Outcome and treatment of acute diverticulitis
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CHAPTER 5

Use of antibiotics in uncomplicated diverticulitis.

de Korte N, Ünlü Ç, Boermeester MA, Cuesta MA, Vrouenraets BC, Stockmann HB

SUMMARY

Background
The exact pathogenesis of uncomplicated left-sided diverticulitis is not well established. What role antibiotics play in its treatment remains unclear.

Objectives
The aim of this review is to assess whether or not antibiotics are needed in the treatment of acute uncomplicated left-sided diverticulitis, which types of antibiotics and which route of administration is most effective.

Data sources
Medline, the Cochrane Library and EMBASE databases were searched.

Study selection
Randomized clinical trials (RCT), prospective or retrospective cohort studies addressing the conservative treatment of uncomplicated left-sided diverticulitis and the use of antibiotics were included.

Results
One retrospective cohort study compared a group treated with antibiotics to observation alone. No difference in success rate was found. One RCT of moderate quality showed no difference when comparing an intravenous regimen to an oral. One other RCT of very poor quality compared two different kinds of intravenous antibiotics and found no difference. A retrospective small cohort study comparing antibiotics with and without anaerobe coverage also showed no difference.

Conclusion and limitations
Evidence on the use of antibiotics in uncomplicated diverticulitis is sparse and of very low quality. Apart from recommendations in several guidelines there is no evidence mandating the routine use of antibiotics in mild diverticulitis. Until high quality evidence becomes available it can be justified to refrain from routine antibiotic use in these patients. When prescribed, an oral regimen seems to be as effective as an intravenous regimen for mild disease. Large prospective trials are needed to provide definite answers.
INTRODUCTION

Diverticular disease is the most common disease of the colon being found in 1 in 3 people over the age of 60 in the western world. (1) The lifetime prevalence of diverticulitis is 10-25% among patients with diverticular disease. (1) Diverticular disease and diverticulitis impose a huge healthcare burden with an estimated 312,000 admissions, 1.5 million days of inpatient care and a total cost of 2.6 billion dollars each year in the United States alone. (2)

Acute diverticulitis is usually graded as complicated or uncomplicated according to the classification of The European Association for Endoscopic Surgeons (3), as mild or severe according to the Ambrosetti CT-criteria (4), or according to the modified Hinchey classification. (5) As only 0-10% of admitted patients present with complicated disease and require surgery or percutaneous drainage, conservative treatment is the management of choice in the majority of patients. (1) The mainstay of treatment for uncomplicated diverticulitis has been bowel rest, intravenous fluids and antibiotics. (1) Usually coverage against both gram negative and anaerobic bacteria is recommended. (1) (6) (7) (8) (9) Contrary to complicated disease, effect of treatment in uncomplicated disease has rarely been subject of research. Recommendations are based on expert opinions and medical dogmas.

Surveys conducted among American, British and Dutch surgeons and gastroenterologists show that the choice of antibiotics and the route of administration differ. All 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) (11) (12)

To assess the grounds for use of antibiotics in uncomplicated diverticulitis, first existing guidelines issued by professional organisations were evaluated. Moreover, a systematic review was performed to evaluate available published evidence with respect to the use of antibiotics in the treatment of acute uncomplicated or mild diverticulitis of the sigmoid colon in adult patients. This review systematically investigated (a) the overall effect of antibiotics on the treatment of diverticulitis, (b) the effect of administration route and (c) the effect of different types of antibiotics. Randomised clinical trials but also comparative cohort studies were included.
METHODS

Published guidelines and practice parameters
A Medline search was performed to identify guidelines issued by professional organisations on the conservative treatment of diverticulitis and recommendations on the use of antibiotics. A Google search was used to identify guidelines not published in Medline indexed journals. We evaluated a) whether or not antibiotics were deemed mandatory, b) which route of administration was recommended and c) which antibiotics were recommended. The evidence supporting the recommendations was noted, specifically references to original research dealing with antibiotics in the treatment of diverticulitis. Only practice parameters and guidelines published by professional organisations between 1999 and 2009 were included.

Systematic review
The latest PRISMA guidelines for conducting and reporting a systematic review or a meta-analysis were used. (13)

Search strategy
Two reviewers (NdK and CU) independently searched the following databases: Medline (January 1966 to December 2009, 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 December 2009, search strategy: ("Diverticulitis") AND ("Anti-Bacterial Agents:))

After identifying relevant titles all abstracts were read and eligible articles were 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. Last search update was 01-06-2010.

Inclusion and exclusion criteria

Studies
Because of the paucity of data on the conservative treatment of diverticulitis of the sigmoid colon we chose not only to include randomized clinical trials but all comparative studies addressing the conservative treatment of uncomplicated or mild diverticulitis of the sigmoid colon and the use of antibiotics.
Participants
Patients eighteen years or older diagnosed with acute uncomplicated or mild diverticulitis of the sigmoid colon.

Interventions and controls
Studies that compare (a) antibiotics versus observation alone, (b) different types of antibiotics or (c) oral versus intravenous regimens were included.

Outcome measures
Primary outcome parameter is success rate of the treatment. Secondary outcome parameters were time to recovery, occurrence of complicated diverticulitis (defined as abscess, perforation, stricture, fistula or bleeding), resolution of symptoms, morbidity, mortality, readmission rate, recurrence rate, duration of hospitalization, serial infection parameters, costs, side effects and antibiotic resistance development.

Data collection process
Data were registered on preformatted sheets. Information was extracted from each included study on: (1) characteristics of trial participants (including age, severity of disease, and method of diagnosis), and the trial’s inclusion criteria; (2) type of intervention (antibiotics versus observation, different types of antibiotics, and route of administration of antibiotics) and (3) types of outcome measures.

Risk of bias in individual studies
Two authors (NdK and CU) independently assessed the methodological quality and bias of the RCT’s using the Jadad score (14) and the checklist of the Cochrane collaboration (15). Disagreement was resolved by consensus. Although designed to evaluate the quality and bias of randomised controlled trials they were also used to assess the quality of the other studies included in the review. For each individual 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 and summary measures
The effectiveness of a specific therapy compared to its control group for the primary outcome measure success rate was expressed using odds ratios (ORs) with 95% confidence intervals (CIs). When odds ratios were not available in the original article, they were calculated. An OR of less than 1 favors the intervention group over the control group. Because of the fact that of none of the three areas of interest concerning antibiotic use in uncomplicated diverticulitis revealed more than one RCT, pooling of data was not possible or needed.
Data analysis was performed using the Cochrane Review Manager (RevMan) version 5 (Cochrane Collaboration, Oxford, UK).

RESULTS

Published guidelines and practice parameters
Total of four guidelines were identified after searching Medline. The Society of Surgery of the Alimentary Tract (8), the American Society of Colon and Rectal Surgeons (7), the European Association for endoscopic Surgery (3) and the American College of Gastroenterology (6) 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 Organization. (16) All guidelines recommend the use of antibiotics, but references to original research are lacking. For the recommendation on the type of antibiotic only in two guidelines a reference to original research is given. (17) All guidelines indicate that antibiotics should be given intravenous, but that in mild disease where outpatient treatment is considered it can be given orally. No references to original research are given.
Systematic review
The first search resulted in a combined total of 545 articles in all databases combined. After reviewing the abstracts only 4 articles addressed the use of antibiotics specifically in colonic diverticulitis and met our inclusion criteria (Figure 1). A summary of includes studies is shown in table 1. Two randomized controlled trials were found. In addition, two studies were found that compared two cohorts of patients. Quality assessment of studies is shown in table 2.

Antibiotics versus no antibiotics
No randomised clinical trials were found. Only one study was retrieved in the search strategy. Hjern et al. performed a retrospective study in a group of patients with diverticulitis treated without antibiotics and compared those to a group of patients treated with antibiotics. (18) The groups were comparable at baseline for age, sex and co-morbidity. Diagnosis was confirmed using CT. Disease severity was compared using laboratory parameters and Ambrosetti CT classification. The group that received antibiotics had significantly higher infection parameters and more severe diverticulitis on CT at baseline.

The primary outcome measure was success rate and it was similar between the antibiotics group (115 of 118, 97%) and the control group (186 of 193, 95%). No odds ratios or confidence intervals were reported for the primary outcome, but can be calculated. Calculated odds ratios for success of treatment without antibiotics is 1.44 (95%CI 0.37-5.69). Time to recovery also did not significantly differ between groups. Hospital stay was significantly shorter in the control group (3 days) compared with the antibiotics group (5 days, P<0.001). During follow-up, 29% of patients treated with antibiotics had further events (recurrent acute diverticulitis and/or subsequent surgery) compared with 28% of those treated without antibiotics. In a multivariable analysis, the risk of a further event was not influenced by prior antibiotic treatment (OR 1.03, CI 95% 0.61-1.74).

Different types of antibiotics
Only one RCT was found examining this question. Kellum et al. conducted a randomized trial comparing cefoxitin and gentamycin-clindamycine in the treatment of acute uncomplicated diverticulitis (17). 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, 90%) versus gentamycin/clindamycin (18 of 21, 86%), P=0.48. No odds ratios or confidence intervals were reported, but can be calculated.
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### Table 2. Quality and bias assessment of studies

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Use of antibiotics in uncomplicated diverticulitis.
Calculated odds ratio for success of gentamycin/clindamycin treatment is 1.50 (95% CI 0.27-8.26).

A retrospective study by Fink et al. evaluated two different intravenous antibiotic regimens with and without anaerobic coverage, defined as in vitro activity against Bacteroides fragilis (19). The primary outcome measure used 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, 65%) and the anaerobic coverage group (10 of 15, 67%; P>0.05). No odds ratios or confidence intervals were reported for the primary outcome, but can be calculated. The calculated odds ratio for success of treatment with anaerobic coverage is 1.06 (0.31-3.57). The extremely small numbers of patients in this study, especially in the anaerobic group hampers interpretation of the data.

No pooling of data was possible for these two studies because of major differences in design and difference in antibiotic coverage used.

**Oral versus intravenous regimens**

Ridgeway et al. conducted a randomized controlled trial comparing an oral antibiotic regimen (N=41) with an intravenous regimen (N=38) of clindamycin and metronidazol in patients with uncomplicated diverticulitis. (20) Diagnosis was based solely on clinical grounds. The two patient groups were comparable with respect to baseline characteristics and laboratory infection parameters. 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 arm (score 1.26) versus the intravenous arm (1.20, P=0.79). Hospital stay did not differ between oral regimen (5.5 days) and intravenous regimen (6.6 days, P=0.12). There was a 100% success rate as both groups had no treatment failures, and no odds ratio calculation is possible for that reason.

**DISCUSSION**

Diverticulitis of the sigmoid colon is one of the most common disorders of the gastrointestinal tract with a huge healthcare burden. When reviewing existing guidelines issued by professional organisations, all recommend the use of antibiotics. There is however no
published evidence that supports the use of antibiotics in mild uncomplicated diverticulitis. In the present systematic review four studies were identified, shedding some additional light on the use of antibiotics in left-sided uncomplicated diverticulitis. A recent retrospective comparative cohort study has found no advantage of antibiotics in patients with uncomplicated diverticulitis. There is some evidence from one randomized controlled trial that treatment of uncomplicated diverticulitis with oral antibiotics alone is as effective as treatment with intravenous antibiotics, although verification of the diagnosis of diverticulitis has been sub-optimal in that study. High quality evidence as to what type of antibiotic is most effective is lacking. Until high quality evidence becomes available it can be justified to refrain from routine antibiotic use in these patients.

It has long been believed that all forms of diverticulitis are the result of a colonic (micro) perforation. The original Hichey classification is based on this premises. (21) More recently a different or complementary pathogenesis of diverticulitis has been proposed, where diverticulitis is regarded as a form of inflammatory bowel disease. (22) This concept of some form of chronic inflammation (not infection) of the colon in the presence of diverticula has been substantiated recently in a study that showed inflammation in pathologic specimens taken from around the mucosa of diverticula in asymptomatic individuals without endoscopic findings of inflammation. (23) 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 mesalazine contribute to this notion. (24) (25) Uncomplicated diverticulitis could be a self-limiting disease in which the local host defence can eradicate the 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, cost reduction, less antibiotic resistance development and side effects. Antibiotic resistance in particular is becoming a serious and hard to combat health-care threat.

In this light the cohort study of Hjern et al. is interesting, concluding that antibiotics might not be necessary in the majority of patients. (18) The study is, however, retrospective and non-randomized and affected by selection bias. No firm conclusions can be drawn, but this study does give some evidence to the common practice in some European countries that do not use 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 largely based on findings in studies not specifically investigating diverticulitis. (26) Only one study has tackled this subject for perforated diverticulitis and showed a similar microbiology in diverticulitis compared to other forms of intra-abdominal infections. (27) Three quarters of the specimens were
polymicrobial with E. Coli being cultured in three quarters of specimens. Bacteroides fragilis was cultured in half of the specimens and other anaerobes found were Clostridium spp. and Fusiform spp. (24) On these grounds coverage against gram-negative and anaerobe bacteria is generally advised. (1) (6) (7) (8) (9) (16) (26) (27) These culture results are however from patients with abscesses and diffuse peritonitis and there is question whether or not these results can be translated to uncomplicated diverticulitis.

There is little debate about the need for gram-negative and anaerobic coverage in intra-abdominal infections in general. A number of studies have shown higher failure and mortality rates when anaerobe coverage is inadequate (28), but high quality evidence is lacking. When agents used to cover gram-negative bacteria lack anaerobic coverage usually metronidazole or clindamycin is added. Emerging resistance to Bacteroides fragilis and a possible association with the outbreak of clostridium colitis is however increasingly becoming a problem with clindamycin use. (29) Whether or not Enterococcus spp. should be covered remains unclear. Research in other abdominal infections shows coverage against these species is only clinically beneficial in certain subsets of patients. (30) These issues underscore the need for large prospective trials comparing different antibiotic regimes specifically for patients with mild diverticulitis, if and when preceding randomized trials demonstrate effectiveness of antibiotics treatment in these types of patients.

The only randomized trial ever performed comparing oral and intravenous antibiotics in mild diverticulitis is underpowered. (20) Their conclusion that treatment with oral antibiotics alone is as effective as treatment with intravenous antibiotics cannot be drawn without reservation. Results from this trial are 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 regimens of antibiotics. (31) In addition, a prospective randomised trial for complicated intra-abdominal infections of all origins showed that a switch from intravenous to oral antibiotics is safe when oral intake was tolerated. (32)

One of the problems with the design of three of the four retrieved studies is the 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 patients being included not having diverticulitis. (33) CT or ultrasound should be the method of choice in identifying patients with diverticulitis. (34) Moreover, all patients in a study should undergo the same strategy for verification of diagnosis, as different tests have different accuracy.

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. Results of two
randomised clinical trials (NCT01111253 and NCT01008488) randomising 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 that advise the use of antibiotics in uncomplicated diverticulitis are not evidence-based.
REFERENCES