

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existing local policy. To reduce heterogeneity for the meta-analysis, included studies had to compare post-operative antibiotic regimens with either placebo or standard of care.

Outcomes

Follow-up needed to be at least 30 days. Desirable time points of outcome assessment were pre-operative, 12-weeks and 6-months. Various subjective outcome measures were included, such as sinonasal outcome test (SNOT-20 or 22) and Visual Analogue Scales (VAS). For objective assessments, again various scores were accepted including Perioperative Sinus Endoscopy (POSE) and Lund-Mackay endoscopy score.

Other criteria

The preferred study design was a randomised controlled trial (RCT) with the above comparators. However, we were apprehensive of not identifying a significant number of RCTs and as we were mindful of capturing all currently available evidence, we also considered observational study designs for inclusion in the review (but not in the meta-analysis).

Assessment of risk of bias

The Cochrane collaboration tool for assessing risk of bias in RCT was used for assessing methodological quality. The Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) was used for non-randomised studies. Two authors performed bias assessment independently.

Data Extraction and Data Analysis

Data was extracted into a standardised document to summarise key outcomes. Where data was not sufficient, authors were contacted.

Meta-Analysis

Meta-analysis was performed to compare the primary and secondary outcomes between groups where the treatment intervention was antibiotic usage versus a comparator of placebo or standard of care. The meta-analysis was performed using R software[10–12] on the standardised mean between-group difference because of the inconsistency in the outcomes measured for each

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study. If the outcome was measured at multiple time points, the measurement obtained following the end of course of antibiotics was selected. This was to reduce the influence of repeated measures from the same participants may have upon estimates, i.e. this is likely to introduce a spurious reduction of variance. As some studies measured baseline before surgery (Albu, Jiang and Schalek) and some after (Amali and Haxel), we were unable to adjust for baseline measurements. As the length of antibiotic course ranged from two weeks to three months with varying regimens of antibiotics, random effects models were fitted to the whole dataset. Sub-group analyses was performed for short (<30 days) versus long (>30 days) course of antibiotics. This was an important sub-analysis to ensure that patients are not prescribed antibiotic courses for longer than optimal. However, for the sub-group analysis, fixed effects were used to examine differences between short and long intervention lengths, as we assumed studies within long or short interventions would be more similar. The I^2 and Q statistics were calculated as measures of consistency. As there were only 4 to 5 studies included in the meta-analysis there was no formal assessment of publication bias, as usually 10 studies are required.

Results

Study selection

The literature search yielded 1,045 records (Figure 1)[9]. Two additional records were identified through review of references. 757 articles remained after removal of duplicates. Based on title and abstract, 729 articles were excluded due to incompatibility with eligibility criteria. Of the remaining 28 full-text articles, 7 articles were initially included in this systematic review[13–19]. Two were later excluded prior to the meta-analysis due to lack of comparators or control group[17,19]. Due to the small number of studies and therefore the inability to sub-cohort studies into CRSwNP vs CRSsNP, it was decided to cohort all studies together as per sub-section analysis within International Consensus Statement on Allergy and Rhinology when insufficient studies exist[2].

Risk of bias assessment

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The risk of bias summary for the randomised trials and observational study is presented in Supplementary Material B and C [Insert Supplementary Material B and C]. There were concerns regarding lack of blinding of participants in 2 RCTs. This was due to the method of comparator provided: either no placebo or only 3-month provision of antibiotics without subsequent placebo whilst the other group proceeded with 6-month course of antibiotics. Incomplete data was presented leading to high risk of bias in two trials[15,17].

Study characteristics

Six RCTs and one retrospective cohort study were included in the qualitative synthesis. 5 were included in the meta-analysis. The retrospective cohort study was excluded; the exclusion was due to heterogeneous comparator being used (pre-specified long-term antibiotics as opposed to placebo or standard of care). An overview of included studies and details on their participants is provided in Table 1. Five RCTs compared antibiotic therapy to either placebo or no antibiotics; Table 2 provides an overview of interventions, outcomes and adverse events[13–16,18]. Of these, three provided a short course of antibiotics (3-weeks or less)[13,16,18] and two provided a 12-week course[14,15]. The other RCT compared 3-month versus 6-month erythromycin therapy[17]. The number of patients ranged from 43 and 61, respectively, before surgery with an attrition rate to 17 and 22 after 12 months. The retrospective cohort evaluated 376 patients and compared outcomes of culture-appropriate versus inappropriate antibiotics[19]. The outcomes for these papers are presented in Table 3.

None of the identified studies included patients with immunodeficiency or who were immunosuppressed. These conditions were a specific exclusion criterion in 5 articles[13,15,16,18,19] or were not specified in 2 articles[14,17]. The number of participants in all the studies was 817, with a range of 23 to 376 participants per study. 349 patients with nasal polyps and 274 without nasal polyps were described across the 7 studies. 2 studies did not specify the number of patients with or without polyps[16,17]; 1 study only described patients with polyps[18].

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Table 1*:* characteristics of the included studies; SEM, standard error of the mean; SD, standard deviation; TDS, three times a day; BD, twice daily; OD, once daily

Study	Design	Treatment intervention	Comparator	Intervention start?	Age in years (mean)()	Gender (number of males)	Nasal polyposis (number with polyps)	Sample size Intervention v comparator (recruited)	Follow-up points
Jiang, 2008 Single centre	Randomised controlled trial	Co-amoxiclav 375mg TDS, 3 weeks	Standard of care (no antibiotic)	Three times daily after surgery	30.5 (range 9-83)	41	Not specified	41 vs. 43	3 weeks
Schalek, 2009 Single centre	Randomised controlled trial	Anti-staphylococcal antibiotics (various), 3 weeks	Placebo	After surgery	52.7 (range 26-72)	13	23	13 vs. 10	3 months 6 months
Albu, 2010 Single centre	Randomised controlled trial	Co-amoxiclav 625mg BD, 2 weeks	Placebo	Twice daily after surgery	41 (range 18-65) vs. 44 (range 18-68)	25 vs. 20	40	50 vs. 50	5 days 12 days 21 days 30 days
Haxel, 2015 Single centre	Randomised controlled trial	Erythromycin 250mg OD, 12 weeks	Placebo	10-14 days post-op	45.7(SEM 12.8) vs. 47.7(SEM 12.5)	17 vs. 17	32	29 vs. 29 (Planned 35 vs. 35 but unable to recruit)	12 weeks 24 weeks
Amali, 2015 Single centre	Randomised controlled trial	Azithromycin 250mg OD, 12 weeks	Placebo	Daily after surgery	37.7 (range 15-62)	46	28	22 vs. 44	12 weeks
Nakamura, 2013 Single centre	Randomised controlled trial	Broad spectrum antibiotic for 1 week post-op then Clarithromycin 200mg OD, 3 months	Broad spectrum antibiotic for 1 week post-op then Clarithromycin 200mg OD, 6 months	1 week after surgery	52.6 (range 22-72) vs. 51.7(range 21-76)	Not specified	Not specified	44 vs. 66	3 months 6 months 1 year
Zhang, 2014 Single centre	Retrospective cohort	Culture-appropriate, 2 weeks	n/a	After surgery	48(SD 13)	217	226	376	1 month 3 months 6 months

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Table 2*:* comparison of subjective and objective outcomes in patients treated following FESS with and without antibiotics

Study	Follow-up point	Subjective outcome measures		Objective outcome measures		Missing data	Adverse events (AEs)	Authors' conclusions
		Outcome measure	Result	Outcome measure	Result			
Short-term results (less than one month)								
Jiang, 2008 SHORT COURSE	**3 weeks**	Symptom score (VAS; Lund-Mackay)[20] (median)	Ab: pre 23, post 14 NA: pre 25.5, post 16.5	Endoscopy score (Lund-Mackay, overall score)	Ab: pre 6, post 6 (p=0.627) NA: pre 7, post 6 (p=0.406)	10 in Ab group 3 in NA group Reasons not given	Not reported	Ab show no improvement in short-term outcomes post-FESS
Albu, 2010 SHORT COURSE	**5 days** **12 days** **21 days** **30 days**	Overall symptom score (VAS 0-10; Lund-Mackay) (mean)	Ab: pre 5.8, day-5 3.8, day-12 2.8, day-21 1.3, day-30 1.3 NA: pre 6.4, day-5 4.1, day-12 2.5, day-21 1.4, day-30 1.6 (p=0.66)	Perioperative Sinus Endoscopy (POSE, maximum score 20) – 1st reported at day-5 (mean)	Ab: pre NR, day-5 14.2, day-12 9.05, day-21 8.2, day-30 7.07 NA: pre NR, day-5 15.02, day-12 10.12, day-21 8.8, day-30 6.85 (p=0.81)	10 in Ab group 15 in NA group Reasons not given	Not reported	Ab modestly improved early healing phase
3-month results								
Schalek, 2009 SHORT COURSE	**3 months**	SNOT-22 (mean)	Ab: pre 41.46, post 17.62 NA: pre 39.10, post 20.6 (p=0.852)	Endoscopy score (maximum 9) (mean)	Ab: pre 7.62, post 2.92 NA: pre 7.8, post 4.1 (p=0.056)	No missing data	Not reported	Ab showed no improvement in symptoms; "approaching significance" in endoscopy
Amali, 2015 LONG COURSE	**12 weeks**	SNOT-22 (mean±SD)	Ab: pre 34.05±9.31, post 5.85±2.56 NA: pre 36.2±19.72, post 10.07±6.3 (p=0.001)	n/a	n/a	2 in Ab group 4 in NA group Lost to follow up	Nil serious AEs	Ab could reduce symptom recurrence post-FESS but need more evidence
Haxel, 2015 LONG COURSE	**12 weeks**	SNOT-20 (mean±SD) Initial scores at 2 weeks	Ab: initial 21.5±13.7, post 16.7±14.2 NA: initial 19.7±9.3, post 14.6±14.2 (p=0.6230)	Endoscopy score (maximum 7) (mean±SD) Initial scores at 2 weeks	Ab: initial 2.6±1.4, post 1.9±1.5 NA: initial 2.5±1.3, post 2.6±1.5 (p=0.0351)	8 in Ab group (2 lost, 1 withdrew consent, 4 AE, 1 SAE) 2 in NA group (1 withdrew consent, 1 AE)	2 SAE: epistaxis, dyspnoea AE: URTI, GI disturbances	No clinical advantage of Ab over placebo Small advantage of Ab in endoscopic scores
6-month results								
Schalek, 2009 SHORT COURSE	**6 months**	SNOT-22 (mean)	Ab: pre 41.46, post 19.23 NA: pre 39.10, post 20.7 (p=0.975)	Endoscopy score (maximum 9) (mean)	Ab: pre 7.62, post 3.4 NA: pre 7.8, post 2.31 (p=0.192)	No missing data	Not reported	Ab showed no improvement in symptom or endoscopy scores at 6-months
Haxel, 2015 LONG COURSE	**24 weeks**	SNOT-20 (mean)	Ab: initial 21.5±13.7, post 14.3±12.4 NA: initial 19.7±9.3, post 14.4±14.0 (p=0.8916)	Endoscopy score (maximum 7)	Ab: initial 2.6±1.4, post 1.9±1.6 NA: initial 2.5±1.3, post 2.0±1.5 (p=0.2524)			No clinical advantage of Ab over placebo

Ab = Post-operative antibiotics, NA = placebo or no post-operative antibiotics, SMD = standardised mean difference, SNOT = sino-nasal outcome test, VAS = visual analogue scale, LMS = Lund-Mackay scale, SD = standard deviation

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Table 3*:* outcomes of other publications; **raw data not provided and therefore numbers are extrapolated from graphs, † statistically significant difference between groups, CA = culture appropriate antibiotics, CIA = culture inappropriate antibiotics, CAAA = culture appropriate after adjustment, U = undetermined, 3m = 3-month course of antibiotic, 6m = 6-month course*

Study	Follow-up point	Subjective outcome measures		Objective outcome measures		Missing data	Adverse events	Authors' conclusions
		Outcome measure	Result	Outcome measure	Result			
Culture-appropriate versus culture-inappropriate antibiotics								
Zhang, 2014	**Before FESS**	SNOT-22 (mean)	CA: 38 CIA: 37 CAAA: 45 U: 41	n/a		Not specified	Not reported	CIA reduced short-term quality of life improvements after FESS. Culture guided selection of Ab may improve short-term FESS outcome
	1 month		CA: 20 CIA: 26 CAAA: 17 U: 19					
	3 months		CA: 12 CIA: 22 CAAA: 25 U: 20					
	6 months		CA: 23 CIA: 23 CAAA: 22 U: 20					
3-month versus 6-month course of antibiotics								
Nakamura*, 2013	**Before FESS**	Symptoms: 1. Rhinorrhoea 2. Postnasal drip 3. Obstruction 4. Headache VAS 0-100mm	1. 3m: 40 6m: 40 2. 3m: 40 6m: 35 3. 3m: 55 6m: 50 4. 3m: 28 6m: 18	Endoscopy score (% of patients with change in visible postnasal drip (0 nil; 1 mucous; 2 mucopurulent; 3 purulent)	3m: 62% 6m: 55%	3m: 1 6m: 4	No serious AEs	Macrolide administration for 3 months cannot fully restore the mucosa, and over secretion of mucus from the submucosal glands may persist. At 12 months after surgery, 6-month treatment group showed significantly higher disappearance rates and lower VAS symptoms than the 3-month antibiotic group. There was over 50% drop-out from 6 to 12-months
	3 months		1. 3m: 18 6m: 20 2. 3m: 18 6m: 18 3. 3m: 10 6m: 8 4. 3m: 5 6m: 10		3m: 20% 6m: 23%	3m: 5 6m: 9		
	6 months		1. 3m: 19 6m: 21 2. 3m: 19 6m: 19 3. 3m: 7 6m: 10 4. 3m: 6 6m: 11		3m: 21% 6m: 20%	3m: 5 6m: 15		
	12 months		1. 3m: 31 6m: 7† 2. 3m: 27 6m: 6† 3. 3m: 12 6m: 8 4. 3m: 9 6m: 5		3m: 20% 6m: 0%†	3m: 27 6m: 44		

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Follow-up periods

There was no consistency in length of follow-up. Three studies reported outcomes at 30-days or less only[13,16,19]. Three articles considered the 12-week time-point[14,15,17–19] and two also reported 6-month data[15,17–19].

Antibiotic regimens

Of interest, the regimens were different in terms of antibiotic selection, course duration, dosage, and timing commenced post-operatively. Two prescribing strategies were identified.

The first strategy, utilised in 4 articles, was to administer short-course (2-3 weeks) anti-staphylococcal agents. Jiang and Albu administered co-amoxiclav at doses of 375mg three times a day for 3 weeks and 625mg twice daily for 2 weeks, respectively[13,16]. The remaining RCT provided patients with various anti-staphylococcal antibiotics for 3 weeks (quinolone, co-amoxiclav or co-trimoxazole) according to pre-operative swab[18]. In the prospective observational study, a 2-week course of culture-appropriate antibiotics was prescribed[19]. In the second strategy, a macrolide antibiotic was provided for a minimum of 12 weeks, at doses that would be sub-therapeutic for treating active infections[14,15,17]. Nakamura compared 3-month versus 6-month course of macrolide antibiotic[17].

Haxel screened patients for inclusion in the study post-operatively and, therefore, erythromycin 250mg daily was only commenced between 10 and 14 days post-operatively[15]. Nakamura, provided all patients with a broad-spectrum antibiotic (e.g. piperacillin treatment dose) for 1-week and then commenced clarithromycin 200mg daily for either 3 or 6-months[17]. The 3-month group did not receive placebo upon completion of their shorter course of antibiotics.

Primary outcome: Subjective outcome measures

Subjective outcomes were reported in all articles. Two subjective outcome measures were used; four used the sinonasal outcome test (either SNOT-22[14,18,19] or SNOT-20[15]) and three used visual analogue scales of common nasal symptoms (0-100mm)[13,16,17]. Of the studies that compared

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antibiotics versus either placebo or no antibiotics, all showed a subjective benefit after sinus surgery, irrespective of whether patients had been given antibiotics, placebo or no antibiotics.

In articles studying the first antibiotic strategy (short course), there was no significant difference in symptom scores between the antibiotic and placebo groups[13,16,18]. With respect to the second strategy group (long course), one author concluded that long-term antibiotics might reduce symptom recurrence post-FESS, although it would require more investigation (difference in SNOT-22 between antibiotic and placebo, p=0.0001)[14]. Nakamura indicated that 6-month course was associated with better symptom scores (improved VAS for rhinorrhoea and postnasal drip, $p<0.05$)[17].

Meta-analysis: Subjective outcome measures

The forest plot of the meta-analysis for symptom scores is presented in Figure 2. The I^2 was 31% (95% confidence interval (CI) 0-73.7%). As the point estimate for I^2 is greater than 30% this indicates moderate heterogeneity between studies. Although the Cochran's Q statistic of 5.82, 4 degrees of freedom, p-value > 0.2 shows no evidence of heterogeneity, this has low power due to the small number of studies included. Therefore, a random effects model was fitted to the whole data set. The results of the overall random effects model in Figure 2 suggested that there was no statistically significant difference between placebo and antibiotics in subjective symptoms, with a standardised mean difference (SMD) of -0.215 (95% CI: -0.637 to 0.207), where a negative difference would favour antibiotics.

Sub-analysis suggested that within intervention length groups (<30-days versus >30-days), there was insufficient evidence to suggest a difference between antibiotic and placebo/no antibiotics. Although no statistically significant difference was identified, there was a trend of both the means and overall dataset to suggest that if the power was improved, outcomes may favour antibiotics. The SMD from the fixed effect subgroup model was -0.146 (95% CI: -0.449 to 0.158) for short and -0.314 (95% CI: -0.704 to 0.080) for long courses. However, with only two studies with prolonged intervention, it was difficult to produce precise estimates.

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Secondary outcomes

i) Objective outcome measures

Objective endoscopy outcomes were reported in 4 randomised studies[13,15,16,18]. Two formal endoscopic outcome scores were used: Lund-Mackay endoscopy score[16] and Perioperative Sinus Endoscopy score(POSE)[13]. Other studies assessed a variety of objective measures such as appearance of secretions and presence of polyps[15,17,18].

In articles studying the first antibiotic strategy, there was no consistency in results. One article reported no improvement in endoscopic scores in either groups[16]; two reported a modest improvement in endoscopic scores with antibiotics[18] and improvement in early healing phases[13], although differences were not statistically significant.

With respect to the second strategy, one article reported objective measures; there was a significant improvement in outcomes in the antibiotic group at 12-weeks, but the clinically significant difference had equalised by 6-months[15]. The endoscopic outcomes reported by Nakamura were the same at 3- and 6-months but by 12-months post-operatively, the 6-month antibiotic group showed significantly higher resolution of endoscopic appearances[15].

Meta-analysis: Objective outcome measures

The forest plot for objective endoscopy scores is presented in Figure 3. The I^2 value was 28%, 95% CI 0.0-73.2%, which suggests low heterogeneity between studies. There was insufficient evidence of a difference in effect size between studies based on the Q statistic of 4.17 with 3 degrees of freedom, *p*-value > 0.2, but again there is low power with only 4 studies. Therefore, a fixed effect model was appropriate. There was insufficient evidence of a difference between antibiotic and placebo, with SMD of -2.86 (95% CI: -0.846 to 0.273). Sub-group analysis by intervention length could not be performed as only one study reported endoscopy scores and provided antibiotics for more than 30 days[15].

ii) Local infection rates

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There was no clear consistent definition in reporting of infection rates and, therefore, this outcome cannot be comprehensively considered in this review. The perioperative endoscopy scores (POSE and Lund-Mackay) both included an assessment of the presence of 'obstructed/infected/inflamed' sinuses and presence of purulent secretions. However, the breakdown of the score was not provided, thus precluding further interpretation of the significance.

iii) Adverse events

Only three articles directly reported whether adverse events (AEs) had occurred, and of these, only Haxel reported any AEs[14,15,17]. Episodes of acute upper respiratory tract bacterial infections occurred in both treatment groups[15]. Infections were grouped together and included acute sinusitis, bronchitis and otitis media. The overall all-cause infection rate was higher in the treatment group (18 all-cause infections in 13 patients versus 10 in 9 patients). No severe adverse events were seen attributable to the antibiotics. The ratio of side effects was higher in the antibiotic group. Side effects included gastrointestinal disturbances (causing 4 antibiotic patients to drop out versus 1 in the placebo group).

Discussion

This review examined relevant studies in the literature to date but when analysing the primary endpoint (patient-reported outcomes) and secondary outcomes (objective endoscopy scores, infection and adverse events), there was insufficient evidence to suggest an advantage of either short-term or long-term post-operative antibiotics over placebo (or standard of care) in terms of symptom and endoscopic scores. The quality of life scores and endoscopic scores were higher in the antibiotic group; however, these results were not significant upon meta-analysis.

Clinical implications

Patients with CRS have usually been treated with multiple different antibiotics prior to sinus surgery. This can make these patients especially susceptible to antibiotic resistance. In recent surveys of the US[21] and UK[22], it has been reported that over 90% of doctors will prescribe

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antibiotics for CRS. Reasons included treating an active infection, improving postoperative symptoms, healing, preventing post-operative infections and preventing symptom recurrence. Postoperative infection rate after FESS is estimated to occur in 15% of patients[23,24]. This review indicated that there is still a lack of understanding of the need and utility of postoperative antibiotics. The review identified certain trends, which require discussion, pertaining to (1) antibiotic duration, (2) antibiotic type and (3) culture-directed treatment.

Two antibiotic duration strategies were identified: short (<30-days) versus long (>30-days). The two main theoretical functions of short-term postoperative antibiotics are (i) eradication therapy to treat intraoperative infections and (ii) to prevent postoperative infections. Endoscopic sinus surgery provides a unique surgical consideration in contrast to other clean or clean-contaminated procedures as patients may have concurrent bacterial infections. None of the RCTs considered the significance of concurrent mucopurulent secretions and whether this group required different treatment. An RCT comparing 25 *S. aureus*-positive CRS patients, who received either topical mupirocin sinonasal rinse versus saline rinse plus oral augmentin, indicated that the oral antibiotic arm were unable to eradicate *S. aureus* by 28 days post-surgery[25]. Further studies that stratify differences between cases based upon peri-operative findings of mucopurulent discharge would be of critical importance.

In the treatment of CRS, there is no clear consensus regarding type of antibiotics. North American guidelines support the use of culture-directed antibiotics, or a broad-spectrum antibiotic, such as co-amoxiclav, in the absence of culture results[2]. By contrast, EPOS recommends antibiotic choice to be primarily linked to associated anti-inflammatory effects; macrolides for CRSsNP and doxycycline for CRSwNP. Macrolides exhibit immunomodulatory effects through inhibition of neutrophilic inflammation, mucus synthesis and macrophage activation[26]. Doxycycline downregulates production of endopeptidases and thus inhibits tissue damage. However, irrespective of antibiotic choice, it is essential that surgeons collaborate with microbiologists and infection-control counterparts so that effective protocols are in place in each institution. At present, the majority of studies evaluating antibiotics in CRS are patients who have not undergone surgery. Furthermore, studies do not specifically compare antibiotics with

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immunomodulatory and antibacterial effects to those with antibacterial alone. This makes overall treatment judgements on antibiotic usage challenging.

There is a weak evidence base for prophylactic culture-directed antibiotics in the absence of acute exacerbation. One RCT that provided patients with a 3-week course of anti-staphylococcal antibiotics, dependent upon pre-operative swab results, showed initial improvements in early endoscopic healing scores, but this difference was nullified at 6-months[18]. The single cohort study suggested better short-term outcomes for patients who were provided a 2-week course of culture appropriate antibiotics[19], although this difference was not maintained in the longer term. By contrast, an important factor to consider is that postoperative infections may represent *de novo* infections[24]. This is demonstrated in a prospective cohort study of 113 patients who underwent FESS; of 20 cases of acute postoperative exacerbations, only 25% of bacterial isolates corresponded to bacteria identified at the time of baseline culture[24].

By contrast, the role of *Staphylococcus aureus* in the postoperative period appears to be important[27]. A retrospective analysis of 48 cases indicated that in patients with intraoperative *S. aureus* infection, the 90-day postoperative period was complicated by mucosal infection with *S. aureus* in 87.5% of cases, compared to 13.9% without infectious aetiology at surgery ($p=0.0001$)[27]. This is in contrast to the above study[24], and indicates that postoperative infection with *S. aureus* may not be the result of *de novo* infection, but rather the result of persistent *S. aureus* infection refractory to surgery, indicating a potential role for aggressive anti-Staphylococcal therapy postoperatively. There is strong evidence that recognises the persistence of *S. aureus* in a sub-set of refractory CRS patients. Drilling *et al*. genetically sequenced *S. aureus* cultured intraoperatively and postoperatively in CRS patients and found that 79% of patients included in the study harboured the same strain of bacteria after surgery[28]. Perhaps this strengthens the argument for effective eradication therapy.

Co-morbidities may be important. A retrospective observational study of 294,039 patients evaluating the impact of antibiotics following reconstructive surgery demonstrated reduced infection rates in those provided a short-course of antibiotics[29]. In this study, diabetes, tobacco

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use, and immunodeficiency were associated with higher infection rates, indicating that patient comorbidities should be considered when determining whether to prescribe antibiotics[29].

Limitations

An important factor that was not assessed in this review was the differences in outcomes following antibiotic usage within the subtypes, including the classic polyp and non-polyp groups, but also by characterizing whether inflammation is Th1, Th2 or Th17-driven. The lack of trial data reporting outcomes by endotypes precluded this analysis but would be an important aspect of future study.

The review includes only five single-centre RCTs with small numbers of participants, which led to wide confidence intervals. There was significant heterogeneity between studies with different antibiotic regiments. There were no high quality large multicentre trials. The rate of revision surgery was not reported in any of the included studies. This limited the conclusions that can be reached regarding the utility of postoperative antibiotics.

Recommendations

This review highlights the need for further research regarding antibiotic use in endoscopic sinus surgery. The low incidence of surgical infection rates[23,24] indicates that large sample sizes are essential to adequately power these studies. The study requires defined reasons for prescribing postoperative antibiotics, as well as clear definitions of acute infections. Trials should ideally stratify patients by populations, for example, age and diabetes. Furthermore, the stratification of intraoperative disease into those that contain frank pus versus those that do not may allow us to choose to use antibiotics in more appropriate settings.

In terms of outcome reporting, it is recommended that early endoscopic scores are documented as there appears to be preliminary evidence that antibiotics may modestly improve the early healing phase[13]. Postoperative infections must be documented accurately, with concurrent endoscope-guided microbiology swabs taken for analysis. Adverse events should be reported clearly. Database studies do not easily capture possible complications of prophylactic antibiotic

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use, which is important when considering possible cardiac or gastrointestinal side effects with macrolides. These complications would be best assessed by a multicentre randomised controlled trial to power the study, document nuances of treatment and identify adverse events.

Conclusions

CRS is a broad syndrome, which requires individualised decisions regarding the role and duration of antimicrobial therapies following FESS. Important areas for consideration appear to be presence of intraoperative infection, particularly *S. aureus* isolates, and patient co-morbidities. Considering the high frequency of FESS being performed globally, combined with the lack of consensus on post-operative management, usage of postoperative antibiotics is an important question to consider. The available evidence at present is not enough to make a recommendation in either direction.

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Figure Legend

Figure 1: PRISMA flow diagram

Figure 2*:* Forest Plot of the standardised mean difference of subjective symptom measurements between treatment groups (Sub-group analyses of: long intervention - 30 days or more; short intervention - less than 30 days). Standardised mean difference, SMD; Confidence interval, CI

Figure 3: Forest Plot of the standardised mean difference of Endoscopy score between treatment groups. Standardised mean difference, SMD; Confidence interval, CI