Antibiotics for uncomplicated diverticulitis (Review)

Shabanzadeh DM, Wille-Jørgensen P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 11

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Antibiotics for uncomplicated diverticulitis

Daniel M Shabanzadeh[1], Peer Wille-Jørgensen[1]

[1]Department of Surgical Gastroenterology K, Bispebjerg Hospital, Copenhagen NV, Denmark

Contact address: Daniel M Shabanzadeh, Department of Surgical Gastroenterology K, Bispebjerg Hospital, 23, Bispebjerg Bakke, Copenhagen NV, DK 2400 NV, Denmark. dmshaban@gmail.com.

Editorial group: Cochrane Colorectal Cancer Group.
Publication status and date: New, published in Issue 11, 2012.
Review content assessed as up-to-date: 5 July 2012.

Citation: Shabanzadeh DM, Wille-Jørgensen P. Antibiotics for uncomplicated diverticulitis. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD009092. DOI: 10.1002/14651858.CD009092.pub2.

ABSTRACT

Background

Diverticulitis is an inflammatory complication to the very common condition diverticulosis. Uncomplicated diverticulitis has traditionally been treated with antibiotics with reference to the microbiology, extrapolation from trials on complicated intra-abdominal infections and clinical experience.

Objectives

To assess the effects of antibiotic interventions for uncomplicated diverticulitis on relevant outcome.

Search methods

Studies were identified by computerised searches of the *The Cochrane Library* (CENTRAL), MEDLINE and EMBASE. Ongoing trials were identified and reference lists of identified trials and relevant review articles were screened for additional studies.

Selection criteria

RCTs including all types of patients with a radiological confirmed diagnosis of left-sided uncomplicated diverticulitis. Interventions of antibiotics compared to any other antibiotic treatment (different regime, route of administration, dosage or duration of treatment), placebo or no antibiotics. Outcome measures were complications, emergency surgery, recurrence, late complications and duration of hospital stay and recovery of signs of infection.

Data collection and analysis

Two authors performed the searches, identification of RCTs, trial assessment and data extraction. Disagreements were resolved by discussion or involvement of a third part. Authors of trials were contacted to obtain additional data if needed or were contacted for preliminary results of ongoing trials. Effect estimates were extracted as relative risks (RR).

Main results

Three RCTs were identified. A qualitative approach with no meta analysis was performed because of variety in interventions between included studies. Interventions compared were antibiotics to no antibiotics, single to double compound antibiotic therapy and short to long IV administration. None of the studies found significant difference between the tested interventions. Risk of bias varied from low to high. The newest RCT overall had the best quality and statistical power.

Authors' conclusions

The newest evidence from one RCT says there is no significant difference between antibiotics versus no antibiotics in the treatment of uncomplicated diverticulitis. Previous RCTs have only suggested a non-inferiority between different antibiotic regimes and treatment lengths. This new evidence needs confirmation from more RCTs before it can be implicated safely in clinical guidelines. Ongoing RCTs will be published in the years to come and more are needed. The role of antibiotics in the treatment of complicated diverticulitis has not been investigated yet.

PLAIN LANGUAGE SUMMARY

Antibiotics for uncomplicated diverticulitis

Diverticulitis is a condition with inflammation of big bowel herniations termed diverticulae. Diverticulae are common in the elderly above age 70 and usually do not cause symptoms. However, in some cases inflammation cause a condition, diverticulitis, with pain in the abdomen and signs of infection like fever. Diverticulitis causes no complications in most cases, however, some develop complications and need surgery. The uncomplicated diverticulitis is the focus of this review. It has traditionally been viewed as an infection with bacterial overgrowth in the big bowel and has therefore been treated with antibiotics. We aimed to investigate if there existed any clinical research, evidence, on the effects of antibiotics for uncomplicated diverticulitis in this review.

We found 3 randomized controlled trials (RCTs) on the use of antibiotics for uncomplicated diverticulitis tested on hospitalised patients. The newest trial investigating the actual need for antibiotics when compared to no antibiotics, a second investigated two different antibiotic cures and a third investigated the length of IV antibiotic treatment. None of the studies found a statistical difference in the tested antibiotic regimes. The newest trial had the overall best quality and had the biggest groups of patients making it the overall best trial. It found no difference in the occurrence of surgery needing complications like abscesses and perforations of the big bowel.

Antibiotics can cause serious adverse events for patients like allergic reactions and can even cause other life threatening infections of the bowel. Ultimately, there is a growing antibiotic resistance meaning that the drugs loose their ability to function as bactericidals. This causes limitations in the clinical use of antibiotics when they are needed for treating patients with infections. Therefore there exists strong arguments for limiting the use of antibiotics. The trial that showed no effect of antibiotics is very new and needs confirmation from other similar trials. Ongoing trials will in the next few years be published on the subject.

BACKGROUND

Description of the condition

Diverticulitis is a complication to the common diverticular disease and diverticulosis. The prevalence of diverticulosis is reported to be as high as 45-60% in those over the age of 70 (Hughes 1969a, Parks 1968) and affects 2/3 of patients at age 85 (Welch 1953). Most will remain asymptomatic but diverticulitis is estimated to occur in 10-25% (Parks 1975). Of patients admitted with a first attack of diverticulitis 80% will have uncomplicated diverticulitis (Anaya 2005). The majority (70%) are initially treated conservatively (Frileux 2010, Moreno 2007). Conservative treatment has traditionally consisted of antibiotics and bowel rest (Peppas 2007, Tursi 2004). Patients treated conservative are more common to be re-admitted due to diverticular disease than patients treated with surgery (26% vs 6%) (Peppas 2007). Of these, those with their first attack of uncomplicated diverticulitis have a recurrence rate of 19% but only 5,5% will develop complications requiring emergency surgery or stoma (Anaya 2005). Conservative treatment appears to be effective in the majority of patients in resolving attacks of uncomplicated diverticulitis.

The pathology behind the formation of diverticulae is a herniation of the mucosal layer through the muscular layers of the colonic wall at sites where the mesenteric blood vessels enter the colon (Slack 1962). The primary pathology is believed to be a muscular abnormality with a thickening of the colonic wall (Hughes 1969b). An altered composition of collagen fibres and metalloproteinase possibly results in a weakened colonic wall favouring the formation of diverticulae (Stumpf 2001). Patients with sigmoid diverticulae have a higher intra-sigmoid pressure (Arfwidsson 1964) and local-

ized compartments of high-pressures resulting in pulsation forces shown by manometric and cineradiographic studies. This "theory of segmentation" hypothesized that the high intraluminal pressures were excessive colonic responses to natural stimuli and caused the development of diverticulae (Painter 1964, Painter 1965). The etiology of diverticulosis has not been conclusively established. Painter and Burkitt suggested the etiology to be caused by a western type diet rich in refined carbohydrates and poor in fibres (Painter 1971). The progression from diverticulae to diverticulitis is possibly caused by faecal obstruction of one narrow-necked diverticulum (Berman 1968, Wolf 1957). The subsequent abrasion of the mucosa results in inflammation, bacterial overgrowth of colonic flora, localised ischaemia and perforation (Williams 1995).

In western societies diverticular disease affects the left side of the large bowel involving the distal descending and sigmoid colon (Boles 1958, Hughes 1969a, Kang 2004). In contrast, 70% of diverticulae in Asia are located within the right side affecting the caecum and ascending colon (Chia 1991, Miura 2000, Nakaji 2002) but is believed to be a different condition caused by different pathophysiology and clinical features (Ryan 1983, Stollman 2004). The typical clinical presentation of diverticulitis is a left-sided abdominal pain with localized tenderness to abdominal guarding on clinical examination reflecting the presence and extend of complications (Floch 2004). Clinical signs are helpful in the diagnosis, identifications of complications and as surrogate markers of therapeutic efficacy in daily clinical evaluation. Several clinical classification systems are used to stage perforated diverticulitis (Hinchey 1978) and diverticulitis based on CT-findings (Ambrosetti 1992, Ambrosetti 1997, Baker 2008, Wasvary 1999). Complications to diverticulitis include pelvic or other distant abscess, perforation with purulent or feculent peritonitis, sepsis colonic obstruction, strictures or formation of fistula (Stollman 1999). Uncomplicated diverticulitis is characterised by the presence of localised inflammation with or without a small abscess formation of the bowel wall only (Stollman 2004). Ultra sonography (US) and computed tomography (CT) appear equally accurate in the diagnosis of diverticulitis. A CT-scan is more accurate for detecting alternative diagnoses (Leméris 2008) therefore being the gold standard for the diagnosis and classification of diverticulitis. Barium and contrast enemas have been used as diagnostic tools for diverticulitis in the past but appear less accurate (Liljegren 2007). Colono- or sigmoidoscopy are recommended during follow up when inflammation has subsided to confirm diagnosis, to rule out malignancy and for identification of late complications (Szojda 2007).

Description of the intervention

There are several published guidelines for antibiotic treatment of uncomplicated diverticulitis (see Table 1). They state that, if tolerated, oral antibiotics are preferred. If not tolerated, IV antibiotics and fluids are required. The only underlying reference behind these guidelines is one single RCT (Kellum 1992). Many studies exist on antibiotic treatment for complicated intra-abdominal infections including patients with complicated diverticulitis. It may not be appropriate to extrapolate this evidence to the management of uncomplicated diverticulitis (Byrnes 2009). These antibiotic guidelines reflect the key principles of European and US clinical practice. They are based on clinical experience and microbiological knowledge about the gram-negative rods and anaerobes involved in diverticulitis (*Escherichia coli, Bacterioides fragilis* and *Clostridium*) rather than evidence.

How the intervention might work

If antibiotics are effective they are believed to prevent the development of complications as well as shorten the duration and severity of symptoms. Antibiotics might prevent or lower the rate of recurrences of diverticulitis.

Why it is important to do this review

To clarify the evidence for the use of antibiotics in the treatment of uncomplicated acute diverticulitis.

OBJECTIVES

The object of this review was to assess the effects of antibiotics for uncomplicated diverticulitis. Interventions accepted were all available antibiotic compounds, administration and doses to determine the effect on immediate or late complications and recurrence of diverticulitis.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were included. All requirements to study design, participants, interventions, comparators, primary and secondary outcomes, search strategies and data analysis were predefined in a published study protocol (Shabanzadeh 2011).

Types of participants

Inclusion criteria were left-sided diverticulitis confirmed by CT, US or contrast enemas. Diverticulitis was considered uncomplicated in the absence of pelvic or other distant abscess, fistula, stricture, peritonitis and sepsis. We had no requirements to the participants. Therefore both initial and recurring diverticulitis and all ages, genders, races and comorbidity were included.

Types of interventions

Interventions included a variety of antibiotic treatments and comparators:
1. Antibiotics compared to placebo or no antibiotics including usual care (bowel rest).
2. Comparison of different antibiotic regimes compared to each other.
3. Comparison of different routes of administration, dosage and duration of treatment. Duration was divided into short (less than 7 days) vs. long (7 days or more).

Types of outcome measures

Reporting of at least one primary outcome was required in order to include the RCT in this review.

Primary outcomes

Primary outcomes were failure of treatment during intervention reported as:
1. Complication-rate (abscess, fistula, stricture, perforation with peritonitis or sepsis)
or
2. Emergency surgery-rate related to diverticulitis.
Outcomes had to occur within 30 days of admission/diagnosis or less.

Secondary outcomes

Secondary outcomes were included where available:
1. Rate of recurrence during follow up over 30 days
2. Rate of late complications (same as above) in follow up over 30 days
3. Duration of hospital stay
4. Time to recovery of signs of infection (fever, leucocytosis, CRP, ESR)

Search methods for identification of studies

Electronic searches

Electronic searches were performed in EMBASE and MEDLINE using Ovid search form and in *The Cochrane Library* (including CENTRAL). The trial search coordinator of The Cochrane Colorectal Cancer Group was involved in producing the search strategies and accepted search strings before the conduction of searches. Following strategies were employed: EMBASE (1980 to 2011) index terms: diverticulitis and antibiotic agent; antiinfective agent and a randomised controlled trial-filter. MEDLINE (1948-2011) index terms: diverticulitis, colonic; diverticulitis and anti-bacterial agents; anti-infective agents. A sensitive filter for randomised controlled trials was build into the search strategies as described in the Cochrane Handbook (Higgins 2009). *The Cochrane Library* (CENTRAL) index terms: diverticulitis; diverticulitis, colonic and anti-bacterial agents; anti-infective agents. Additional free-text terms diverticulit* and antibiotic* were added to all database searches. Additional ongoing trials where searched at controlled-trials.com searching all registers (including U.S. National Institutes of Health). Searches were limited to only human trials. For full search strategy see Appendix 1.

Searching other resources

Reference lists from relevant RCTs and reviews identified during the search were screened for additional RCTs.

Data collection and analysis

Selection of studies

All titles and abstracts obtained by the electronic searches were screened for identification of relevant RCTs. Full text of articles were obtained if trial eligibility could not be assessed by title or abstract or if an abstract was not available. A full text was obtained when eligible RCTs were identified. Identification and assessment was done by both authors and RCTs were marked eligible, not eligible or doubtful. Uncertainty about adequacy of trials or disagreements were resolved by discussion or by involvement of a third part.

Data extraction and management

Data extraction was performed on preformatted data extraction form. It was performed by the primary author and checked by the secondary author.

Assessment of risk of bias in included studies

The methods described in The Cochrane Handbook for Systematic Reviews of Intervention 2009 (Higgins 2009) were used. The Cochrane Collaboration's Tool for assessing risk of bias was used to assess the methodological quality of the identified trials. This tool

focuses on sequence generation, allocation concealment, blinding (patients, personnel and outcome assessors), incomplete outcome data and selective outcome reporting. Studies were ranked for risk of bias as low, unclear or high.

Measures of treatment effect

Treatment effect was extracted from RCT and if not reported calculated by the author. Dichotomous outcomes were extracted and assessed from the identified RCTs. Where possible the predefined outcomes were expressed in a 2 x 2 table with treatment effect calculated as relative risk (RR) with the goal of performing meta analysis or qualitative analysis. The outcomes of this review were adverse events and an RR below 1 was interpreted in favour of the intervention and above 1 in favour of the comparator. Uncertainty was expressed as 95% confidence interval (CI).

Dealing with missing data

Authors of included RCTs were contacted by email in order to obtain missing data. An attempt to retrieve preliminary results of ongoing trials was done by contact to authors.

Assessment of heterogeneity

The identified RCTs were assessed for clinical heterogeneity by evaluating the interventions and outcomes.

Data synthesis

A qualitative analysis was to be performed if few or non-homogenous RCTs only were identified. If enough homogenous RCTs were identified meta-analysis was preferable. The template of Review Manager 5 was used as reporting guidelines and for production of this review.

RESULTS

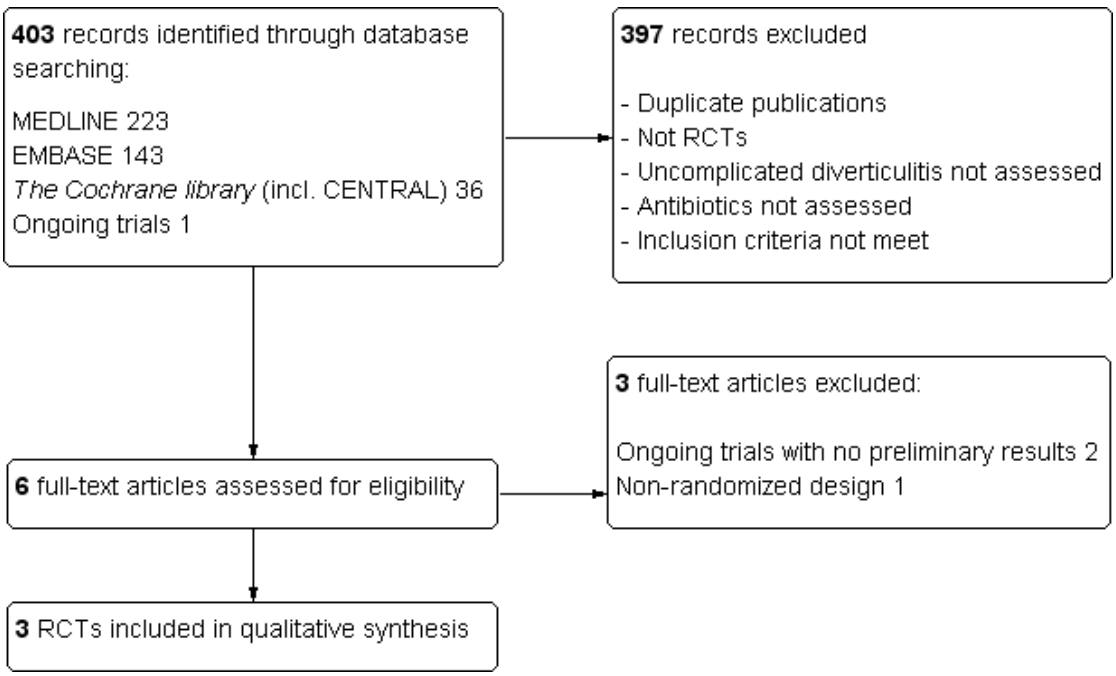
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Our search strategy resulted in 402 studies from the online databases. Searching ongoing trials identified 1 additional RCT. Screening reference lists of reviews and identified trials did not provide additional RCTs. A total of 403 hits were identified with 6 RCTs eligible for assessment. All relevant articles were identified regardless of language. For study selection see study flow diagram Figure 1.

Figure 1. Study flow diagram.



Included studies

Of the 6 RCTs that met the predefined inclusion criteria 2 were ongoing trials (Biondo 2010, Ünlü 2010) and no additional data could be obtained from the authors of these trials. The preliminary result from one RCT was published as a conference abstract (Chabok 2010a) which later was published as a full RCT article (Chabok 2012) and was therefore to be included. Two further trials were excluded (see Excluded studies) leaving 3 RCTs for analysis (Chabok 2012, Kellum 1992, Ribas 2010). Unfortunately it was impossible to combine data from these 3 trials due to the heterogeneity particularly in terms of interventions. Therefore a qualitative analysis of each trial was performed. For detailed description of RCTs see Characteristics of included studies.

Antibiotics versus no antibiotics

One single RCT investigated the effects of antibiotic therapy in uncomplicated diverticulitis and was performed in Sweeden. The groups consisted of a no antibiotic group versus an antibiotic treated group in patients with a CT-confirmed diagnose of uncomplicated acute diverticulitis. It included 669 randomised patients (Chabok 2012). Complications, abscess and perforation, were reported to develop in 9 patients with 3 abscess in the no-antibiotic group and 3 perforations in each group. These complications did not differ significant between the two groups within 30 days of discharge from the hospital (Analysis 3.1). Emergency surgery during hospital stay occurred in 1 patient from the no-antibiotic group and in 3 from the antibiotic group and did not differ significant between the groups (Analysis 3.2). Recurrence at 12 months follow-up and median hospital stay at 2,9 days (P= 0,72) in each group was not significant different between the two groups (Analysis 3.3). The study concludes no difference in the outcomes between antibiotic therapy versus no antibiotic therapy.

Comparison of different antibiotic agents

Kellum 1992 compared single compound antibiotic therapy Cefoxitin to combination therapy Gentamicin-Clindamycin in patients where the majority had a radiographic diagnosis of uncomplicated acute diverticulitis and included 77 patients. Only two patients had a diagnosis solely based on clinical findings. Our calculated estimate for emergency surgery had wide confidence intervals and therefore no significant difference between these to antibiotic regimes was found (see Analysis 1.1). Leucocytosis resolved quicker in the single compound group (2,5 days) than in the combination group (4,1 days) and this was significant (P= 0,03). Duration of hospital stay was similar in both groups. The study concludes that there were no significant differences in the cured rates (P=0,48) and failure rates (P=0,48) between the two treatment arms.

Comparison on routes of administration and duration of therapy

Ribas 2010 compared a short 24-48 hour IV antibiotic treatment to a longer IV treatment of 7 days in patients with a CT-verified diagnosis of uncomplicated diverticulitis. All 50 included patients were treated with antibiotics for 12 days in total. Failure of treatment was observed in both groups but was not significantly different between the two groups. A correspondence with the author confirmed that none of these failure of treatment patients were re-evaluated with CT or received emergency surgery, but were unable to be discharged solely because of persistent pain. Thereby this RCT has zero events of our primary outcomes. However, secondary outcomes were reported. Colonoscopy 4-6 weeks after discharge revealed late complications with strictures in 1 patient from each group. The difference in strictures between the two groups was not significant (see Analysis 2.1). Short IV treatment of 24-48h was therefore not inferior to long IV treatment of 7 days when treated 12 days with antibiotics in total.

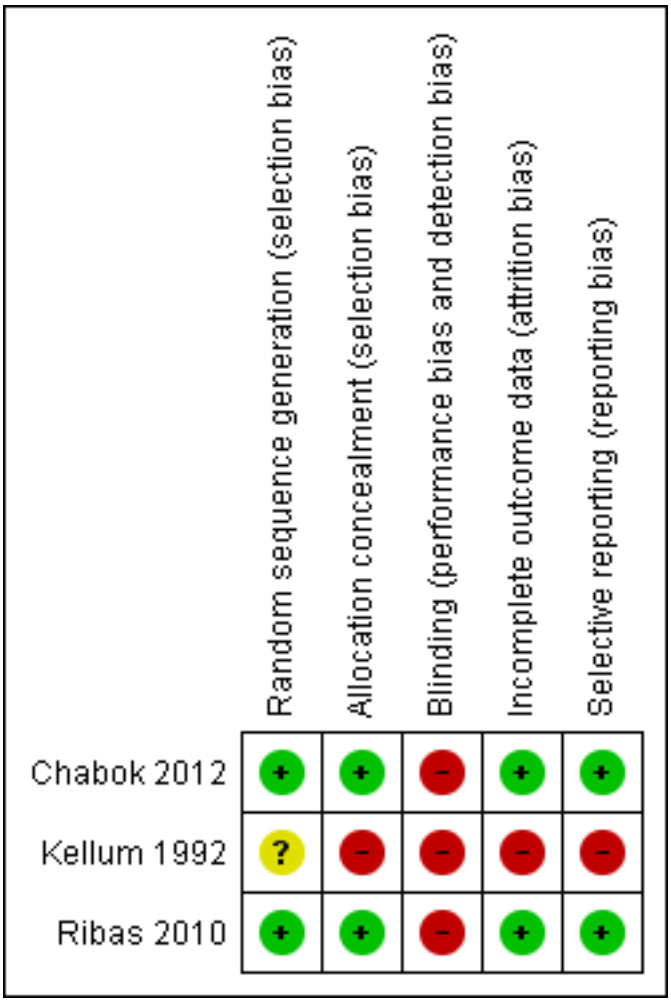
Excluded studies

397 where excluded because they were duplicate publications, were not randomised controlled trials, patients did not have a diagnosis of uncomplicated diverticulitis on CT or antibiotics where not assessed. One trial was excluded because study design introduced selection bias and could not be considered a randomised study for this review although is was labelled as a RCT (Schug-Pass 2010). For details on exclusion see Characteristics of excluded studies. No studies were excluded due to language.

Risk of bias in included studies

Risk of bias for all three studies can be seen in section Risk of bias in included studies with a summary in Figure 2.

Figure 2. Risk of bias summary



Allocation

Kellum 1992 lacked descriptions of randomizations process and allocation thereby introducing a high risk of selection bias. The remaining two RCTs supplied an adequate description on allocation method and concealment (Chabok 2012, Ribas 2010).

Blinding

No blinding of patients, health care providers or data assessors was carried out in the 3 included RCTs.

Incomplete outcome data

Attrition and exclusion of patients after randomizations was adequately reported in two studies (Chabok 2012; Ribas 2010). Kellum 1992 had inadequate reporting on attrition. Thirty-four percent of the randomised patients were excluded from analysis and some without reported reasons. Attrition during the 6 weeks of follow up was not addressed (see Characteristics of included studies). Therefore Kellum 1992 was deemed as high risk of attrition bias.

Selective reporting

All of the included studies describe the existence of a protocol but none of them has a published protocol. From the articles no clear assessment of whether the outcomes in the protocols were reported or if they had been changed could be performed. Chabok 2012 had predefined primary and secondary outcomes and these were available throughout the whole trial period online (Smedh

2009). One author (Ribas 2010) reported in a correspondence that the outcomes were the same in the protocol as described in the article. Kellum 1992 never describes outcomes as predefined and therefore it was impossible to judge the primary outcomes. See Characteristics of included studies with risk of bias tables for description of why this study was evaluated as having a high risk of bias.

Other potential sources of bias

Chabok 2012 was the only RCT providing power calculations for the group sizes (Characteristics of included studies).

Effects of interventions

When intervention included antibiotics verus no antibiotics no significant difference was found on the complications abscess and perforation, rate of recurrence during 12 months of follow up or duration of hospital stay. Non-inferiority was found when comparing Cefoxitin to Gentamicin-Clindamycin and when comparing short versus long IV treatment on rate of emergency surgery or complications.

DISCUSSION

Summary of main results

According to the identified trials in this review there are no significant effects of the tested antibiotic therapies in the treatment of uncomplicated diverticulitis. This was outlined as no effect of antibiotics when compared to no antibiotics, a non-inferiority between single compound compared to double compound therapy and as short versus long IV antibiotic therapy.

Overall completeness and applicability of evidence

Only three RCTs were identified to assess the outcomes of this review. All studies included isolated groups of patients with verified uncomplicated diverticulitis. Of these RCTs, only one study actually investigated the role of antibiotics compared to no antibiotics. It states that there is no difference in the pooled complications or abscess and perforation alone between the two groups. However, a non-significant trend towards more abscess formation in the no antibiotic group was seen. In addition to CT verification the trial included only patients with a body temperature above 38°C and an elevated white blood cell count. Some patients with uncomplicated diverticulitis on CT might therefore have been excluded due to these missing para clinical signs of infection, which are not obligate for diverticulitis. The second study revealed no difference between single compared to double antibiotic treatment and the third reported zero events of the primary outcome of this review and thereby confirmed that length of IV antibiotic treatment has no effect on outcome. Overall, small amount of evidence is currently provided for the clinical question of this review.

Quality of the evidence

Of the three included RCT only one (Chabok 2012) was of better quality with an overall low risk of bias. This study had a high risk of performance and detection bias due to the lack of blinding. None of the outcomes depended on patient-reporting and therefore patient blinding would unlikely have resulted in a better quality study, however, the lack of blinding in outcome assessment contributes negatively to the quality of this study. The power calculations of this study makes the estimates more reliable. The other included RCTs both included very small amounts of patients and therefore had the risk of type II error. The RCT of older date (Kellum 1992) had an overall high risk of bias.

Potential biases in the review process

The methodology to evaluate the evidence was carried out according to Cochrane's tool for assessing risk of bias resulting in a uniform and strict analysis of each RCT. No meta analysis was performed because the three included RCTs in this review all investigate different interventions resulting in clinical heterogeneity. Two authors performed the study selection and data extraction and agreed upon study inclusion and exclusion. Two studies were excluded due to the review's inclusion criteria (Ridgway 2008) and due to the identification of a non-randomized design although the study labelled itself as an RCT (Schug-Pass 2010). Reasons for exclusion are outlined in Characteristics of excluded studies. Even inclusion of these studies would not have changed the conclusion of this review. Hence, this review has very low risk of potential bias.

Agreements and disagreements with other studies or reviews

That antibiotics have no effect on uncomplicated diverticulitis was investigated in a Swedish retrospective observational study. It included 311 patients with a CT-verified diagnosis of acute diverticulitis not requiring emergency surgery on admittance. Patients were treated conservatively with or without antibiotics and authors found no significant difference between the two treatment arms on emergency surgery or recurrence(Hjern 2007). Another observational study on patients with a radiological diagnosis of mild diverticulitis or Hinchey stage 1a investigated the effect of antibiotics compared to no antibiotics. Likewise, this study

found no significant difference on emergency surgery, percutaneous drainage, recurrence or late complications between treatment arms during a 12 month follow-up (de Korte 2011a). These studies have the methodological flaws of non-randomized trials, however they definitely suggest the same conclusion as Chabok 2012. Other studies have addressed the subject of antibiotics for uncomplicated diverticulitis without investigating the actual need for antibiotics. A retrospective study of patients with a clinical diagnosis of diverticulitis not requiring surgery compared anaerobe antibiotic coverage to aerobe coverage only and found no significant difference in emergency surgery (Fink 1981). A RCT including 80 patients with a clinical diagnosis of uncomplicated diverticulitis compared oral to IV administration and found no significant difference in abdominal tenderness used as a surrogate for complications (Ridgway 2008, see Characteristics of excluded studies). These previous studies have low diagnostic accuracy and methodological quality but they suggest a non-inferiority to different antibiotic regimes and routes of administration just as the studies included in this review (Kellum 1992, Ribas 2010).

Treatment without antibiotics for uncomplicated diverticulitis might currently be controversial due to clinical guidelines (Table 1). However, antibiotic treatment can cause serious adverse events for the patients and reduces the utility of these drugs due to resistance. This evidently rising clinical problem of resistance includes the aerobe and anaerobic microbes associated with diverticulitis (Chabok 2010b, Sartelli 2010). Studies including antibiotics for intra-abdominal infections report high-mortality events such as *Clostridium difficile* superinfection causing pseudomembranous colitis and eventually toxic megacolon (Goldstein 2011). The included studies reported adverse events to antibiotics in 3 patients with allergic reactions (Chabok 2012), 4 with elevated kreatinine and 1 pruritic rash (Kellum 1992). None of the studies assessed resistance and we therefore cannot judge the scope of this problem in these clinical trials but have to refer to solely refer to the literature. However the adverse events of these included RCTs and the literature on antibiotic resistance calls evidently for, if possible, a reduction in the clinical use of antibiotics.

The sparse amount of evidence on need of antibiotics for uncomplicated diverticulitis is being emphasized in another systematic review (de Korte 2011b). This review has included a broader selection of studies than our review. The conclusion of this review is the same as ours but does not include the newest published evidence. It is produced by a Dutch group that currently is working on a RCT investigating effects of antibiotics on time to full recovery, development of complications, recurrence and quality of life in patients with uncomplicated diverticulitis. The trial is expected to be completed in 2014 (Ünlü 2010). Another ongoing RCT is investigating what effects surgery has on recurrence of diverticulitis or persisting symptoms of diverticular disease compared to a conservative approach (van de Wall 2010). The role of antibiotics in the treatment of complicated diverticulitis is not explored in RCTs. Retrospective studies show that small diverticular abscess can resolve on antibiotics alone and that bigger abscesses (>4cm) require CT-guided percutaneous drainage (Kumar 2006, Siewert 2006, Soumian 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The newest evidence on antibiotic treatment for uncomplicated diverticulitis suggests that antibiotics have no effects on complications, emergency surgery and recurrence. However, this evidence is very fresh and sparse and will need some more confirmation from future ongoing trials before clinical guidelines can be changed safely. An interest in lowering the use of antibiotics exists due to antibiotic resistance and adverse events.

Implications for research

More RCTs on the use of antibiotics versus no antibiotics is needed. Both to confirm the safety of a no-antibiotic regime and to reveal the role of antibiotics in the bigger spectrum of diverticular disease. At least one ongoing RCTs is bringing new evidence to the guidelines for antibiotics in diverticular disease in the years to come. This will investigate the same issues as the evidence on the no-antibiotic regime described in this review and introduce quality of life. The effects of antibiotics for patients with complicated diverticulitis needs to be investigated as no RCTs has done this before.

ACKNOWLEDGEMENTS

Thanks and appreciation goes to Cagdas Ünlü, Steve Brown and Scott R. Steele for taking the time to peer-review the protocol. To Vivienne Goodfellow for linguistic corrections, to trial search coordinator Marija Barbatoskovic for her assistance with the electronic searches and to managing editor Henning Keinke Andersen from Cochrane for supervision.

REFERENCES

References to studies included in this review

Chabok 2012 ***{published and unpublished data}***
Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. British Journal of Surgery 2012; Vol. [Epub ahead of print].

Kellum 1992 ***{published data only}***
Kellum JM, Sugerman HJ, Coppa GF, Way LR, Fine R, Herz B, et al.Randomized, prospective comparison of cefoxitin and gentamicin-clindamycin in the treatment of acute colonic diverticulitis. *Clinical Therapeutics* 1992;**14**: 376–84.

Ribas 2010 ***{published and unpublished data}***
Ribas Y, Bombardó J, Aguilar F, Jovell E, Alcantara-Moral M, Campillo F, et al.Prospective randomized clinical trial assessing the efficacy of a short course of intravenously administered amoxicillin plus clavulanic acid followed by oral antibiotic in patients with uncomplicated acute diverticulitis. *International Journal Of Colorectal Disease* 2010;**25**:1363–70.

References to studies excluded from this review

Ridgway 2008 ***{published data only}***
Ridgway PF, Latif A, Shabbir J, Ofriokuma F, Hurley MJ, Evoy D, et al.Randomized controlled trial of oral vs intravenous therapy for the clinically diagnosed acute uncomplicated diverticulitis. *Colorectal Disease* 2008;**11**: 941–6.

Schug-Pass 2010 ***{published data only}***
Schug-Pass C, Geers P, Hügel O, Lippert H, Köckerling F. Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis. *International Journal Of Colorectal Disease* 2010;**25**:751–9.

References to ongoing studies

Biondo 2010 ***{published data only}***
Biondo S. Hospitalization or ambulatory treatment of acute diverticulitis (01DIVER). clinicaltrials.gov, search antibiotics AND diverticulitis, ID: NCT01081054 2010.

Ünlü 2010 ***{published data only}***
Unlü C, de Korte N, Daniels L, Consten EC, Cuesta MA, Gerhards MF, et al.A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (diabolo trial) [protocol]. *BMC Surgery* 2010; **10**:23.

Additional references

Ambrosetti 1992
Ambrosetti P, Robert J, Witzig JA, Mirescu D, de Gautard R, Borst F, et al.Prognostic factors from computed tomography in acute left colonic diverticulitis. *British Journal Of Surgery* 1992;**79**:117–9.

Ambrosetti 1997
Ambrosetti P, Grossholz M, Becker C, Terrier F, Morel P. Computed tomography in acute left colonic diverticulitis. *British Journal Of Surgery* 1997;**84**:532–4.

Anaya 2005
Anaya DA, Flum DR. Risk of emergency colectomy and colostomy in patients with diverticular disease. *Archives Of Surgery* 2005;**140**:681–5.

Arfwidsson 1964
Arfwidsson S, Knock NG, Lehmann L, Winberg T. Pathogenesis of multiple diverticula of the sigmoid colon in diverticular disease. *Acta Chirurgica Scandinavica* 1964;**63: suppl 342**:1–68.

Baker 2008
Baker ME. Imaging and interventional techniques in acute left-sided diverticulitis. *Journal Of Gastrointestinal Surgery* 2008;**12**:1314–7.

Berman 1968
Berman LG, Burdick D, Heitzman ER, Prior JT. A critical reappraisal of sigmoid peridiverticulitis. *Surgery, Gynecology & Obstetrics* 1968;**127**:481–91.

Boles 1958
Boles RS Jr, Jordan SM. The clinical significance of diverticulosis. *Gastroenterology* 1958;**35**:579–82.

Brook 2000
Brook I, Frazier EH. Aerobic and anaerobic microbiology in intra-abdominal infections associated with diverticulitis. *Journal Of Medical Microbiology* 2000;**49**:827–30.

Byrnes 2009
Byrnes MC, Mazuski JE. Antimicrobial therapy for acute colonic diverticulitis. *Surgical Infections* 2009;**10**:143–54.

Chabok 2010a
Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K. No value of antibiotics for acute uncomplicated diverticulitis: a randomised study. Colorectal Disease. 2010; Vol. 12.

Chabok 2010b
Chabok A, Tarnberg M, Smedh K, Pahlman L, Nilsson LE, Lindberg C, et al.Prevalence of fecal carriage of antibiotic-resistant bacteria in patients with acute surgical abdominal infections. *Scandinavian Journal of Gastroenterology* 2010; **45**:1203–10.

Chia 1991
Chia JG, Wilde CC, Ngoi SS, Goh PM, Ong CL. Trends of diverticular disease of the large bowel in a newly developed country. *Diseases Of The Colon And Rectum* 1991;**34**: 498–501.

de Korte 2011a
de Korte N, Kuyvenhoven J PH, van der Peet DL, Felt-Bersma RJ, Cuesta MA, Stockmann HBAC. Mild colonic

diverticulitis can be treated without antibiotics. a case-control study. *Colorectal Disease* 2011;**14**:325–30.

de Korte 2011b

de Korte N, Unlü C, Boermeester MA, Cuesta MA, Vrouenreats BC, Stockmann HB. Use of antibiotics in uncomplicated diverticulitis. *British Journal of Surgery* 2011;**[Epub ahead of print]**:[Epub ahead of print].

Fink 1981

Fink M, Smith LE, Rosenthal D. Antibiotic choice in the nonoperative management of acute diverticulitis coli. *The American Surgeon* 1981;**47**:201–3.

Floch 2004

Floch MH, Bina I. The natural history of diverticulitis - fact and theory. *Journal Of Clinical Gastroenterology* 2004;**38**: 2–7.

Frileux 2010

Frileux P, Dubrez J, Burdy G, Roullet-Audy JC, Dalban-Sillas B, Bonnaventure F, et al.Sigmoid diverticulitis. Longitudinal analysis of 222 patients with a minimal follow up of 5 years. *Colorectal Disease: The Official Journal Of The Association Of Coloproctology Of Great Britain And Ireland* 2010;**12**:674–80.

Goldstein 2011

Goldstein EJ. Beyond the target pathogen: ecological effects of the hospital formulary. *Current Opinion In Infectious Diseases* 2011;**24**:21–31.

Higgins 2009

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *Available from www.cochrane-handbook.org.*. The Cochrane Collaboration, [updated March 2011].

Hinchey 1978

Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. *Advances In Surgery* 1978;**12**:85–109.

Hjern 2007

Hjern F, Josephson T, Altman D, Holmström B, Mellgren A, Pollack J, et al.Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory?. *Scandinavian Journal Of Gastroenterology* 2007;**42**:41–7.

Hughes 1969a

Hughes LE. Postmortem survey of diverticular disease of the colon. *Gut* 1969;**10**:336–44.

Hughes 1969b

Hughes LE. Postmortem survey of diverticular disease of the colon. II. The muscular abnormality of the sigmoid colon. *Gut* 1969;**10**:344–51.

Kang 2004

Kang JY, Melville D, Maxwell JD. Epidemiology and management of diverticular disease of the colon. *Drugs & Aging* 2004;**21**:211–28.

Kumar 2006

Kumar RR, Kim JT, Haukoos JS, Macias LH, Dixon MR, Stamos MJ, et al.Factors affecting the successful management of intra-abdominal abscesses with antibiotics and the need for percutaneous drainage. *Diseases Of The Colon And Rectum* 2006;**49**:183–9.

Köhler 1999

Köhler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. *Surgical Endoscopy* 1999;**13**:430–6.

Leméris 2008

Laméris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. *European Radiology* 2008;**18**:2498–511.

Liljegren 2007

Liljegren G, Chabok A, Wickbom M, Smedh K, Nilsson K. Acute colonic diverticulitis: a systematic review of diagnostic accuracy. *Colorectal Disease: The Official Journal Of The Association Of Coloproctology Of Great Britain And Ireland* 2007;**9**:480–8.

Miura 2000

Miura S, Kodaira S, Shatari T, Nishioka M, Hosoda Y, Hisa TK. Recent trends in diverticulosis of the right colon in Japan: retrospective review in a regional hospital. *Diseases Of The Colon And Rectum* 2000;**43**:1383–9.

Moreno 2007

Moreno AM, Wille-Jørgensen P. Long-term outcome in 445 patients after diagnosis of diverticular disease. *Colorectal Disease: The Official Journal Of The Association Of Coloproctology Of Great Britain And Ireland* 2007;**9**:464–8.

Nakaji 2002

Nakaji S, Danjo K, Munakata A, Sugawara K, MacAuley D, Kernohan G, et al.Comparison of etiology of right-sided diverticula in Japan with that of left-sided diverticula in the West. *International Journal Of Colorectal Disease* 2002;**17**: 365–73.

Painter 1964

Painter NS. The aetiology of diverticulosis of the colon with special reference to the action of certain drugs on the behaviour of the colon. *Annals Of The Royal College Of Surgeons Of England* 1964;**34**:98–119.

Painter 1965

Painter NS, Truelove SC, Ardran GM, Tuckey M. Segmentation and the localization of intraluminal pressure in the human colon, with special reference to the pathogenesis of colonic diverticula. *Gastroenterology* 1965; **49**:169–77.

Painter 1971

Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of western civilization. *British Medical Journal* 1971;**2**:450–4.

Parks 1968

Parks TG. Post-mortem studies on the colon with special reference to diverticular disease. *Proceedings Of The Royal Society Of Medicine* 1968;**61**:932–4.

Parks 1975
Parks TG. Natural history of diverticular disease of the colon.Clin Gastroenterol 1975;4:53- 69. *Clinics In Gastroeneterology* 1975;**4**:53–69.

Peppas 2007
Peppas G, Bliziotis IA, Oikonomaki D, Falagas ME. Outcomes after medical and surgical treatment of diverticulitis: A systematic review of the available evidence. *Journal of Gastroenterology and Hepatology* 2007;**22**:1360–8.

Rafferty 2006
Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. *Disease Of The Colon And Rectum* 2006;**49**:939–44.

Ryan 1983
Ryan P. Changing concepts in diverticular disease. *Diseases Of The Colon And Rectum* 1983;**26**:12–8.

Sartelli 2010
Sartelli M. A focus on intra-abdominal infections. *World Journal Of Emergency Surgery* 2010;**5**:9.

Shabanzadeh 2011
Shabanzadeh DM. Antibiotics for uncomplicated acute diverticulitis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD009092]

Siewert 2006
Siewert B, Tye G, Kruskal J, Sosna J, Opelka F, Raptopoulos V, et al.Impact of CT-guided drainage in the treatment of diverticular abscesses: size matters. *American Journal Of Roentgenology* 2006;**186**:680–6.

Slack 1962
Slack WW. The anatomy, pathology, and some clinical features of diverticulitis of the colon. *British Journal Of Surgery* 1962;**50**:185–90.

Smedh 2009
Smedh K. Antibiotic Therapy of Acute Uncomplicated Colonic Diverticulitis. Assesed February 16, 2012. Available from http://clinicaltrials.gov/ct2/show/NCT01008488?term=diverticulitis+and+antibiotics&rank=2 2009.

Soumian 2008
Soumian S, Thomas S, Mohan PP, Khan N, Khan Z, Raju T. Management of Hinchey II diverticulitis. *World Journal Of Gastroenterology* 2008;**14**:7163–9.

SSAT 1999
[No authors listed]. Surgical treatment of diverticulitis. Patient Care Committee of the Society for Surgery of the Alimentary Tract (SSAT). *Journal Of Gastrointestinal Surgery: Official Journal Of The Society For Surgery Of The Alimenatry Tract* 1999;**3**:212–3.

Stollman 1999
Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *The American Journal Of Gastroenterology* 1999;**94**:3110–21.

Stollman 2004
Stollman N, Raskin JB. Diverticular disease of the colon. *The Lancet* 2004;**363**:631–9.

Stumpf 2001
Stumpf M, Cao W, Klinge U, Klosterhalfen B, Kasperk R, Schumpelick V. Increased distribution of collagen type III and reduced expression of matrix metalloproteinase 1 in patients with diverticular disease. *International Journal Of Colorectal Disease* 2001;**16**:271–5.

Szojda 2007
Szojda MM, Cuesta MA, Mulder CM, Felt-Bersma RJ. Review article: management of diverticulitis. *Alimentary Pharmacology & Therapeutics* 2007;**26 Supplement 2**:67–76.

Tursi 2004
Tursi A. Acute diverticulitis of the colon - current medical therapeutic management. *Expert Opinion On Pharmacotherapy* 2004;**5**:55–9.

van de Wall 2010
van de Wall BJ, Draaisma WA, Consten EC, van der Graaf Y, Otten MH, de Wit GA, et al.DIRECT trial. Diverticulitis recurrences or continuing symptoms: Operative versus conservative treatment. A multicenter randomised clinical trial [protocol]. *BMC Surgery* 2010;**10**:25.

Wasvary 1999
Wasvary H, Turfah F, Kadro O, Beauregard W. Same hospitalization resection for acute diverticulitis. *The American Surgeon* 1999;**65**:632–5.

Welch 1953
Welch CE, Allen AW, Donaldson GA. An appraisal of resection of the colon for diverticulitis of the sigmoid. *Annals Of Surgery* 1953;**138**:332–43.

Williams 1995
Williams RA, Davis IP. Diverticular disease of the colon. *Bockus Gastroenterology 5th ed.* Saunders, 1995:1637–56.

Wolf 1957
Wolf BS, Khilnani M, Marshak RH. Diverticulosis and diverticulitis: roentgen findings and their interpretation. *The American Journal Of Roentgenology, Radium Therapy And Nuclear Medicine* 1957;**77**:726–43.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chabok 2012

Methods	RCT, multicenter, October 2003 to January 2010
Participants	669 patients *Inclusion*: CT with uncomplicated acute diverticulitis, elevated WBC, temperature 38C or more *Exclusion*: CT with complicated diverticulitis (abscess, fistula, free air), receiving antibiotic or immunosuppressive therapy,high fever, affected general condition, peritonitis or sepsis
Interventions	Intervention: No antibiotic group (IV fluids only) Control: Antibiotic group. Broad-spectrum antibiotics were used according to the participating centres' routines, covering gram-negative and anaerobic bacteria. Treatment was initiated with an IV combination of a second- or third generation cephalosporin (cefuroxime or cefotaxime) and metronidazole, or with carbapenem antibiotics (ertapenem, meropenem or imipenem) or piperacillin-tazobactam. Orally administrated antibiotics such as ciprofloxacin or cefadroxil combined with metronidazole were initiated subsequently on the ward or at discharge. The total duration of antibiotic therapy was at least 7 days
Outcomes	*Primary*: discharge without complications (fistula, abscess, perforation) within 30 days. Decision to discharge patients was made by the attending surgeon based on an improvement in clinical status as well as a reduction in the white blood cell count (WBC) and C-reactive protein (CRP) level, and the absence of fever. Fistula, abscess and perforation was registered. Readmission with recurrence after 12 months was assessed by questionnaires *Secondary*: length of hospital stay, costs and late complications one year after admission One year follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization in blocks of four and stratified by the centres. The sizes of the blocks were unknown to the participating units. At each centre, a local investigator was responsible for recruiting patients to the trial and controlling the randomizations process *From author:* The centre for clinical research performed the randomizations. This centre was independent from the clinic and was not involved in patient recruitment

Chabok 2012 (*Continued*)

Allocation concealment (selection bias)	Low risk	Opening a sealed envelope, distributed by the Centre for Clinical Research in Väasterås *From author*: envelopes were not possible to see through in order to figure out randomisation group
Blinding (performance bias and detection bias) All outcomes	High risk	Not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	669 patients were randomised, 46 excluded with adequate reasons (25 in no antibiotic group and 21 in antibiotic group). 41 patients were lost-so follow up after 12 months (19 in no-antibiotic group and 22 in antibiotic group). In total 87 randomised patients did not complete the trial corresponding to an attrition rate of 13%. This attrition rate is acceptable and reasons for exclusion are all justified. Group sizes with α=0·05 and a power of 80 per cent were calculated and reported to be 240 in each group which was fulfilled for analysed study-population
Selective reporting (reporting bias)	Low risk	Method and outcomes were specified and were available during the study period on clinicaltrials.gov (Smedh 2009)

Kellum 1992

Methods	RCT, multicenter
Participants	77 participants randomised *Inclusion*: abdominal tenderness, fever/leucocytosis (WBC=9,5 cells/mm^3 or more), CT findings with colonic wall thickening/increased density of pericolic fat or contrast enema with intramural/extramural tracking/abscess or other (2 patients with clinical diagnosis, 1 with colonoscopy, 2 with operation, 1 with pathological examination only included) *Exclusion*: requirement of immediate emergency surgery, admission creatinine of 3mg/dL or more, need of additional antibiotics not permitted by the study protocol
Interventions	*Intervention*: IV Cefoxitin 1-2g/6h (n=30 patients) *Control*: IV Gentamicin (1,7mg/kg followed by 1-1,4mg/kg/8h maintenance dose) and IV Clindamycin (2,4-2,7mg/d) (n=21 patients) Duration of treatment was determined by attending physician based on clinical assessment

Outcomes	*Cured*: resolved clinical findings and discharged with no recurrence for at least 6 weeks or alternatively a candidate for elective surgery with primary anastomosis and no septic complications (wound infection, intra-abdominal abscess or anastomotic leak). *Failure*: at least 48h of antibiotic therapy with subsequent need of emergency surgery or switch of antibiotics. Alternatively the patients had undergone elective surgery with septic complications following a successful antibiotic therapy Resolution of leucocytosis measured by WBC. Measured at admittance but not described when measured for outcome
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	From article: Patients were randomly assigned to receive either CFX or a combination of gentamicin and clindamycin
Allocation concealment (selection bias)	High risk	not described
Blinding (performance bias and detection bias) All outcomes	High risk	Described as open label study
Incomplete outcome data (attrition bias) All outcomes	High risk	*From article*: 26 were deemed non-evaluable. Ten had been randomised to receive CFX and sixteen to receive G/C. Seven [patients] received additional antibiotics not permitted by study protocol *Interpretation*: 34% of randomised patients were excluded from analysis. The exclusion is described in numbers and reasons adequately for nineteen patients. However seven randomised patients were excluded and it is not reported how they were distributed between the two intervention arms. Lost to follow up during the six weeks described in method section is not addressed in the results section. The questionable exclusion of patients, the big exclusion rate, the missing reporting on lost to follow up and the overall small sample size of the study all contribute to high risk attrition bias Frequency and time-points for white blood cell count measurements is not described. This makes the stated significant conclusion that leucocytosis resolved more rapid in single compound group than in the combination group questionable. All of the above factors result in a high risk of reporting bias
Selective reporting (reporting bias)	High risk	A protocol is mentioned once in result section. Specification of outcomes exists in method section but they are never described as predefined. Recurrence outcome is never addressed in results section although mentioned in methods section

Ribas 2010

Methods	RCT, parallel, multicenter, pilot study
Participants	50 patients randomised, 44 analysed. *Inclusion:* abdominal pain localized to left lower quadrant and tenderness at examination, CT (within 24-48h) (bowel wall thickness and pericolic fat infiltration) *Exclusion*: complicated diverticulitis on CT or clinical suspicion.
Interventions	*Intervention*: Short IV group 24-48h + 10 days of oral antibiotic *Control*: Long IV group with IV antibiotics for 7 days + 5 days of oral antibiotic Amoxicillin-Clavulanic acid was used for both administration routes and intervention groups with the same dose (1g/8h). Total duration of treatment was 12 days in both groups. The only difference between the interventions where the length of IV administration thereby testing if long IV administration is superior to oral treatment
Outcomes	*Failure of treatment*: not able to discharge patient because of symptoms on fourth or eighth day, emergency admission after discharge for reasons related to diverticulitis or hospital readmission with same diagnosis within 30 days. *Late complications: c*olonoscopy 4-6 weeks after discharge.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*From article*: Patients were randomly assigned to one of the two treatment groups by a computer-generated randomizations list that was prepared by an external observer
Allocation concealment (selection bias)	Low risk	*From article*: Patients were allocated to each group by means of numbered sealed envelopes that corresponded to the randomizations list that were opened after the written consent was provided
Blinding (performance bias and detection bias) All outcomes	High risk	*From author*: Patients are not blinded due to intervention. Personell and outcome assessor blinding procedures not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout after randomizations described adequately: 6 excluded because of withdrawal of consent or different CT-diagnosis. No patients were excluded from analysis 3 patients (two in the short-term and one in long-term IV group) had failure of treatment and could not be discharged *From author*: none of the 3 patients required

		surgery or had reevaluation on CT. The patients had persistent pain and therefore could not be discharged on scheduled day. The table of results from the 3 failure patients was obtained and stated that it was because of pain that these patients were not discharged. *Interpretation*: patients that failed treatment was not because of emergency surgery requiring complications
Selective reporting (reporting bias)	Low risk	No specification of a protocol in the study. All defined outcomes in method section are reported and assessed *From author*: "a document [protocol] was written in Catalan. The article summarizes quite well what we did, the inclusion and exclusion criteria, the two groups with different treatments, as well as the outcomes" *Interpretation*: relevant outcomes and relevant outcome reporting when combining article and comments plus data from author

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ridgway 2008	This study does not fulfil the inclusion criteria and should therefore not have been mentioned here. The reason it is displayed here is that it is often referred to in studies on diverticulitis and therefore we here report our reasons for exclusion *Study description*: This RCT compares IV vs. oral antibiotic treatment. *Resons for exclusion*: Diagnosis was based on clinical symptoms only with no radiographic confirmation or classification of disease and thereby did not meet the inclusion criteria
Schug-Pass 2010	*Study description*: RCT comparing treatment with IV Ertapenem for 4 days vs 7 days on patients with CT/US-verified diagnosis of uncomplicated acute diverticulitis. Primary outcome was successful treatment with resolved clinical signs, resolved leucocytosis, absence of peritonitis and abdominal complaints and no need for additional antibiotic or surgery *Reasons for exclusion*: In the design all included patients were treated with same IV treatment the first 4 days. Randomization was performed on day 4 if treatment had been successful. 17 patients where excluded from being randomised at day 4 including patients with persisting symptoms and complicated diverticulitis. This design excludes patients of interest for this review before randomizations. The study design is introducing selection bias by undermining the concept of randomizations before intervention-start and by selecting patients for randomizations. Thereby this study is not considered a randomised trial in this review and therefore does not follow inclusion criteria

Characteristics of ongoing studies *[ordered by study ID]*

Biondo 2010

Trial name or title	Randomized trial comparing two treatment strategies for acute diverticulitis. Hospitalisation or ambulatory antibiotic treatment
Methods	RCT, parallel
Participants	Inclusion: CT with mild diverticulitis. Exclusion: severe diverticulitis, suspicion of colon cancer, pneumoperitoneum, intolerance for oral feeding, antibiotics for diverticulitis in the last months
Interventions	Intervention: Ambulatory treatment with oral antibiotic for 10 days. Control: Hospital treatment with IV antibiotics first days and diet progression orally
Outcomes	Primary: Treatment failure meaning persistent or increasing pain, treatment resistant fever, intestinal occlusion, necessity to drain new intraabdominal abscess, indication for surgery, mortality. Secondary: Recurrence, Quality of life, costs. Time for outcome measure: 30 days.
Starting date	September 2009
Contact information	Sebastiano Biondo, sbiondo@bellvitgehospital.cat
Notes	Estimated completion: March 2012

Ünlü 2010

Trial name or title	A multicenter randomised clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial)
Methods	RCT, parallel
Participants	264 patients are needed in each arm to detect difference in outcomes. A total of 533 Inclusion: left sided, primary attack, mild acute diverticulitis confirmed by CT/US performed first 24h. Only modified Hinchey stages 1a and 1b and Ambrsetti's mild diverticulitis. Exclusion: US/CT suspicion of cancer, inflammatory bowel disease, Hinchey stage 2,3 and 4 or Ambrosetti's severe stage, sepsis
Interventions	Intervention: Liberal strategy = supportive measures only with no antibiotics. Oral intake as tolerated. Hospital admission with IV fluids if clinical condition requires it. Antibiotics will be started if subsequent complicated diverticulitis, another infective focus or sepsis. Adequate pain relief Control: Conservative strategy = IV antibiotics for 48h and switch to oral if tolerated. Total treatment duration will be 10 days of amoxicillin-clavulanic acid with IV-dose 1200mg 4 times daily and oral dose 625mg 3 times daily. In case of allergy a combination of ciprofloxacin and metronidazole will be used
Outcomes	Primary: Time to full recovery within follow-up of 6 months = discharge, normal diet (solid food and more than 1L fluid orally), temperature<38C, VAS<4, no use of daily pain medication/back to pre-illness pain medication, resume to pre-illness working activities assessed by questionnaires and out-patient clinic visits.

Ünlü 2010 (*Continued*)

	A clinically relevant difference of more than 5 days in time to full recovery is not expected between the two treatment arms Secondary: Rate of development of complicated diverticulitis that requires surgery or non-surgical interventions, number of days outside hospital during 6 months follow-up, direct/indirect medical costs at 6 months follow-up, occurrence of complications (abscess, perforation, stricture or fistula), predefined side effects of antibiotics(resistance/sensitivity pattern, allergy), morbidity, mortality, readmission-rate within 6 months, acute diverticulitis recurrence-rate at 12 and 24 months follow-up. Generic and disease specific quality of life questionnaires (Euro-Qol 5D, SF-36 and Gastro-Intestinal Quality of Life Index) on admission and after 3, 6, 12 and 24 months
Starting date	May 2010
Contact information	Cagdas Ünlü c.unlu@amc.uva.nl
Notes	Estimated Study Completion Date: May 2014 Estimated primary completion date: November 2012 (final data collection date)

DATA AND ANALYSES

Comparison 1. Emergency surgery risk for Cefoxitin vs Gentamicin-Clindamycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Emergency surgery	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.11, 4.58]

Comparison 2. Late complications in short vs long-term IV antibiotic treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Late complications (stricture)	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.00]

Comparison 3. No-antibiotic vs antibiotic group

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications (abscess and perforation)	1	623	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.51, 8.05]
2 Emergency surgery	1	623	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.24]
3 Recurrence at 12 months follow-up	1	582	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]

Analysis 1.1. Comparison 1 Emergency surgery risk for Cefoxitin vs Gentamicin-Clindamycin, Outcome 1 Emergency surgery.

Review: Antibiotics for uncomplicated diverticulitis

Comparison: 1 Emergency surgery risk for Cefoxitin vs Gentamicin-Clindamycin

Outcome: 1 Emergency surgery

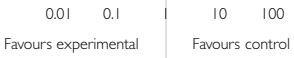
Study or subgroup	Cefoxitin n/N	Gentamicin-Clindamycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kellum 1992	2/30	2/21		100.0 %	0.70 [0.11, 4.58]
Total (95% CI)	**30**	**21**		**100.0 %**	**0.70 [0.11, 4.58]**

Total events: 2 (Cefoxitin), 2 (Gentamicin-Clindamycin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Late complications in short vs long-term IV antibiotic treatment, Outcome 1 Late complications (stricture).

Review: Antibiotics for uncomplicated diverticulitis

Comparison: 2 Late complications in short vs long-term IV antibiotic treatment

Outcome: 1 Late complications (stricture)

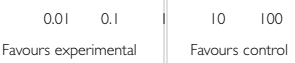
Study or subgroup	Short-term IV (24-48h) n/N	Long term IV (7 days) n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ribas 2010	1/22	1/22		100.0 %	1.00 [0.07, 15.00]
Total (95% CI)	**22**	**22**		**100.0 %**	**1.00 [0.07, 15.00]**

Total events: 1 (Short-term IV (24-48h)), 1 (Long term IV (7 days))

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 No-antibiotic vs antibiotic group, Outcome 1 Complications (abscess and perforation).

Review: Antibiotics for uncomplicated diverticulitis

Comparison: 3 No-antibiotic vs antibiotic group

Outcome: 1 Complications (abscess and perforation)

Study or subgroup	No antibiotics n/N	Antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chabok 2012	6/309	3/314		100.0 %	2.03 [0.51, 8.05]
Total (95% CI)	**309**	**314**		**100.0 %**	**2.03 [0.51, 8.05]**

Total events: 6 (No antibiotics), 3 (Antibiotics)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 No-antibiotic vs antibiotic group, Outcome 2 Emergency surgery.

Review: Antibiotics for uncomplicated diverticulitis

Comparison: 3 No-antibiotic vs antibiotic group

Outcome: 2 Emergency surgery

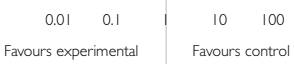
Study or subgroup	No antibiotics n/N	Antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chabok 2012	1/309	3/314		100.0 %	0.34 [0.04, 3.24]
Total (95% CI)	**309**	**314**		**100.0 %**	**0.34 [0.04, 3.24]**

Total events: 1 (No antibiotics), 3 (Antibiotics)

Heterogeneity: not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable

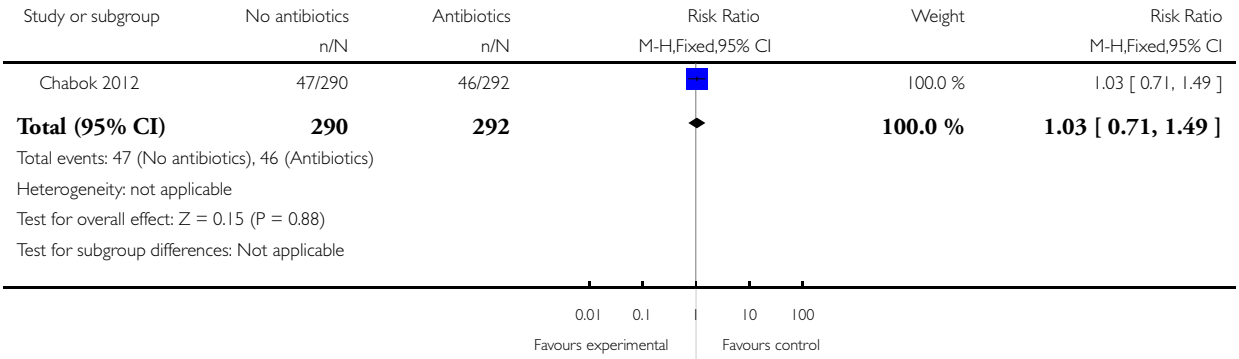


Analysis 3.3. Comparison 3 No-antibiotic vs antibiotic group, Outcome 3 Recurrence at 12 months follow-up.

Review: Antibiotics for uncomplicated diverticulitis

Comparison: 3 No-antibiotic vs antibiotic group

Outcome: 3 Recurrence at 12 months follow-up



ADDITIONAL TABLES

Table 1. Published guidelines for antibiotic treatment of uncomplicated diverticulitis

Published guidelines for antibiotic treatment of uncomplicated diverticulitis (inspired by Ünlü 2010)

	Choice of antibiotic	Administration	Duration of therapy	Reference to evidence
Society forSurgery of the Alimentary Tract (SSAT 1999)	Broad-spectrum	IV	7-10 days	-
Scientific Committee of the European Association for Endoscopic Surgery (Köhler 1999)	Broad spectrum with anaerobe coverage: Ciprofloxacin + metronidazole Ampicillin, gentamicin + metronidazole Piperacilin or Tazobactam	Oral or IV	7-10 days	-
American College of Gastroenterology (Stollman 1999)	Broad spectrum with Gram-neg. rods and anaerobic cover: Amoxicillin-Clavulanic acid	Oral or IV	Initiation 2-4 days with oral continuation 7-10 days	Kellum 1992

Table 1. Published guidelines for antibiotic treatment of uncomplicated diverticulitis (*Continued*)

	Sulfmethoxazole-trimethoprim + metronidazole Quinolone + metronidazole Metronidazole/clindamycin + aminoglycoside/monobactam/3rd gen. cephalosporins 2nd gen. cephalosporins Combinations with β-lactamase inhibitor			
The American Society of Colon and Rectal Surgeons (Rafferty 2006)	Gram-neg. rods and anaerobic cover Single and multiple regimes are equally effective	Oral or IV	-	Kellum 1992

APPENDICES

Appendix 1. Full search strategy

MEDLINE (1948 to January 28, 2011), with sensitive search-filter for RCTs

1. randomised controlled trial.pt. 294141
2. controlled clinical trial.pt. 80633
3. randomized.ab. 203098
4. placebo.ab. 119722
5. drug therapy.fs. 1400121
6. randomly.ab. 147806
7. trial.ab. 209540
8. groups.ab. 988644
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 2582046
10. exp animals/ not humans.sh. 3477110
11. 9 not 10 2189325
12. exp Diverticulitis, Colonic/ or exp Diverticulitis/ 4344
13. diverticulit*.mp. 5357
14. exp Anti-Bacterial Agents/ad, ae, dt, ec, me, py, pk, pd, ph, po, se, tu, th, to [Administration & Dosage, Adverse Effects, Drug Therapy, Economics, Metabolism, Pathogenicity, Pharmacokinetics, Pharmacology, Physiology, Poisoning, Secretion, Therapeutic Use, Therapy, Toxicity] 384761
15. exp Anti-Infective Agents/ad, ae, an, ct, ec, me, pk, pd, ph, po, se, st, tu, to [Administration & Dosage, Adverse Effects, Analysis, Contraindications, Economics, Metabolism, Pharmacokinetics, Pharmacology, Physiology, Poisoning, Secretion, Standards, Therapeutic Use, Toxicity] 888720
16. antibiotic*.mp. 199089
17. 14 or 15 or 16 978635

18. 12 or 13 5359
19. 11 and 17 and 18 223

EMBASE (1980- January 28, 2011), with search filter for RCTs

1. randomised controlled trial/ 287964
2. exp RANDOMIZATION/ 53288
3. controlled study/ 3431015
4. multicenter study/ 82557
5. phase 3 clinical trial/ 12705
6. phase 4 clinical trial/ 1018
7. double blind procedure/ 101029
8. single blind procedure/ 13776
9. ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. 127809
10. (random* or cross* over* or factorial* or placebo* or volunteer*).ti,ab. 817714
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 3918082
12. "human*".ti,ab. 1761841
13. (animal* or nonhuman*).ti,ab. 722225
14. 12 and 13 168842
15. 13 not 14 553383
16. 11 not 15 3699521
17. exp DIVERTICULITIS/ 3270
18. diverticulit*.mp. 5608
19. exp antibiotic agent/ 753570
20. antibiotic*.mp. 406146
21. exp antiinfective agent/bd, ct, ad, an, cb, cm, cr, do, dt, to, dl, ig, im, iv, po, pe, pk, rc, sc, th [Buccal Drug Administration, Clinical Trial, Drug Administration, Drug Analysis, Drug Combination, Drug Comparison, Drug Concentration, Drug Dose, Drug Therapy, Drug Toxicity, Intradermal Drug Administration, Intragastric Drug Administration, Intramuscular Drug Administration, Intravenous Drug Administration, Oral Drug Administration, Pharmacoeconomics, Pharmacokinetics, Rectal Drug Administration, Subcutaneous Drug Administration, Therapy] 801635
22. antibacterial agent.mp. 1568
23. 17 or 18 5608
24. 19 or 20 or 21 or 22 1226562
25. 16 and 23 and 24 143

***The Cochrane Library*search (including CENTRAL)**

#1 MeSH descriptor Diverticulitis explode all trees 21
#2 MeSH descriptor Diverticulitis, Colonic explode all trees 49
#3 diverticulit* 127
#4 MeSH descriptor Anti-Bacterial Agents explode all trees 18533
#5 MeSH descriptor Anti-Infective Agents explode all trees 43679
#6 antibiotic* 14597
#7 ((#1 OR #2 OR #3) AND (#4 OR #5 OR #6)) 36

HISTORY

Protocol first published: Issue 4, 2011

Review first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Both authors contributed to the production of the protocol and the review.

DECLARATIONS OF INTEREST

No declarations of interest

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A language restriction to English, German, Danish, Norwegian and Sweedish trials was stated in the protocol, but all relevant articles were identified regardless of language.

The search did not identify enough homogenous RCTs to perform pooling of data and thereby none of the described methods for production of a meta analysis were used and no numbers needed to treat (NNT) or I^2 was calculated as stated in the protocol.

No continuous outcomes were extracted because RCTs did not report them so none of their protocol described methods were used.

Identified RCTs did not report the secondary outcomes time to recovery of clinical signs or mortality and therefore not included in the review.

The protocol stated that ITT would be performed where possible. All included RCTs had non-inferiority designs and therefore no ITT was performed (see Quality of the evidence).

INDEX TERMS

Medical Subject Headings (MeSH)

*Intestine, Large; Anti-Bacterial Agents [*therapeutic use]; Diverticulitis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans