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Antibiotic use in prevention of anal fistulas following incision and drainage of anorectal abscesses: A systematic review and meta-analysis

Valentin Mocanu [a, *], Jerry T. Dang [a], Farah Ladak [a], Chunhong Tian [a], Haili Wang [a], Daniel W. Birch [b], Shahzeer Karmali [b]

[a] Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
[b] Centre for the Advancement of Minimally Invasive Surgery (CAMIS), Royal Alexandra Hospital, Edmonton, Alberta, Canada

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ABSTRACT

Background: Treatment of anorectal abscesses continues to revolve around early surgical drainage and control of perianal sepsis. Yet even with prompt drainage, abscess recurrence and postoperative fistula formation rates are as high as 40% within 12 months. These complications are thought to be associated with inadequate drainage, elevated bacterial load, or a noncryptoglandular etiology of disease. Postoperative antibiotics have been used to account for these limitations, but their use is controversial and only weakly supported by current guidelines due to low-quality evidences. The aim of the present study was to perform a systematic review and meta-analysis of the current literature to determine the role of antibiotics in prevention of anal fistula following incision and drainage of anorectal abscesses.

Methods: Literature search was conducted using Medline, EMBASE, Scopus, the Cochrane Library, and Web of Science databases from 1946 to April 2018. Search terms were "perianal OR anal OR fistula-in-ano OR ischiorectal OR anorectal AND abscess AND antibiotics" and was limited to human studies in the English language. Literature review and data extraction were completed using PRISMA guidelines. A total of six studies with 817 patients were included for systematic review. The weighted mean age was 37.8 years, 20.4% of patients were female, and the follow up ranged from one to 30 months. Antibiotic courses varied by study, and duration ranged from five to 10 days. Of included patients, 358 (43.8%) underwent management without antibiotics while 459 (56.2%) patients were treated with antibiotics. Fistula rate in subjects receiving antibiotics was 16% versus 24% in those not receiving postoperative antibiotics. Meta-analysis revealed a statistically significant protective effect for antibiotic treatment (3 studies, OR 0.64; CI 0.43–0.96; P = 0.03).

Conclusions: Antibiotic therapy following incision and drainage of anorectal abscesses is associated with a 36% lower odds of fistula formation. An empiric 5–10-day course of antibiotics following operative drainage may avoid the morbidity of fistula formation in otherwise healthy patients, although quality of evidence is low. Further randomized trials are needed to fully clarify the role, duration, and type of antibiotics best suited for postoperative prevention of fistula following drainage of anorectal abscesses.

Introduction

Management of anorectal abscesses and fistula-in-ano (FIA) can be traced back to the early 14 th century.[1] John Arderne, the father of British Proctology, was first to describe the surgical principles of perianal suppuration.[2] Arderne stressed early opening of abscesses and unroofing of associated tracts to prevent chronic external openings that were "hard of cure".[3] However, despite his reported success, Arderne's principles were not fully adopted until the late

* Corresponding author.Department of Surgery, University of Alberta Hospital, 8440 112 Street NW, Edmonton, AB, T6G 2B7, Canada.
E-mail addresses: vmocanu@ualberta.ca (V. Mocanu), dang2@ualberta.ca (J.T. Dang), fladak@ualberta.ca (F. Ladak), chunhong@ualberta.ca (C. Tian), haili@ualberta.ca (H. Wang), dbirch@ualberta.ca (D.W. Birch), shahzeer@ualberta.ca (S. Karmali).

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20th century. In his landmark 1961 paper, Parks described the modern pathogenesis, classification, and treatment of perianal suppurative disease.[1] Parks' cryptoglandular theory identifies the source of anorectal abscesses as an acute blockage of anal glands with chronic obstruction predisposing to fistula formation.[1,4,5]

Treatment of anorectal abscesses continues to revolve around early surgical drainage and control of perianal sepsis.[4–6] Yet even with prompt drainage, abscess recurrence and postoperative fistula formation rates range from 5% to 83% within 12 months.[7–12] These complications are thought to be associated with inadequate drainage, elevated bacterial load, or a noncryptoglandular etiology of disease.

Postoperative antibiotics have been used to address these complications, but their use is controversial and only weakly supported by current guidelines due to low-quality evidence.[13–15] The American Society of Colon and Rectal Surgeons (ASCRS), for example, only weakly recommends antibiotics for systemic infection, underlying immunosuppression, or abscess complicated by surrounding cellulitis. Yet, recent studies have indeed found evidence of benefit for the use of antibiotics for all patients undergoing surgical drainage.[7–9]

The aim of the present study was to perform a systematic review and meta-analysis of the current literature to determine the role of antibiotics in prevention of anal fistula following incision and drainage of anorectal abscesses. Literature search was conducted using the Medline, EMBASE, Scopus, the Cochrane Library, and Web of Science databases from 1946 to April 2018.

Materials and methods

Search strategy

A comprehensive literature search for both published and unpublished studies of anorectal abscess and antibiotics from 1946 to April 2018 was performed. The search was conducted using the Medline, EMBASE, Scopus, the Cochrane Library, and Web of Science databases as well as conference abstracts. Search terms were "perianal OR anal OR fistula-in-ano OR ischiorectal OR anorectal AND abscess AND antibiotics" and was limited to human studies in the English language. Additional manual searches of reference lists were performed to identify potentially missed articles. Grey literature was also identified using Google. Corresponding authors of selected studies were emailed individually for further information.

Selection criteria

Abstracts and titles were first screened for inclusion by two independent reviewers (VM and JD). Irrelevant papers based on their title and abstract were not included for full-text evaluation. Abstracts were screened based on the following inclusion criteria: adult patients (age $\geq$ 18 years old), studies with >5 subjects, human studies, and studies published in the English language. Discrepancies were resolved by consensus or through assessment by a third independent reviewer (FL). Exclusion criteria included studies with patients with primary inflammatory bowel disease, neoplasm, radiation, horseshoe abscesses or patients who were immunocompromised. Other exclusion criteria included duplicate studies, kin studies, or studies published solely as abstracts. Full text articles of all selected abstracts were then reviewed more thoroughly by two reviewers (VM and JD) using the same criteria and disputes were resolved with a third reviewer (FL). Included studies were then assessed for methodological quality and bias using the Cochrane Risk of Bias tool for randomized trials[16] and the MINORS tool for non-randomized trials.[17]

Data extraction

Pertinent data was collected from selected trials by one reviewer (VM) and a second reviewer checked for accuracy (JD). A third reviewer verified data following primary extraction to ensure data integrity (FL). The primary outcomes of interest included fistula formation. Secondary outcome was abscess recurrence. The following preoperative patient characteristics were assessed: age, sex, smoking, diabetes, body mass index (BMI), and type of anorectal abscess.

Statistical analysis

Categorical variables were reported as frequencies and percentages and continuous data was expressed as mean $\pm$ standard deviation. Meta-analysis was conducted where possible and appropriate for patients with anorectal abscess treated with and without antibiotics. Outcomes assessed in the meta-analysis included fistula formation. The estimated effects were calculated using the Revman 5.3 obtained from the Cochrane website.[16] Included studies were then tested for heterogeneity using the Chi^2 test with significance set at $P < 0.05$ and the amount of heterogeneity quantified by the I^2 statistic: (1) low = 25%; (2) moderate = 50%; and (3) high = 75% (17).

Results

Study selection

Preliminary database search of the literature yielded 816 articles after duplicates were removed (Fig. 1). After initial screening of titles and abstracts, 23 studies underwent full-text assessment for eligibility. Six full manuscripts[7–12] met inclusion criteria and were included in the final systematic review. The included manuscripts

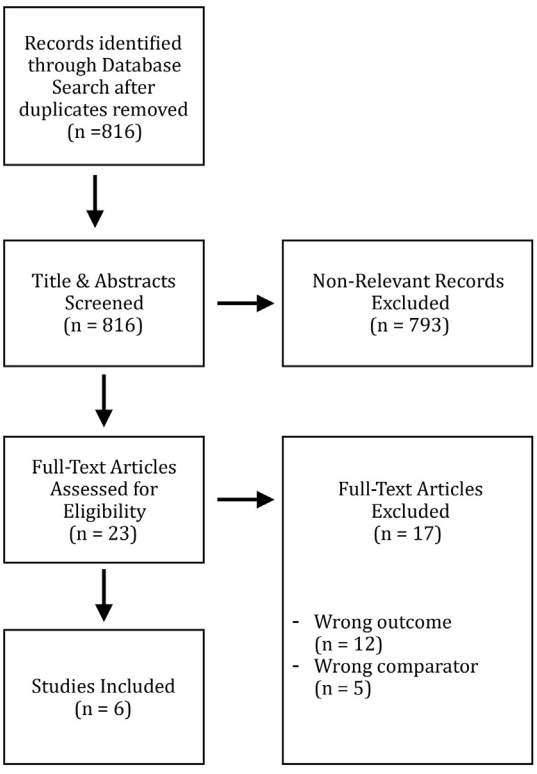

Fig. 1. PRISMA diagram showing search results for systematic review.

comprised of two randomized controlled trials, three retrospective cohort studies, and one prospective case-control study.

Basic demographics

A total of six studies with 817 patients were included for systematic review (Table 1). Of those, 358 (43.8%) underwent management without antibiotics while 459 (56.2%) patients were treated with antibiotics. The weighted mean age was 37.8 years, 20.4% of patients were female, and the follow up ranged from one to 30 months. Only four studies reported rates of diabetes which ranged from 3% to 36%. Of the two studies[7,12] that reported data regarding abscess characteristics, the most common types were perianal (82.3%) followed by intersphincteric (8.5%) and ischiorectal (8.5%) abscesses. Antibiotic courses varied by study protocol (Table 1), and duration ranged from five to 10 days. No statistical significance was observed for baseline patient characteristics between groups of any study.

Quality assessment of included studies

Randomized controlled trials were assessed using the Cochrane Risk of Bias Tool (Appendix 1; Tables 2 and 3). A high risk of bias was noted for the other sources of bias domain in Ghahramani et al. due to limited information regarding baseline patient characteristics. Ghahramani et al. also suffered from potential reporting bias due to the single blinded study design.

Non-randomized trials were assessed for bias and methodology using the MINORS criteria (Appendix 1; Tables 4). No study met ideal criteria. All studies were at high risk of bias due to deficits of inclusion of consecutive patients, prospective calculation of study size, adequate control groups, and baseline equivalence of groups.

Outcomes

Fistulas were identified in follow up by anoscopy, visual identification of a perianal tract, or by a palpable communicating tract on digital rectal exam. The unadjusted overall fistula rate ranged from 8% to 32%. Fistula rate in subjects receiving antibiotics was 16% versus 24% in those not receiving postoperative antibiotics. Of the six studies, only three were included in the meta-analysis as the studies by Hasan et al. and Soew-En et al. did not report fistula rates for both intervention groups. The remaining excluded study by Nunoo-Mensah et al. failed to clearly report baseline demographics and proportions of subjects who were immunocompromised. Overall, meta-analysis revealed a statistically significant protective effect for antibiotic treatment (3 studies,[7,9,12] OR 0.64; CI 0.43–0.96; $P = 0.03$) (Fig. 2). Heterogeneity was statistically significant and high between studies ($P = 0.0003$; $I^2 = 88\%$).

Abscess recurrence was only reported in two studies[11,12] and insufficient data was thus available to perform a meta-analysis for this outcome. Unadjusted abscess recurrence rates for those receiving antibiotics ranged from 0 to 11% at 12 month follow up. In comparison, unadjusted abscess recurrence rates for the non-antibiotic group ranged from 0 to 13%.

Discussion

To our best knowledge, this is the first systematic review and meta-analysis assessing the role of antibiotic therapy in preventing fistula formation following incision and drainage of anorectal abscesses. Results of our meta-analysis reveal a statistically significant protective effect for patients receiving antibiotics following surgical drainage of anorectal abscesses. In other words, the odds of fistula formation in those receiving postoperative antibiotics was 36% lower in comparison to those not receiving antibiotics. Fistula rate in subjects receiving antibiotics was 16% versus 24% in those not

Table 1
Basic demographics of included studies.

Study	Study design	Patients (n)	Antibiotic Regimen	Duration (days)	Follow up (months)	Treatment Arm	Patients (n)	Age (years)	Gender (%female)	Fistula (%)
*Ghahramani 2017	RCT	299	Ciprofloxacin + Metronidazole	7	3	No Antibiotics	144	42	27	30
						Antibiotics	155			14
Hasan 2016	Prospective Cohort	75	Varied	7	12	No Antibiotics	14	40	8	–
						Antibiotics	61			19
*Lohsiriwat 2016	Retrospective Cohort	64	Varied	5–7	30	No Antibiotics	29	44	22	48
						Antibiotics	35			17
Nunoo-Mensah 2006	Retrospective cohort	56	Varied	7	1.25	No Antibiotics	31	45	25	39
						Antibiotics	25			24
Soeow-En 2014	Retrospective cohort	172	Varied	5–7	12	No Antibiotics	64	41	15	6
						Antibiotics	108			
Sozener 2011	RCT	151	Amoxicillin + Clavulanate	10	12	No Antibiotics	76	38	22	22
						Antibiotics	75			37

RCT, randomized controlled trial.
* Studies where use of antibiotics statistically and significantly reduced rates of fistula formation after surgery.

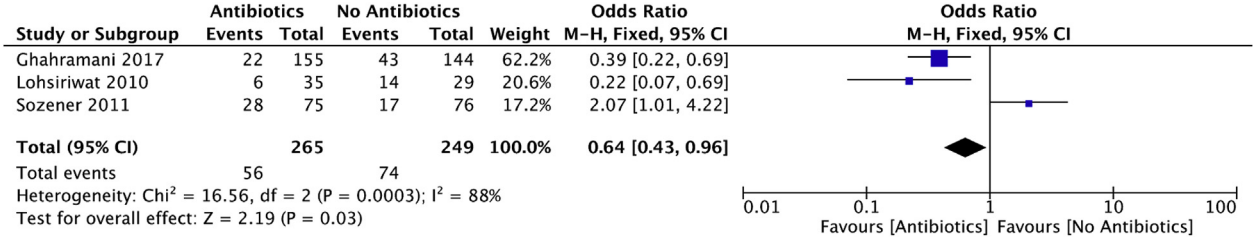

Fig. 2. Overall fistula rates for antibiotic vs. no antibiotic groups.

receiving postoperative antibiotics. Unadjusted overall fistula formation rate ranged from 8% to 32%, in keeping with prior literature reports.[6–15]

While the principles of surgical management of perianal abscesses have been largely unchanged since the 14th century, the current role of postoperative antibiotics continues to be controversial. The ASCRS provides a weak recommendation on the use of antibiotics in co-morbid, immunosuppressed patients.[13] The Italian Society of Colorectal Surgery, likewise, strongly does not recommend antibiotic therapy following drainage for healthy patients with uncomplicated anorectal abscesses.[14] In contrast, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) provides no consensus on the use of postoperative antibiotics.[15] These recommendations are based on low to moderate quality evidence originating from literature examining a heterogeneous immunocompromised population such as bone marrow transplants and active hematologic malignancies. To date, no consensus exists regarding use of empiric postoperative antibiotics for all comers with respect to anorectal suppurative disease.

The true prevalence of empiric antibiotic use in the general population, much like the true prevalence of anorectal suppurative disease, is not fully understood and is likely underestimated.[18] This is in part because the majority of antibiotics prescribed worldwide are done so by general practitioners, which in Europe account for up to 90% of all antibiotic prescriptions.[19] Antibiotics are associated with a number of adverse consequences including increasing antibiotic resistance and *Clostridium difficile* infections[19,20]. An area of particular concern is the mortality and morbidity associated with C. *difficile* infections (CDI) which are strongly associated with antibiotic use. In the United States alone, the direct hospital acquired costs of these infections approached 5 billion dollars in 2008.[20] Rates of *C. difficile* in healthy immunocompetent individuals are approximately 0.4%.[21] Those at highest risk of developing *C. difficile* infections are patients aged over 65 years, the immunosuppressed, and those in long-term care facilities.[20,21] Importantly, the use of local, national, and international antibiotics prescribing guidelines based on best available evidence have led to significant reductions in complications associated over-prescribing[22,23].

Literature examining outcomes of surgical drainage of simple perianal abscesses in otherwise healthy patients is both limited and conflicting. This paucity of evidence in combination with the potential harms associated with liberal antibiotic use is why empiric therapy is currently reserved for high-risk patients. Ghahramani et al. recently published the results of a randomized single blinded clinical trial assessing the role of antibiotic therapy for preventing FIA after drainage of simple perianal abscesses. A total of 299 patients were examined, 155 of which received a seven-day course of oral metronidazole and ciprofloxacin and were followed for 3 months. All patients received a single dose of ceftriaxone (half-life of approximately 6–9 h) which may not have been fully accounted for using the binary logistic regression analysis. However, despite both groups receiving preoperative antibiotics, regression analysis revealed that postoperative antibiotic use remained the single most protective factor against fistula development (OR 0.371; CI 0.20–0.70).

Sozener et al. also conducted a double blinded randomized control trial to assess rate of anorectal fistula formation at one year follow up after surgical drainage of anorectal abscesses. A total of 155 patients were assessed, with 76 receiving a ten-day course of amoxicillin-clavulanic acid postoperatively. Interestingly, 22.4% of patients in the placebo group versus 37.3% of patients in the antibiotic group formed a fistula. Sozener concluded that antibiotic treatment had no protective effect on fistula formation. However, this study may have been underpowered to detect a 20% difference in fistula formation between groups.

Our study was not without its limitations. Selection bias was a potential issue across all included cohort studies, as only one of six studies reported baseline patient characteristics for both control and intervention arms. There is a potential risk where patients with larger, and more complicated abscesses may have been more likely to be treated with antibiotics. In addition, as the true prevalence and distribution of perianal disease is unknown, it is possible that our study population may not be truly generalizable. Males are twice more likely to develop perianal abscesses, however nearly 80% of our population was male. This gender disparity could confound our results as males are more likely to be diabetic and smoke, and potentially develop postoperative fistulas. The majority of the studies also did not fully characterize significant patient comorbidities such as diabetes, smoking, obesity, or history of prior abscesses. Although studies reported no major differences in baseline patient characteristics, it is still possible that patients with significant comorbidities may have been more likely to receive antibiotic therapy. This could lead to an overestimate in the benefit of antibiotic therapy as immunocompromised patients are potentially more likely to develop postoperative fistulae. Therefore, the absolute reduction of 8% in fistula formation may not be clinically significant in the setting of our low quality heterogenous data. Antibiotic course and duration of therapy was also widely different across study populations, although all provided adequate coverage for the usual gut flora pathogens. Lastly, follow up varied greatly between studies. Up to 75% of fistulas are believed to occur within three months of surgical drainage, yet nearly 40% of our study population had no follow-up past this timepoint. A potential loss in roughly 25% of patients that could have later developed a fistula may further impact our findings. Taken together, there may be significant confounding variables or effect modifiers our study was not able to account for that may ultimately affect the interpretation of our analysis. We believe these limitations should be addressed by conducting additional high-quality, long-term studies aimed at addressing the impact of antibiotics of fistula formation following incision and drainage of anorectal abscesses.

Although this review is limited by the number of studies, high degree of heterogeneity, and high risk of bias, it is to date the most comprehensive analysis on the role of antibiotic therapy in preventing fistula formation following incision and drainage of anorectal abscesses. We were able to identify a statistically significant difference in fistula reduction in patients receiving postoperative antibiotics. The ideal duration or type of antibiotic therapy could not be assessed from our study, although coverage of gram-negative and anaerobic pathogens for a 5–10-day course with amoxicillin-clavulanic acid (875 mg orally twice daily) or ciprofloxacin (500 mg orally twice daily) and metronidazole (500 mg orally twice daily) regimens is in keeping with current studies.

While antibiotic-associated complications can be grave, they should not be a barrier to optimal patient management within the correct clinical context. With respect to perianal suppurative disease, the ASCRS currently recommends empiric postoperative antibiotics solely in patients with diabetes or in those that are immunosuppressed. These patients are at the highest risk of developing CDI yet may also stand to gain the most benefit from this therapy. In addition to these recommendations, our study suggests that adoption of an empiric postoperative 5–10-day course of antibiotic therapy for all-comers may reduce perianal fistula formation in otherwise healthy patients. The quality and level of evidence is, however, low and should be further clarified by additional high-quality long-term studies.

Conclusion

Antibiotic therapy following incision and drainage of anorectal abscesses is associated with a 36% lower odds of fistula formation.

An empiric 5–10-day course of antibiotics following operative drainage may avoid the morbidity of fistula formation in otherwise healthy patients, although quality of evidence is low. Further randomized trials are needed to fully clarify the role, duration, and type of antibiotics best suited for postoperative prevention of fistula following drainage of anorectal abscesses.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.01.015.

Appendix

Table 2
Ghahramani 2017 Cochrane Risk of Bias Assessment

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias *Random sequence generation*	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	Low	Random allocation to the treatment or nontreatment groups was done according to the days patients were appointed for surgery. Overall, among 4 days in a week that colorectal surgery (I&D) was performed in the center, during January 2014 to January 2015, 2 days were selected randomly and patients that referred for surgery in the 2 selected days were allocated to the treatment group.
Selection bias *Allocation concealment*	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	Low	The surgeons who performed the operations were unaware of the study protocol. During follow-up visits, patients were first visited by a nurse who was trained for the study protocol and medication history was obtained (to verify compliance with the medication). After which, patients were referred to the attending surgeon and medication history was not questioned in order to insure blindness.
Reporting bias *Selective reporting*	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	Low	Abscesses were well categorized based on anatomic location, but study only single blinded
Other bias *Other sources of bias*	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	High	Limited information regarding patient preoperative baseline characteristics for individual antibiotics/ nonantibiotic groups
Performance bias *Blinding (participants and personnel)*	Described all measures used, if any, to blind study participants and personnel from	Performance bias due to knowledge of the allocated interventions by participants and	Blinding was likely effective.	Not described in sufficient detail	High	Patients not blinded

Table 2 (*continued*)

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
	knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	personnel during the study.				
Detection bias *Blinding (outcome assessment)*	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	Low	See selection bias
Attrition bias Incomplete outcome data	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	Low	All subjects were accounted for with regards to attrition and exclusion for both interventions.

Table 3
Sozener 2011 Cochrane Risk of Bias Assessment

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias *Random sequence generation*	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	Low	Group assignment was performed with Random Allocation Software (Ver. 1.0.0; M. Saghaei, Isfahan University of Medical Sciences, Isfahan, Iran) for each center separately. We used block randomization to ensure an equal number of patients in each group. A medical resident from each center, who was blinded to the research protocol, followed the assignment scheme, and was not otherwise involved in the trial, operated the random-number program.
Selection bias *Allocation concealment*	Described the method used to conceal the allocation sequence in sufficient detail to determine whether	Selection bias (biased allocation to interventions) due to inadequate concealment of	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	Low	See above

(*continued on next page*)

Table 3 (*continued*)

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
	intervention allocations could have been foreseen before or during enrollment	allocations prior to assignment				
Reporting bias *Selective reporting*	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	Low	Abscesses were well categorized based on anatomic location
Other bias *Other sources of bias*	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	Low	Good baseline patient demographics and clinical characteristics
Performance bias *Blinding (participants and personnel)*	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	Low	Both the staff surgeons and the research residents who examined patients during hospitalization were blinded to the randomization procedure and case details. The examiners remained unaware of patients' drug assignments throughout the follow-up period.
Detection bias *Blinding (outcome assessment)*	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	Low	See selection bias
Attrition bias Incomplete outcome data	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	Low	All subjects were accounted from with regards to attrition and exclusion for both interventions.

Table 4
MINORS assessment of included studies

Criteria	Study			
	Hasan 2016	Lohsiriwat 2016	Nunoo-Mensah 2006	Soeow-En 2014
A clearly stated aim	2	2	2	1
Inclusion of consecutive patients	0	0	0	0
Prospective collection of data	0	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	1
Unbiased assessment of the study endpoint	2	2	2	2
Follow-up period appropriate to the aim of the study	2	2	1	2
Loss to follow up less than 5%	2	2	2	2
Prospective calculation of the study size	0	0	0	0
An adequate control group	0	2	2	0
Contemporary groups	2	2	2	0
Baseline equivalence of groups	0	2	0	0
Adequate statistical analyses	2	2	2	2
Total*	14	20	17	12

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

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