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Colonic diverticular disease: medical treatments for acute diverticulitis

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ABSTRACT

INTRODUCTION: Diverticula (mucosal outpouchings through the wall of the colon) are rare before the age of 40 years, after which prevalence increases steadily and reaches over 25% by 60 years. However, only 10% to 25% of affected people will develop symptoms such as lower abdominal pain. Recurrent symptoms are common, and 5% of people with diverticula eventually develop complications such as perforation, obstruction, haemorrhage, fistulae, or abscesses. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of medical treatments for acute diverticulitis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 193 studies. After deduplication and removal of conference abstracts, 75 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 37 studies and the further review of 38 full publications. Of the 38 full articles evaluated, four systematic reviews and one RCT were added at this update. We performed a GRADE evaluation for two PICO combinations CONCLUSIONS: In this systematic overview, we categorised the efficacy for one comparison based on information about the effectiveness and safety of medical treatment (mesalazine, antibiotics [any] only) versus placebo or no treatment.

Key points

- Diverticula (mucosal outpouchings through the wall of the colon) are rare before the age of 40 years, after which prevalence increases steadily and reaches over 25% by 60 years and older. However, only 10% to 25% of affected people will develop symptoms such as lower abdominal pain.

  Recurrent symptoms are common, and 5% of people with diverticula eventually develop complications such as perforation, obstruction, haemorrhage, fistulae, or abscesses.

  Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opiate analgesics have been associated with an increased risk of perforation of diverticula, while calcium antagonists may protect against these complications.

  At this update we have focused on medical treatments for acute diverticulitis, the most commonly occurring complication.

- We searched for RCTs and systematic reviews of RCTs on the effects of medical treatments (mesalazine, antibiotics) versus placebo or no treatment.

  We found few RCTs. There is a need for further RCTs to inform the evidence base.

- Recent evidence suggests that those people with CT-proven uncomplicated acute diverticulitis may not benefit from treatment with intravenous antibiotics.

  This evidence comes from a single RCT, which may have excluded people with severe sepsis, and which had a large percentage of people included in the study with prior episodes of acute diverticulitis.

  However, the results of the study are promising and suggest that, in mild disease, antibiotic treatment may not be beneficial in those with simple CT-proven uncomplicated acute diverticulitis.

- As suggested by one systematic review on the subject, further evidence will be required to change clinical practice.

- We found no RCTs on the effects of antibiotics in people with complicated acute diverticulitis, or on the effects of mesalazine.

Clinical context

GENERAL BACKGROUND

Colonic diverticular disease is a common condition, and its complications cause significant morbidity, mortality, and health care costs. The treatment of its most commonly occurring complication, acute diverticulitis, is changing as evidence from RCTs has started to be published.

FOCUS OF THE REVIEW

For this update we have focused on the issue of medical treatment (either mesalazine or antibiotics) for acute diverticulitis.

COMMENTS ON EVIDENCE

We found four systematic reviews, which identified one RCT of relevance on the use of antibiotics.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, May 2010, to August 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 193 studies. After deduplication and removal of conference abstracts, 75 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 37 studies and the further review of 38 full publications. Of the 38 full articles evaluated, four systematic reviews and one RCT were added at this update.

DEFINITION

Colonic diverticula are mucosal outpouchings through the large bowel wall. They are often accompanied by structural changes (elastosis of the taenia coli, muscular thickening, and mucosal folding). They are usually multiple, and occur most frequently in the sigmoid colon. Most people with colonic diverticula are asymptomatic, with little to find on clinical examination, while 20% develop symptoms at some point. [1] If diverticula are associated with symptoms, then this is termed diverticular disease. If asymptomatic, then the condition is known as diverticulosis. People who go on to develop complications associated with diverticula (inflammation, perforation, fistulae, abscess formation, obstruction, or haemorrhage) are referred to as having complicated diverticular disease. People with uncomplicated diverticular disease may report abdominal pain (principally colicky left iliac fossa pain), bloating, and altered bowel habit, and may have mild left iliac fossa tenderness on examination. Acute diverticulitis occurs when a diverticulum becomes acutely inflamed. People with acute diverticulitis typically present with severe left iliac fossa pain and tenderness associated with fever, tachycardia, malaise, and altered bowel habit.

INCIDENCE/ PREVALENCE

In the UK, the incidence of diverticulosis increases with age; about 5% of people are affected in their fifth decade of life, 25% aged 60 years, and about 50% by their ninth decade. [2] Diverticulosis is common in resource-rich countries, although there is a lower prevalence of diverticulosis in Western vegetarians consuming a diet high in fibre. [3] Diverticulosis was almost unknown in rural Africa and Asia but is becoming more common as these countries industrialise. [4]

AETIOLOGY/ RISK FACTORS

There is an association between low-fibre diets and diverticulosis of the colon, although recent cross-sectional observations challenge this link. [4] [5] A prospective cohort study reported that consuming a vegetarian diet and a high intake of dietary fibre were associated with a lower risk of admission to hospital or death from diverticular disease. [6] High meat intake is also a risk factor for developing diverticular disease. [7] Prospective observational studies have found that both physical activity and a high-fibre diet are associated with a lower risk of developing diverticular disease. [7] [8] The risk of developing diverticulitis or diverticular bleeding has been shown to be associated with regular use of aspirin and NSAIDs. [9] Case-control studies have found an association between perforated diverticular disease and use of NSAIDs, corticosteroids, and opiate analgesics, and have found that calcium antagonists have a protective effect. [10] [11] [12] [13] [14] People in Japan, Singapore, and Thailand develop diverticula that affect mainly the right side of the colon. [15] Observational studies have reported an increased risk of diverticular bleeding and diverticulitis in people with a BMI greater than or equal to 30 kg/m^2 compared with those who have a BMI less than 21 kg/m^2. [16] A population-based study of women reported a 23% increased risk (RR 1.23, 95% CI 0.99 to 1.52) of symptomatic diverticular disease in current smokers compared with non-smokers when accounting for other confounding factors, with a greater risk of developing a perforation or abscess than non-smokers (RR 1.89, 1.15 to 3.10). [17] However, further evidence on this association is required as other studies have not found such a relationship. [17] [18]

PROGNOSIS

Inflammation will develop in 10% to 25% of people with diverticula at some point. [2] It is unclear why some people develop symptoms and some do not. Even after successful medical treatment of acute diverticulitis, almost two-thirds of people suffer recurrent pain in the lower abdomen. [19] Recurrent diverticulitis is observed in 7% to 42% of people with diverticular disease, and after recovery from the initial attack the calculated yearly risk of suffering a further episode is 3%. [20] About 50% of recurrences occur within 1 year of the initial episode, and 90% occur within 5 years. [21] The largest of these retrospective series reported data on 2366 medically treated patients, with a median follow-up of 8.9 years and with a recurrence rate of 13.3%. [22] Complications of diverticular disease (perforation, obstruction, haemorrhage, and fistula formation) are each seen in about

5% of people with colonic diverticula when followed up for 10 to 30 years. [23] In the UK, the incidence of perforation is 2 to 4 cases per 100,000 people a year, leading to approximately 2000 cases annually. [24] [25] Intra-abdominal abscess formation is also a recognised complication.

AIMS OF INTERVENTION

To reduce mortality, symptoms, and complications, with minimal adverse effects.

OUTCOMES

Mortality from complications of diverticulitis; **symptom relief** (includes subjective gastrointestinal symptoms assessed by the use of questionnaires and cure rates; admission and readmission rates as a result of diverticular disease and its complications); **recurrence** incidence of diverticulitis, haemorrhage, perforation, abscess, fistula formation; **adverse effects**. Stool weight and transit time are surrogate outcomes and are not reported in this overview.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date August 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to August 2014, Embase 1980 to August 2014, The Cochrane Database of Systematic Reviews 2014 issue 8 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, including trials described as 'open' or 'open label', and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** We have removed two questions included in the previous version of this systematic overview: What are the effects of treatments for uncomplicated diverticular disease? What are the effects of treatments to prevent complications of diverticular disease? At this update we have added one new option: medical treatment (mesalazine, antibiotics only) versus placebo or no treatment, in people with acute diverticulitis. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 9). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of medical treatments for acute diverticulitis?

OPTION MEDICAL TREATMENT (MESALAZINE, ANTIBIOTICS [ANY] ONLY) VERSUS PLACEBO OR NO TREATMENT FOR ACUTE DIVERTICULITIS New

- For GRADE evaluation of interventions for Colonic diverticular disease: medical treatments for acute diverticulitis, see table, p 9 .
- Recent evidence suggests that those people with CT-proven uncomplicated acute diverticulitis may not benefit from treatment with intravenous antibiotics.
- This evidence comes from a single RCT, which may have excluded people with severe sepsis, and which had a large percentage of people included in the study with prior episodes of acute diverticulitis.
- However, the results of the study are promising and suggest that, in mild disease, antibiotic treatment may not be beneficial in those with simple uncomplicated acute diverticulitis.
- As suggested by one systematic review on the subject, further evidence will be required to change clinical practice.
- A further trial published only in abstract form has confirmed these initial results in people presenting for a first time with CT-proven uncomplicated acute diverticulitis.
- We found no RCTs on the effects of antibiotics in people with complicated acute diverticulitis, or on the effects of mesalazine.

Benefits and harms

Medical treatment (mesalazine, antibiotics) versus placebo or no treatment:

We found four systematic reviews (search dates 2010, [26] 2011, [27] [28] and 2013 [29]), which identified one RCT on the effects of antibiotics. [30] We have reported the RCT directly from its original report. [30] We found no RCTs on the effects of mesalazine. The multi-centre RCT (669 people; AVOD study; see Further information on studies) included people aged over 18 years with acute uncomplicated left-sided diverticulitis. [30] Uncomplicated diverticulitis was defined as an episode with a short history, clinical signs of diverticulitis without sepsis, increased temperature, and inflammatory parameters, verified by CT scan with no evidence of abscess, free air, or fistulae. It compared antibiotics (broad-spectrum according to local centre guidelines, including an intravenous combination of a second- or third-generation cephalosporin [cefuroxime or cefotaxime] and metronidazole, or with carbapenem antibiotics [ertapenem, meropenem, or imipenem] or piperacillin–tazobactam, followed by oral antibiotics, with total duration of antibiotics for at least 7 days) with no antibiotics (intravenous fluids only).

Mortality

No data from the following reference on this outcome. [30]

Symptom relief

Medical treatment (mesalazine, antibiotics) compared with placebo or no treatment We don't know whether antibiotics are more effective than placebo or no treatment (no antibiotics) at reducing symptoms during the first 5 days after hospital admission or at 1 year in people with acute uncomplicated left-sided diverticulitis confirmed by CT scan (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Abdominal pain (recorded on a visual analogue scale [VAS] 0–10 cm) , during the first 5 days following hospital admission** with antibiotics with no antibiotics Absolute results reported graphically Analyses based on 623 people	P = 0.253 to 0.886 The results were presented graphically from baseline to 5 days, and only a range of P values were provided	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Mean difference from baseline in abdominal tenderness on palpation (recorded on a scale 0–4) , day 2 following hospital admission** 1.0 with antibiotics 0.8 with no antibiotics Absolute results reported graphically Analyses based on 623 people	P = 0.041 The RCT did not report individual P values for days other than day 2	○○○	antibiotics
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Abdominal pain (based on 5 degrees of severity ranging from no pain – chronic pain) , at 1 year** with antibiotics with no antibiotics Absolute results reported graphically Results based on 582 people Participants contacted by telephone or letter to complete a questionnaire	P = 0.959	⟷	Not significant

Recurrence

Medical treatment (mesalazine, antibiotics) compared with placebo or no treatment We don't know whether antibiotics are more effective than placebo or no treatment (no antibiotics) at reducing recurrence at 1 year in people with acute uncomplicated left-sided diverticulitis confirmed by CT scan (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Recurrence , at 1 year** 46/292 (16%) with antibiotics 47/290 (16%) with no antibiotics Results based on 582/623 (94%) people who were included in the primary analysis	P = 0.881	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Complication: sigmoid perforation** 3/314 (1%) with antibiotics 3/309 (1%) with no antibiotics	P = 0.985	⟷	Not significant
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed to-	**Complication: abscess** 0/314 (0%) with antibiotics 3/309 (1%) with no antibiotics	P = 0.080	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	mography-verified acute uncomplicated left-sided diverticulitis				
[30] RCT	People, median age 58 years, median BMI 27.7 kg/m^2, with computed tomography-verified acute uncomplicated left-sided diverticulitis	**Sigmoid resections (during hospital stay or follow-up)** 5/314 (1.6%) with antibiotics 7/309 (2.3%) with no antibiotics	P = 0.541	⟷	Not significant

Further information on studies

[30] This RCT had a long accrual period, from October 2003 to January 2010, and the inclusion criteria excluded those with sepsis, so the results may be biased to those with mild disease only. There was also no standard antibiotic treatment in the intervention arm, which fits with the pragmatic nature of the study. There was no blinding during the study. In total, 247/615 (40%) of the included participants were known to have recurrent and not a first episode of acute diverticulitis, with a significant difference of people with recurrent diverticulitis between groups at baseline (previous diverticulitis: 110/309 [36%] with antibiotics *v* 137/306 [45%] with no antibiotics; P = 0.02).

[30] *Methods* Of 669 people initially randomised, 46 people were excluded. Most of these (38 people) did not meet the trial inclusion criteria (other diagnosis, insufficient criteria [e.g., no fever], linguistic problems, unclear CT, cardiac disease, complicated diverticulitis), while seven people had interrupted participation and one person was excluded due to protocol violation. Hence, 623 people (314 with antibiotics, 309 with no antibiotics) were included in the primary analysis at 30 days. The RCT reported data on allocation method and concealment, but was not blinded (participants, medical staff, or data assessors). [27]

Comment:

One systematic review (search date 2010) on the treatment of uncomplicated acute diverticulitis with antibiotics found only one retrospective cohort study comparing antibiotics with observation alone, with no difference reported between success rates in the two groups. [26]

We found one RCT comparing antibiotic treatment with no antibiotic treatment in people presenting with a CT diagnosis of acute diverticulitis. [30] This study reported no difference in the development of complications such as abscess and perforation between the two groups, and little difference in resolution of symptoms in terms of resolution of abdominal pain and VAS pain scores in the 5 days following admission. Recurrence of acute diverticulitis occurred in 93/582 (16%) of people who were available to follow-up at 1 year. Given that recurrences are less frequent with each subsequent recurrence and about 40% of participants had a prior episode of acute diverticulitis, this may underestimate the true recurrence rate. [30]

As suggested in one review on the subject, further evidence will be required to change clinical practice. [27]

A further trial published only in abstract form has confirmed these initial results in people presenting for a first time with CT-proven uncomplicated acute diverticulitis. [31]

Clinical guide

The treatment of acute diverticulitis by intravenous fluid replacement, limiting oral intake, and broad-spectrum antibiotics is common practice but is not supported by a strong evidence base. People with mild symptoms and no evidence of generalised sepsis can be managed at home with oral antibiotics. People with CT-proven mild uncomplicated diverticulitis may not benefit from having intravenous antibiotics. This is in keeping with current thoughts on disease pathophysiology; however, the evidence for this approach is based on one RCT. People with severe pain or signs of compromise should be admitted for analgesia, bowel rest, intravenous fluid replacement, and intravenous antibiotics.

GLOSSARY

Diverticulosis The presence of diverticula that are asymptomatic. Most people with sigmoid colonic diverticula have no symptoms.

Acute diverticulitis A condition that occurs when a diverticulum becomes acutely inflamed. There may be general symptoms and signs of infection (including fever and rapid heart rate) with or without local symptoms and signs (pain and localised tenderness, usually in the lower left abdomen, sometimes with a mass that can be felt on abdominal or rectal examination).

Diverticular disease Association of diverticula with any symptoms. Symptoms commonly include abdominal pain and alteration in bowel habit. Diverticular disease may be complicated by abscess formation, fistulae, perforation, obstruction, or haemorrhage.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Medical treatment (mesalazine, antibiotics [any] only) versus placebo or no treatment for acute diverticulitis New option. Four systematic reviews were added, [26] [27] [28] [29] which identified one RCT. [30] Categorised as 'unknown effectiveness'.

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Competing interests: DH and RCS were given the Dr Falk Pharma award to support the analysis costs of samples from a trial of mesalazine in symptomatic diverticular disease. DH is an author of references cited in this overview. RCS declares that he has no other competing interests.
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GRADE **Evaluation of interventions for Colonic diverticular disease: medical treatments for acute diverticulitis.**

Important outcomes				Mortality, Recurrence, Symptom relief					
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of medical treatments for acute diverticulitis?									
1 (623) [30]	Symptom relief	Medical treatment (mesalazine, antibiotics) versus placebo or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (lack of blinding, baseline differences); directness point deducted for selected population limiting generalisability (sepsis excluded so may be bias towards mild disease, complicated diverticulitis excluded, 40% with recurrent disease)
1 (623) [30]	Recurrence	Medical treatment (mesalazine, antibiotics) versus placebo or no treatment	4	–1	0	–1	0	Low	Quality point deducted for lack of blinding; directness point deducted for selected population limiting generalisability (sepsis excluded so may be bias towards mild disease, complicated diverticulitis excluded, 40% with recurrent disease)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.