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Systematic Review

Does Antibiotics have a Role in the Treatment of Acute Uncomplicated Diverticulitis? A Systematic Review and Meta-Analysis

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Abstract

Introduction: Diverticular disease is a common health problem and is associated with high morbidity and economic costs. The clinical spectrum can range from asymptomatic diverticulosis to varying severity of sepsis. About 75% of the patients would have uncomplicated diverticulitis and the condition is treated with antibiotics, analgesia and dietary advice. Recent evidence has shown that the treatment of uncomplicated diverticulitis is controversial and questioning the use of antibiotics. This study aims to assess the role of antibiotics in the treatment of acute uncomplicated diverticulitis.

Methods: This is a systematic review and Meta-analysis. A literature review of the available studies was conducted using online search engines like Pubmed, Medline, Embase, Google Scholar and Cochrane databases. Statistical analysis was conducted using RevMan 5.4.

Results: 1754 records identified. 1324 were duplicates, remaining 430 studies were screened for inclusion. 395 studies were further excluded. 35 full text articles were assessed for eligibility and in the final review 10 studies were included. PRISMA guidelines were used for this study. Pooled OR for recurrence = 0.92 (95% CI = 0.74 to 1.13). Pooled OR for Hospital stay = -0.66 (95% CI = -1.12 to -0.21). Pooled OR for complications = 1.06 (95% CI = 0.69 to 1.64). Pooled OR for treatment failure = 1.24 (95% CI = 0.90 - 1.69).

Conclusion: We conclude that from the available evidence antibiotics have no role in reducing recurrence, complications, treatment failure and duration of hospital stay in acute uncomplicated diverticulitis. However, risk stratification is required for the selected cases that might benefit from antibiotic use.

Keywords: *Diverticulosis; Antibiotics; Acute Uncomplicated Diverticulitis; Colonic Diverticulosis*

Introduction

Diverticulosis is defined as the development of out pouching's [1]. Colonic diverticulosis can be symptomatic or asymptomatic. While the majority are asymptomatic, 1 to 3% can become infected or inflamed and then the term diverticulitis is used for this condition [2]. Colonic diverticulosis is quite prevalent in the western population. Previously it was considered as a disease of the old age but recently diverticulosis has been seen in the younger population as well. Diverticulosis affects 30% of the population by the age of 60 years and can affect about 65% of the people by the age of 85 years [3]. Diverticulosis can occur over the entire length of the colon, however; right-sided diverticulitis is rare and the clinical presentation differs from left-sided diverticulitis [4].

Diverticulosis is caused due to raised intraluminal colonic pressure and bowel wall weakness that leads to outpouching in the bowel wall. Lack of fiber in the diet, reduced colonic motility, constipation, and bowel wall resistance can all increase intraluminal pressure and bowel wall weakness. Other causes of diverticular disease include increasing age, high BMI and sedentary lifestyle [5]. CT scan has established itself as the primary modality in the diagnosis of diverticular disease [6].

Uncomplicated diverticulitis is defined as a condition in the absence of abscess, fistula formation, hemorrhage, bowel obstruction, or perforation [7]. The clinical spectrum of diverticular disease can range from asymptomatic diverticulosis to varying severity of abdominal sepsis. Diagnosis is based on clinical findings including history and examination followed by investigations. A raised white cell count is present in 55% of the cases with acute diverticulitis; hence a full blood count (FBC) is an essential first-line investigation [8]. C reactive protein (CRP) is another important inflammatory marker that should be measured in patients with suspicion of diverticulitis [9]. Imaging is not essential in all patients with mild symptoms; however, there should be a low threshold for imaging in case of diagnostic uncertainty or suspicion of complications. CT scan has established itself as the primary modality in the diagnosis of diverticular disease [6]. It can help in differentiating between complicated and uncomplicated disease.

Treatment depends on the severity of the disease. Treatment of uncomplicated acute diverticulitis is controversial. About a decade ago antibiotic therapy was an essential part of the treatment of uncomplicated diverticulitis. However, this concept has changed in recent times and now it is believed that diverticulitis is an inflammatory condition rather than an infective one and does not support the routine use of antibiotics in mild cases [10].

Association of coloproctology of Great Britain and Ireland (ACPGBI) recommends that patients with acute diverticulitis should be given a dose of antibiotics therapy for 7 days [11]. However, two randomized controlled trials (RCTs) have questioned the routine use of antibiotics in acute uncomplicated diverticulitis [12,13]. Danish, Dutch and Italian guidelines for the treatment of diverticular disease do not support the routine use of antibiotics in acute uncomplicated diverticulitis but exceptions can be made in selected cases [14-16].

We decided to do a systematic review and Meta-Analysis. The study aims to find out if antibiotics have any role in preventing recurrence, reducing complications, treatment failure, and duration of hospital stay in patients with acute uncomplicated diverticulitis.

We hypothesize that antibiotics have no role in the treatment of acute uncomplicated diverticulitis.

Methods

This is a systematic review and meta-analysis which was performed as per PRISMA guidelines [17].

Figure 1 shows the final study selection for this review.

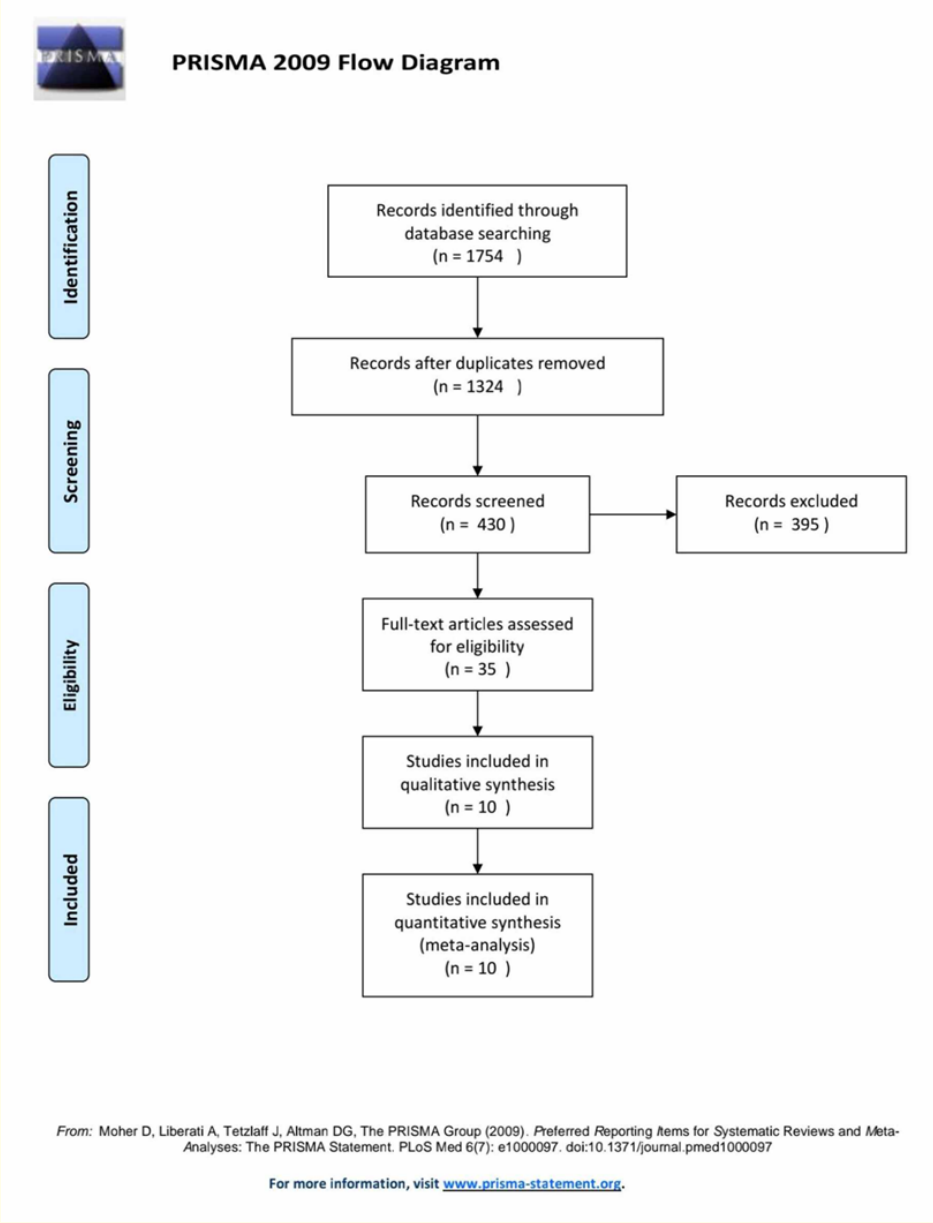

Figure 1: *PRISMA flow diagram.*

Search strategy

A thorough literature review of the available studies was conducted using online search engines like Pub med, Medline, Embase, Google Scholar, and Cochrane databases. Comparative studies that assessed the role of antibiotics in acute uncomplicated diverticulitis

(AUD) were included. Observational studies looking into patients with CT diagnosed acute uncomplicated diverticulitis treated without antibiotics were also included in the study. An electronic search was conducted from the beginning of indexing for all the databases till 14th May 2020. Two independent reviewers were involved in the literature search (AT and KA). Search for relevant studies and abstracts was carried out using the keywords like uncomplicated and early diverticulitis, antibiotics in early and uncomplicated diverticulitis, diverticulitis, and antibiotics.

Inclusion and exclusion criteria

A literature review was conducted by two independent reviewers (AT and KA). Any disagreement was resolved with consensus and mutual agreement. All studies with CT proven acute uncomplicated diverticulitis of the left side of the colon were included in this study. Studies looking into right-sided colonic diverticulosis, moderate and severe acute diverticulitis were excluded from the study. The references retrieved were managed with the Zotero reference manager.

Data extraction

Data were extracted by the two reviewers independently and was verified. Any disagreement was resolved with consensus. Data extracted included the name of the first author, year of study, study design, number of patients in total and each cohort, inclusion, and exclusion criteria. Other data extracted included age, sex, recurrence of diverticulitis, total complications, length of hospital stay, and treatment failure. Limitations of each study were reviewed as well along with the risk of bias. Complications included abscess, perforation, stricture formation, the formation of fistula (colo-enteric or colo-vesical), and small or large bowel obstruction. Treatment failure was defined as the persistence of symptoms, patients who needed surgical or radiological intervention, and readmissions. In the experimental group treated conservatively without antibiotics addition of antibiotics was also considered as treatment failure. Demographic details of all patients included in the studies were collected. This data was tabulated for comparison.

Primary outcome

The primary outcome of interest was the recurrence of diverticulitis.

Secondary outcome

The secondary outcomes of interest were complications (abscess, perforation, fistula, obstruction, and stricture), treatment failure (persistence of symptoms, further intervention with surgery or radiological intervention, readmissions) and hospital stay.

Statistical analysis

Odds ratio (OR) was the measure of the effect of interest. The pooled rate of the primary outcome of interest of our study for recurrent diverticulitis was calculated with a 95% confidence interval (CI) with the random-effects model for heterogeneity in study designs. The pooled odds ratio (OR) was also calculated for our secondary outcomes in this study with a 95% confidence interval (CI). P-value was calculated for both the primary and secondary outcomes.

Statistical software used for the construction of forest plots for pooled Odds Ratio (OR) of the primary and secondary outcomes, measurement of 95% confidence interval (CI) and heterogeneity was Review Manager Version 5.4 (Cochrane).

For all outcomes, a P-value of < 0.05 was considered as statistically significant.

Funnel plots were used to assess publication bias.

Results

Study characteristics

A total of 1754 records were identified. Out of which 1324 were duplicates and were removed. After removing the duplicate records 430 studies were screened for further consideration for inclusion in the review.395 studies were further excluded as they did not fulfill the inclusion criteria. A total of 35 full-text articles were assessed for eligibility and in the final review, 10 studies were included. A preferred reporting item for systematic review and Meta-analysis (PRISMA) flow diagram is shown in figure 1 above.

The characteristics of the included studies are mentioned in table 1.

Studies by Isacson., *et al*. [18] and Dijk., *et al*. [19] are the long term follow up of the AVOD trial [12] and DIABLO trial [13] respectively. These are included in this study as well.

Primary outcome

The primary outcome of interest in our study was the recurrence of diverticulitis.

Figure 2 shows the forest plot of comparison in 9 studies including the studies showing long term follow up of AVOD and DIABLO trial for recurrence. Pooled odds ratio (OR) for recurrent diverticulitis was 0.92 (95% Confidence interval CI, 0.74 - 1.13). The pooled rate of recurrence was high in patients who received antibiotics as compared to the observational group without antibiotics (17.28% vs. 14.29%), however, this difference was not statistically significant (p = 0.40).

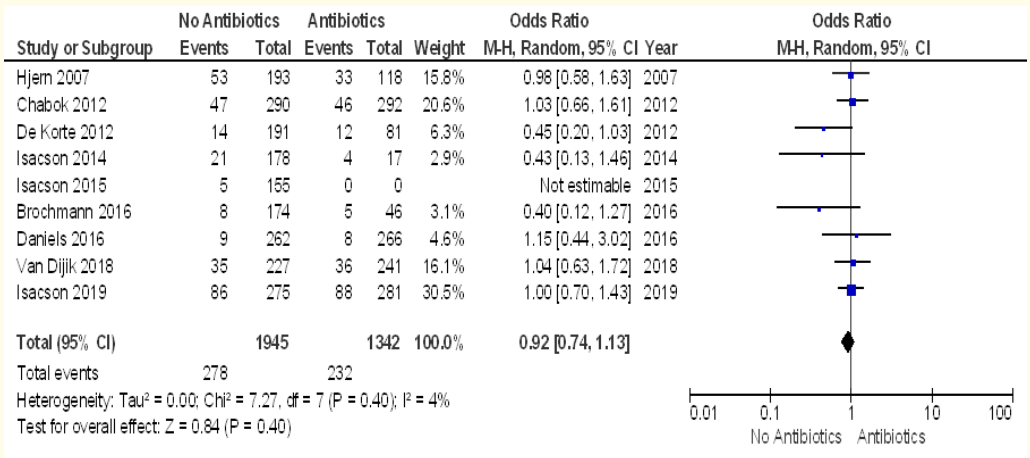

Figure 2: *Forest plot of comparison: No antibiotics vs. antibiotics, outcome: recurrence.*

Results of secondary outcome

The secondary outcome of interest in our study were complications like an abscess, perforation, fistula, obstruction, and strictures) and treatment failure defined as persistence of symptoms, further intervention with surgery or radiological intervention and readmissions) and hospital stay.

Figure 3 shows the forest plot of comparison in 9 studies including the studies showing long term follow up of AVOD and DIABLO trial for complications. The pooled odds ratio (OR) for complications was 1.06 (95% Confidence interval CI, 0.69 - 1.64). The pooled rate of complications was marginally high in patients who received antibiotics as compared to those in the observation group (3.04% vs. 2.70%), however, this difference was not statistically significant (p = 0.53).

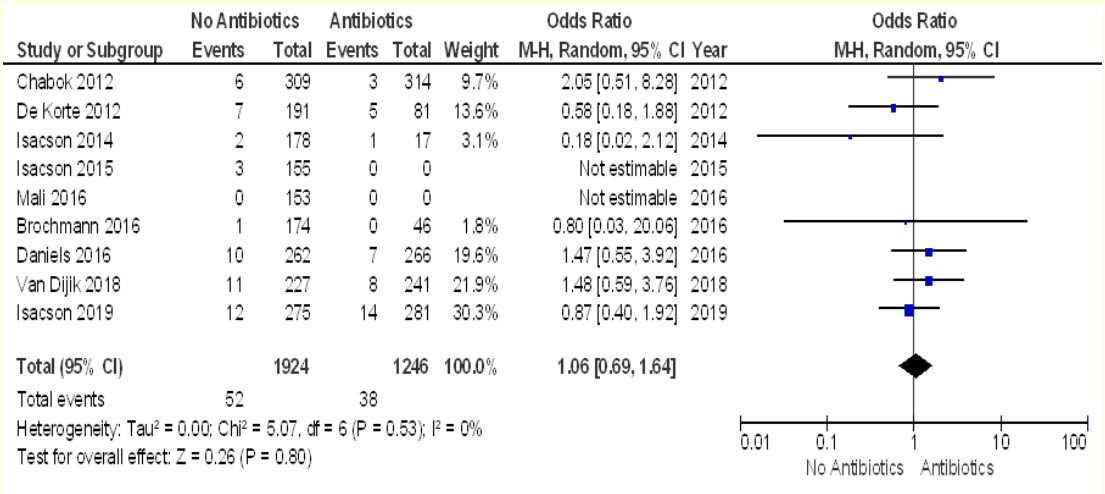

Figure 3: *Forest plot of comparison: No antibiotics vs. antibiotics, outcome: Complications.*

Figure 4 shows the forest plot of comparison in 10 studies including the studies showing long term follow up of AVOD and DIABLO trial for treatment failure. The pooled odds ratio (OR) for treatment failure was 1.24 (95% Confidence interval CI, 0.90 - 1.69). The pooled rate of complications was slightly high in patients who were in the observational group treated without antibiotics as compared to those treated with antibiotics (6.47% vs. 5.49%), however, this difference was not statistically significant (p = 0.19).

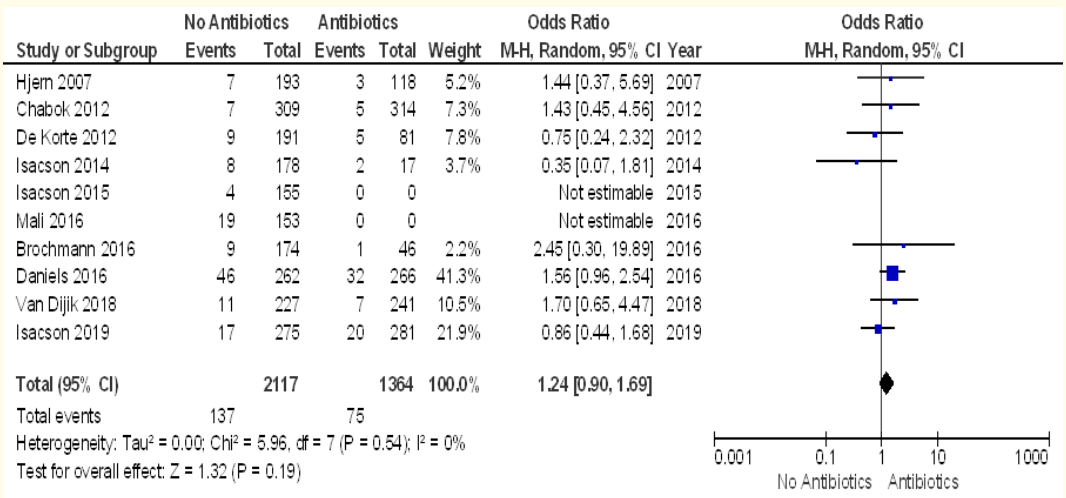

Figure 4: *Forest plot of comparison: No antibiotics vs. antibiotics, outcome: Treatment failure.*

Figure 5 shows the forest plot of comparison of 7 studies which looked into the duration of hospital stay and illustrates that the observational group treated without antibiotics has a shorter duration of hospital stay which is statistically significant with a p-value of 0.04. Moreover, the heterogeneity of the studies in this analysis was highly significant (95% with a P-value < 0.00001) which could be because of the difference of methodology in these studies.

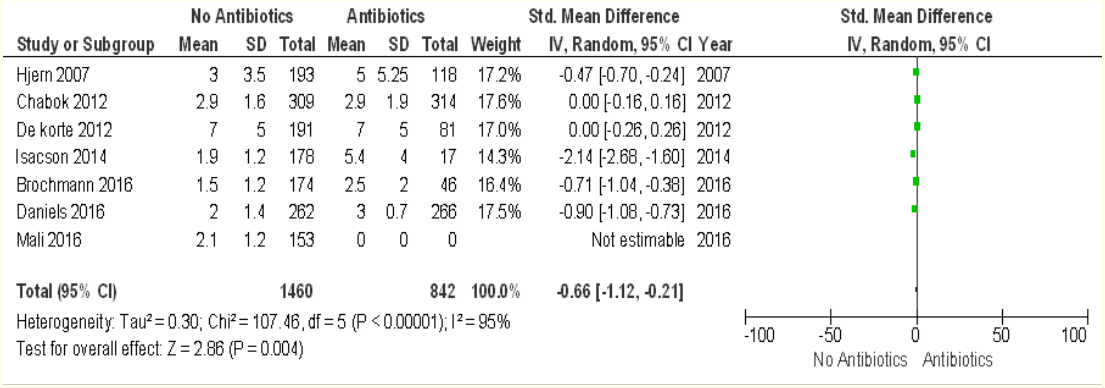

Figure 4: *Forest plot of comparison: No antibiotics vs. antibiotics, outcome: Treatment failure.*

Discussion

This Meta-Analysis shows that patients with acute uncomplicated diverticulitis can be managed safely without antibiotics. and there was no statistically significant difference in the Outcomes. Diverticular disease is prevalent in the western population and is amongst the leading causes of outpatient visits and hospital admissions. Previously considered as a disease of the elderly, however, recently it has been diagnosed in younger patients as well [26]. 75% of the patients with diverticulitis presenting in the acute setting have an uncomplicated disease [27]. The debate about the use of antibiotics in acute uncomplicated diverticulitis (AUD) is ongoing for over a decade now. Acute uncomplicated diverticulitis is believed to be inflammatory rather than an infectious condition [28]. Recent evidence has been advocating against the use of antibiotics in acute uncomplicated diverticulitis to avoid complications like antibiotic resistance and other adverse effects. This debate has been ongoing, about the controversial role of antibiotics in acute uncomplicated diverticulitis (AUD). The two randomized controlled trials (RCTs) that are a part of this systematic review and meta-analysis by Chabok., *et al*. [12] and Daniels., *et al*. [13] known as AVOD and DIABLO trial respectively do not support the routine use of antibiotics in patients with acute uncomplicated diverticulitis. Although this is high-quality evidence and was acknowledged by the Cochrane review but also warned the clinicians that further studies are required before this practice can be safely incorporated into current guidelines [29].

This lack of evidence and consensus has led to varying recommendations by different guidelines. Association of coloproctology of Great Britain and Ireland (ACPGBI) recommends the routine use of antibiotics in patients with acute uncomplicated diverticulitis [11]. On the other hand, Danish, Dutch, and Italian guidelines do not recommend the routine use of antibiotics in all cases of acute uncomplicated diverticulitis [14-16].

The results of our study question the usefulness of the routine use of antibiotics in patients with acute uncomplicated diverticulitis. However, the lack of consensus has resulted in the reluctance of the health care workers to adopt the recommendations of the available

studies against the routine use of antibiotics in patients with acute uncomplicated diverticulitis. If the routine use of antibiotics can be safely avoided in patients with acute uncomplicated diverticulitis (AUD), it will not only prevent the patients from adverse effects of antibiotics but will also reduce antibiotic resistance and would reduce the economic burden on the health system as well. The rationale behind the routine use of antibiotics is to reduce the risk of complications and treatment failure. Our study has shown that based on the available evidence there is no statistically significant difference between the two groups treated with or without antibiotics in cases of acute uncomplicated diverticulitis.

The ambiguity in every health care worker's mind is due to the fear of treatment failure and getting complications in the patients treated without antibiotics in acute uncomplicated diverticulitis. Guidelines mentioned above which are in favor of observational treatment without antibiotics usually say routine use of antibiotics should be avoided while treating patients with acute uncomplicated diverticulitis and advise us to be careful with observational treatment.

A study by Bolkenstein., *et al*. [30] is a remarkably interesting study that shows us a way forward in settling this debate and to reach to a consensus in the guidelines for the treatment of acute uncomplicated diverticulitis. This study aimed to identify risk factors for treatment failure in patients with acute uncomplicated diverticulitis. The only statistically significant risk factor for treatment failure in this study was a C reactive protein (CRP) of > 170 mg/l. ASA > 2 although not statistically significant was also considered as a potential risk factor for treatment failure in patients with acute uncomplicated diverticulitis.

There is an ongoing trial by Lopez., *et al*. [31] which is very interesting. This study aims to identify and further stratify the risk factors for treatment failure in acute uncomplicated diverticulitis and would help in developing a consensus in the guidelines.

The limitation of our review is that there are only two randomized controlled trials on this subject which have certain limitations. We think that although they looked into the role of antibiotics in patients with acute uncomplicated diverticulitis but did not concentrate on the presentation of the patients in terms of systematic inflammatory response syndrome (SIRS) or inflammatory markers on presentation. Hence the risk stratification was not done for recurrences, complications, prolonged hospital stay, and treatment failure. The ongoing trial mentioned above is considering the presentation of the patients in terms of SIRS and inflammatory markers in the inclusion and exclusion criteria. Included studies in this review are not homogenous affecting the generalizability of the pooled outcomes.

Conclusion

Acute diverticulitis is an important health problem with significant morbidity and economic costs on the health care system. 75% of the cases are uncomplicated and the available evidence does not support the routine use of antibiotics in acute uncomplicated diverticulitis with no added advantage in reducing recurrence, complications, treatment failure, or hospital stay. This meta-analysis of published studies does not support the routine use of antibiotics in acute uncomplicated diverticulitis.

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