

Use of antibiotics in uncomplicated diverticulitis

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Background: The value of antibiotics in the treatment of acute uncomplicated left-sided diverticulitis is not well established. The aim of this review was to assess whether or not antibiotics contribute to the (uneventful) recovery from acute uncomplicated left-sided diverticulitis, and which types of antibiotic and route of administration are most effective.

Methods: Medline, the Cochrane Library and Embase databases were searched. Randomized controlled trials (RCTs), prospective or retrospective cohort studies addressing conservative treatment of mild uncomplicated left-sided diverticulitis and use of antibiotics were included.

Results: No randomized or prospective studies were found on the topic of effect on outcome. One retrospective cohort study was retrieved that compared a group treated with antibiotics with observation alone. This study showed no difference in success rate between groups. Only one RCT of moderate quality compared intravenous and oral administration of antibiotics, and found no differences. One other RCT of very poor quality compared two different kinds of intravenous antibiotic and also found no difference. A small retrospective cohort study comparing antibiotics with and without anaerobe coverage showed no difference in group outcomes.

Conclusion: Evidence on the use of antibiotics in mild or uncomplicated diverticulitis is sparse and of low quality. There is no evidence mandating the routine use of antibiotics in uncomplicated diverticulitis, although several guidelines recommend this.

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Introduction

Diverticular disease is the most common disease of the colon, being found in one in three people over the age of 60 years in the Western world¹. The lifetime prevalence of diverticulitis is 10–25 per cent among patients with diverticular disease, and is increasing^{1,2}. Acute diverticulitis is usually graded as ‘complicated’ or ‘uncomplicated’ according to the classification of the European Association for Endoscopic Surgery³, as ‘mild’ or ‘severe’ according to the Ambrosetti computed tomography (CT) criteria⁴, or according to the modified Hinchey classification⁵. As only 0–10 per cent of admitted patients present with complicated disease and require surgery or percutaneous drainage, conservative treatment is the management of choice in the majority of patients¹.

The mainstay of treatment for uncomplicated diverticulitis has been bowel rest, intravenous fluids and antibiotics¹. Usually coverage against both Gram-negative

and anaerobic bacteria is recommended^{1,6–9}. Contrary to complicated disease, the effect of treatment in uncomplicated disease has rarely been the subject of research. Recommendations are based on expert opinion and medical dogma. Surveys conducted among American, British and Dutch surgeons and gastroenterologists show that the choice of antibiotics and the route of administration differ. Most American and British surgeons use antibiotics for the treatment of uncomplicated diverticulitis, but the majority of surgeons and gastroenterologists in the Netherlands believe antibiotics are not mandatory in the treatment of uncomplicated diverticulitis^{10–12}.

First, to assess the grounds for use of antibiotics in uncomplicated diverticulitis, guidelines issued by professional organizations worldwide were evaluated. The systematic review aimed to investigate the overall effect of antibiotics in the treatment of diverticulitis, the effect of administration route and the effect of different types of

antibiotic in the treatment of acute mild (uncomplicated) diverticulitis of the sigmoid colon in adult patients.

Methods

The latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting a systematic review or a meta-analysis were used¹³.

Search strategy

Two reviewers independently searched the following databases: MEDLINE (January 1966 to May 2010, search strategy: ('Diverticulitis'[Mesh] OR 'Diverticulitis, Colonic'[Mesh]) AND ('Anti-Bacterial Agents'[Mesh] OR 'Anti-Bacterial Agents'[Pharmacological Action])); Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Register, Database of Abstracts on Reviews and Effectiveness (search strategy: Diverticulitis AND antibiotics); and Embase (January 1950 to May 2010, search strategy: ('Diverticulitis') AND ('Anti-Bacterial Agents')).

After identifying relevant titles, all abstracts were read and eligible articles retrieved. A manual cross-reference search of the bibliographies of relevant articles was performed to identify other studies not found in the search. The 'related articles' function in PubMed was also used to identify articles not found in the original search. Clinical studies published in English, German or Dutch were included. No unpublished data or abstracts were included. The last search update was 1 June 2010.

Inclusion and exclusion criteria

Because of the paucity of data on the conservative treatment of diverticulitis of the sigmoid colon, the authors chose to include not only randomized controlled trials (RCTs) but all comparative studies addressing the conservative treatment of uncomplicated or mild diverticulitis of the sigmoid colon and the use of antibiotics.

Participants included were patients aged 18 years or more diagnosed with acute uncomplicated or mild diverticulitis of the sigmoid colon. Studies that compared antibiotics *versus* observation alone, different types of antibiotic, or oral *versus* intravenous regimens were included. The primary outcome parameter was the success rate of the treatment.

Data collection process

Data were registered on preformatted sheets. The following information was extracted from each included

study: characteristics of trial participants (including age, severity of disease, and method of diagnosis) and the trial's inclusion criteria; type of intervention (antibiotics *versus* observation, different types of antibiotic, and route of antibiotic administration); and types of outcome measure.

Risk of bias in individual studies

Two authors independently assessed the methodological quality and bias of the RCTs using the Jadad score¹⁴ and the checklist of the Cochrane Collaboration¹⁵. Disagreement was resolved by consensus. For each study included, other forms of bias were evaluated on a case-by-case basis. This was done specifically for method of diagnosing diverticulitis.

Statistical analysis

The effectiveness of a specific therapy compared with that of its control group for the primary outcome measure of success rate was expressed using odds ratios (ORs) with 95 per cent confidence intervals, and calculated from the original data, if not provided. An OR of less than 1 favours the intervention group over the control group. As none of the three research questions concerning antibiotic use in uncomplicated diverticulitis revealed more than one RCT, pooling of data was not possible or necessary. Data analysis was performed using Review Manager (RevMan) 5 (Cochrane Collaboration, Oxford, UK).

Results

Published guidelines and practice parameters

Four guidelines were identified after searching MEDLINE. The Society for Surgery of the Alimentary Tract⁸, the American Society of Colon and Rectal Surgeons⁷, the European Association for Endoscopic Surgery³ and the American College of Gastroenterology⁶ have published guidelines concerning the treatment of mild diverticulitis of the sigmoid colon and the use of antibiotics. A further search using Google identified one other guideline by the World Gastroenterology Organisation¹⁶. All guidelines recommend the use of antibiotics, but references to original research are lacking. For the recommendation on the type of antibiotic, in only two guidelines (the American Society of Colon and Rectal Surgeons and the American College of Gastroenterology) is there a reference to original research¹⁷. All guidelines indicate that antibiotics should be given intravenously, but can be given orally in

mild disease where outpatient treatment is being considered. Broad-spectrum antibiotics covering Gram-negative and anaerobic bacteria are recommended in all guidelines. No references to original research are given.

Systematic review

The first search resulted in a combined total of 549 articles from all databases. After reviewing the abstracts only four articles were found specifically to address the use of antibiotics in colonic diverticulitis and met the inclusion criteria (*Fig. 1*). A summary of included studies is shown in *Table 1*. Individual study quality assessment is listed per methodological item in *Table S1* (supporting information). Two RCTs were found. In addition, two studies were found that compared two cohorts of patients.

Antibiotics versus no antibiotics

No RCTs were found. Only one study was retrieved in the search strategy. Hjern and colleagues¹⁸ performed a retrospective case–control study in a group of patients with diverticulitis treated without antibiotics and compared their outcome with that in a group of patients treated with antibiotics. The groups were comparable at baseline for age, sex and co-morbidity. Diagnosis was confirmed by means of CT. Disease severity was compared using laboratory parameters and the Ambrosetti CT classification⁴. The group that received antibiotics had

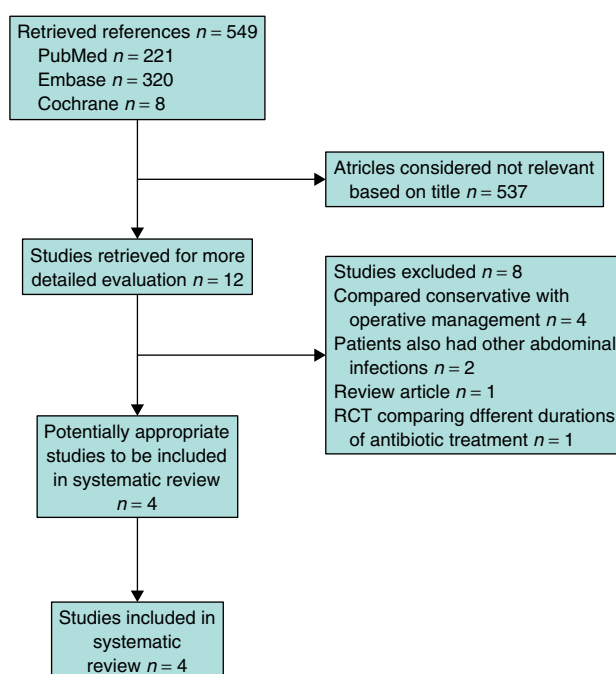


Fig. 1 Search strategy. RCT, randomized controlled trial

significantly higher infection parameters and more severe diverticulitis on CT at baseline.

The primary outcome measure was success rate, which was similar between antibiotic (115 of 118, 97.5 per cent)

Table 1 Characteristics of included studies

Reference	Design	Interval	Country	Patient included	Method of diagnosis	Group intervention	n	Control	n
Antibiotics versus observation alone 18	Retrospective comparative cohort study	2000–2002	Sweden	Adults with acute diverticulitis	CT	Antibiotics	118	Observation alone	193
Oral versus intravenous regimen 19	RCT	2002–2004	UK	Adults with acute diverticulitis	Clinical grounds	Oral regimen	41	Intravenous regimen	38
Different types of antibiotic 17	RCT	1992	UK	Adults with acute diverticulitis	Combination of clinical grounds and radiology, pathology or surgical evidence of diverticular disease	Cefoxitin	30	Gentamicin–clindamycin	21
20	Retrospective comparative cohort study	1974–1978	USA	Adults with acute diverticulitis	NS	Anaerobic coverage	15	No anaerobic coverage	52

CT, computed tomography; RCT, randomized controlled trial; NS, not stated.

and control (186 of 193, 96.4 per cent) groups. No ORs or confidence intervals were reported for the primary outcome, but could be calculated: the OR for success of treatment without antibiotics was 1.44 (0.37 to 5.69). Time to recovery also did not differ significantly between the groups. Hospital stay was significantly shorter in the control group than in the antibiotics group (3 *versus* 5 days respectively; $P < 0.001$). During follow-up 29 per cent of patients receiving antibiotics had further events (recurrent acute diverticulitis and/or subsequent surgery) compared with 28 per cent of those treated without antibiotics. In a multivariable analysis, the risk of a further event was not influenced by previous antibiotic treatment (OR 1.03, 0.61 to 1.74).

Different types of antibiotic

Only one RCT was found that had examined this question. Kellum and co-workers¹⁷ conducted a randomized trial comparing cefoxitin and gentamicin–clindamycin in the treatment of acute uncomplicated diverticulitis. The primary outcome measure was success rate. No power calculation was reported. Diagnosis was based on clinical grounds and contrast enema or CT. The two patient groups were comparable with respect to baseline characteristics and clinical disease severity (fever, laboratory parameters and abdominal tenderness). No difference in success rate was found between patients treated with cefoxitin (27 of 30) *versus* gentamicin–clindamycin (18 of 21) ($P = 0.48$). No ORs or confidence intervals were reported, but could be calculated: the OR for success of gentamicin–clindamycin treatment was 1.50 (0.27 to 8.26). Quality assessment revealed a Jadad score of 0, indicating very poor quality.

A retrospective study by Fink *et al.*²⁰ evaluated two different intravenous antibiotic regimens with and without anaerobic coverage, defined as *in vitro* activity against *Bacteroides fragilis*. The primary outcome measure was success rate of treatment. The two groups were comparable with respect to baseline characteristics (age and sex). Fever, laboratory findings and abdominal tenderness were used to assess disease severity. How diverticulitis was diagnosed was not stated. The authors found no difference in success rate between the no anaerobic coverage group (34 of 52) and the anaerobic coverage group (10 of 15) ($P > 0.050$). No ORs or confidence intervals were reported for the primary outcome, but could be calculated: the OR for success of treatment with anaerobic coverage was 1.06 (0.31 to 3.57). The extremely small numbers of patients in this study, especially in the anaerobic group, hampered interpretation of the data.

No pooling of data was possible for these two studies because of differences in design and the use of antibiotic cover.

Oral *versus* intravenous regimens

Ridgeway and colleagues¹⁹ conducted a RCT comparing an oral antibiotic regimen (41 patients) with an intravenous regimen (38) of clindamycin and metronidazole in patients with uncomplicated diverticulitis. Diagnosis was based solely on clinical grounds. The two patient groups were comparable with respect to baseline characteristics and laboratory infection parameters. The primary outcome parameter was resolution of disease. Resolution of left iliac fossa tenderness (by Wexford tenderness score), length of stay and failures of oral therapy (requiring supplemental parenteral therapy) were used as surrogate markers for resolution of disease or success of treatment. There was no significant difference in Wexford tenderness score on day 3 between the oral treatment and the intravenous arm (score 1.26 *versus* 1.20 respectively; $P = 0.79$). Hospital stay did not differ between the two regimens (5.5 *versus* 6.6 days; $P = 0.12$). There was a 100 per cent success rate as neither group had any treatment failures; no OR calculation was possible for that reason. Quality assessment showed a Jadad score of 4, indicating moderate quality.

Discussion

Diverticulitis of the sigmoid colon is one of the most common disorders of the gastrointestinal tract, with a huge healthcare burden. Nevertheless, evidence of the use of antibiotics in mild uncomplicated diverticulitis is sparse and of low quality. There is no evidence mandating the routine use of antibiotics in mild uncomplicated diverticulitis, although several guidelines recommend this.

In the present systematic review four studies were identified, shedding some additional light on the use of antibiotics in uncomplicated left-sided diverticulitis. A recent retrospective case–control study¹⁸ found no advantage of antibiotics in patients with uncomplicated diverticulitis. There is some evidence from one RCT that treatment of uncomplicated diverticulitis with oral antibiotics alone was as effective as treatment with intravenous antibiotics, although verification of the diagnosis of diverticulitis was suboptimal in that study¹⁹. High-quality evidence regarding the most effective type of antibiotic is lacking.

It has long been believed that all forms of diverticulitis are the result of a colonic (micro)perforation. The original Hinchey classification was based on this premise²¹. More

recently a different or complementary pathogenesis of diverticulitis was proposed, in which diverticulitis is regarded as a form of inflammatory bowel disease²². This concept of some form of chronic inflammation (not infection) of the colon in the presence of diverticula was substantiated recently in a study that showed inflammation in pathological specimens taken from around the mucosa of diverticula in asymptomatic individuals with no endoscopic evidence of inflammation²³. This chronic low-grade inflammation could be a precursor stage to the clinically manifest stages of diverticulitis. Recent success in preventing attacks of diverticulitis with probiotics and mezasaline contribute to this notion^{24,25}.

Uncomplicated diverticulitis could be a self-limiting disease in which local host defences can eradicate bacterial invasion of a diverticulum without antibiotics in immunocompetent individuals. Antibiotics may, therefore, not be necessary in the treatment of uncomplicated disease. Potential benefits of a more liberal treatment strategy for acute diverticulitis without antibiotics include shorter duration of hospital admission (no intravenous medication needed), cost reduction, less development of antibiotic resistance and fewer side-effects. Antibiotic resistance, in particular, is becoming a serious and hard-to-combat healthcare threat. In this light the cohort study of Hjern *et al.*¹⁸ is interesting, with its conclusion that antibiotics may not be necessary in the majority of patients. The study was, however, retrospective and non-randomized, and affected by selection bias. No firm conclusions can be drawn, but this study does provide some evidence for the common practice in some European countries of not using antibiotics in the treatment of uncomplicated diverticulitis^{12,18}.

Intra-abdominal infections have been studied extensively but recommendations on the use of antibiotics in diverticulitis are based largely on findings from studies that did not specifically investigate diverticulitis²⁶. Only one study tackled this subject for perforated diverticulitis and showed a similar microbiology in diverticulitis compared with that in other forms of intra-abdominal infection²⁷. The two studies^{17,20} found in this review were of very poor quality and added nothing to the existing narrative on antibiotic choice in intra-abdominal infections in general.

The only randomized trial performed to compare oral and intravenous antibiotics in mild diverticulitis was underpowered¹⁹, and the authors' conclusion that treatment with oral antibiotics alone is as effective as treatment with intravenous antibiotics cannot be accepted without reservation. The results of this trial were, however, in line with recommendations from published

guidelines. Recent literature shows that patients with mild diverticulitis are increasingly being treated safely as outpatients with oral antibiotic regimens²⁸. In addition, a prospective randomized trial on complicated intra-abdominal infections of all origins showed that a switch from intravenous to oral antibiotics was safe when oral intake was tolerated²⁹.

One of the problems with the design of three of the four retrieved studies related to verification of the diagnosis of diverticulitis. Were the correct patients included in the studies? Diagnosis on clinical grounds alone leads to a high percentage of included patients not actually having diverticulitis^{30,31}. CT or ultrasonography should be the method of choice in identifying patients with diverticulitis³². Two recent papers have stated that there may be a subset of patients who can be positively diagnosed without imaging based on a decision rule^{33,34}. However, this decision rule needs first to be externally validated.

The treatment of mild uncomplicated left-sided diverticulitis lacks evidence. Future patients with mild diverticulitis could benefit from the results of prospective trials with sound criteria for diagnosis, with stratification of disease stage and adequate power, investigating one of the many unproven issues of diverticulitis treatment. The results of two RCTs (NCT01111253 and NCT01008488; <http://www.clinicaltrials.gov>) in the Netherlands and Sweden, randomizing patients with uncomplicated diverticulitis to antibiotics or observation alone, are not expected for several years. Until these results become available it is useful to note that current guidelines advising the use of antibiotics in uncomplicated diverticulitis are not evidence-based. In the majority of patients with mild diverticulitis, antibiotics can probably be omitted.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Quality assessment (Word document)

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