Systematic review

doi:10.1111/codi.14013

Antibiotics *vs* no antibiotics in the treatment of acute uncomplicated diverticulitis – a systematic review and meta-analysis

A. Tandon*, V. L. Fretwell†, Q. M. Nunes†‡ and P. S. Rooney†

*Aintree University Hospital, Liverpool, UK, †Royal Liverpool Hospital NHS Foundation Trust, Liverpool, UK, and ‡NIHR Liverpool Pancreas Biomedical Research Unit, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK

Received 25 July 2017; accepted 30 December 2017; Accepted Article online 11 January 2018

Abstract

Aim Acute uncomplicated diverticulitis (AUD) is common and antibiotics are the cornerstone of traditional conservative management. This approach lacks a clear evidence base and studies have recently suggested that avoidance of antibiotics is a safe and efficacious way to manage AUD. The aim of this systematic review is to determine the safety and efficacy of treating AUD without antibiotics.

Method A systematic search of Embase, Cochrane Library, MEDLINE, Science Citation Index Expanded and ClinicalTrials.gov was performed. Studies comparing antibiotics *vs* no antibiotics in the treatment of AUD were included. Meta-analysis was performed using the random effects model with the primary outcome measure being diverticulitis-associated complications. Secondary outcomes were readmission rate, diverticulitis recurrence, mean hospital stay, requirement for surgery and requirement for percutaneous drainage.

Results Eight studies were included involving 2469 patients: 1626 in the non-antibiotic group (NAb) and 843 in the antibiotic group (Ab). There was a higher complication rate in the Ab group; however, this was not significant (1.9% *vs* 2.6%) with a combined risk ratio of 0.63 (95% CI 0.25–1.57, $P = 0.32$). There was a shorter mean length of hospital stay in the NAb group (standard mean difference −1.18 (95% CI −2.34 to −0.03, $P = 0.04$). There was no significant difference in readmission, recurrence and surgical intervention rate or requirement for percutaneous drainage.

Conclusion Treatment of AUD without antibiotics may be feasible with outcomes that are comparable to antibiotic treatment and with potential benefits for patients and the National Health Service. Large scale randomized multicentre studies are needed.

Keywords Diverticular disease, diverticulitis, antibiotics, management, treatment

Introduction

Colonic diverticulosis is thought to affect up to 50% of over 60-year-olds in the western world and both the incidence and hospital admission rate are increasing [1], with 10–25% of these patients expected to encounter complications such as acute diverticulitis [2]. There are a number of scales and scores to classify acute diverticulitis, however broadly; uncomplicated acute diverticulitis refers to acute inflammation of the colon without the presence of abscess, perforation, stricture or obstruction [3]. The majority of patients with acute uncomplicated diverticulitis (AUD) are treated conservatively with intravenous antibiotic administration, bowel rest, intravenous fluids and analgesia [4]. This approach is not evidence based and currently there exists ambiguity in the published guidelines [5] with respect to the use of antibiotics in AUD. Recent studies have suggested that conservative management without the use of antibiotics is at least as safe as treatment with antibiotics, with no significant deleterious effects on the patient [6]. Antibiotic treatment exposes patients to potentially avoidable side effects, development of antibiotic resistance and is a potentially unnecessary cost. Conversely, poorly managed AUD can progress to complications such as perforation, abscess, fistula and

Correspondence to: Victoria Fretwell, Royal Liverpool University Hospital, Prescot St, Liverpool L7 8XP, UK.
E-mail: vicky_fretwell@hotmail.com
@vixfrets

colonic obstruction, which are associated with significant morbidity [7]. We undertook this systematic review and meta-analysis to determine the safety and efficacy of managing AUD without antibiotics, with a view to informing future practice.

Method

Search strategy

Two authors (AT and QMN) conducted the literature search of the Cochrane Central Register of Controlled Trials (2016, Issue 12) in the Cochrane Library, MEDLINE, Embase, Science Citation Index Expanded and ClinicalTrials.gov (www.clinicaltrials.gov), according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance [8]. Search terms used included 'antibiotics' AND 'uncomplicated diverticulitis' OR 'treatment' AND 'uncomplicated diverticulitis'. To achieve maximum sensitivity, all search terms were combined with Boolean operators and searched as both keywords and MeSH terms. All citations and abstracts identified were thoroughly reviewed by independent investigators (AT, QMN). The last date for this search was 24 January 2017.

Inclusion criteria

Studies considering the effect of non-antibiotic treatment for AUD and randomized and non-randomized studies which compared the effect of interventions (antibiotics *vs* no antibiotics) in AUD were included. The diagnosis of AUD had to be confirmed on imaging for a study to be included. For studies that published duplicate or overlapping datasets, only the most recent or best quality reports were included.

Exclusion criteria

Studies were excluded if they were case reports or small case series (<10 cases) [9]. Due to insufficient data, conference abstracts and editorials were excluded. Non-English reports were also excluded.

Outcome measures

The primary outcome was complications related to diverticulitis such as colonic perforation, intra-peritoneal abscess, large bowel obstruction, bleeding and colovesical fistula.

The secondary outcomes were.

1 Readmission to hospital due to either recurrence of symptoms or complications,
2 Recurrence of diverticulitis,
3 Mean hospital stay,
4 Requirement of surgery during follow-up after completing index treatment,
5 Requirement for percutaneous drainage of intra-peritoneal abscess.

Study selection

Two authors (AT and QMN) independently performed the search strategy. Both the authors reviewed the abstracts of each study identified by the search to exclude those that did not satisfy the inclusion criteria and obtained the full copies of the remaining studies. Only studies that met the inclusion criteria were used for data extraction. The references of the selected studies were hand searched to identify related studies. Differences of opinion between the two authors (AT and QMN) were resolved by consensus with the senior author (PSR). If the selection of the study was still not resolved by consensus between the three authors, the lead author's (PSR) decision was considered final.

Data extraction

Primary and secondary outcome data were collected by the primary author (AT) and confirmed by the second author (VF) using a data extraction form. Any disagreement was resolved by consensus with the senior author (PSR). Study characteristics including first author, year of publication, number of patients, type of study (prospective or retrospective case-controlled studies or randomized clinical trials) and patient demographics (age, sex) were recorded. Other data were extracted for comorbidities, American Society of Anesthesiologists grades, mean with standard deviation of white cell count (WCC) and C-reactive protein (CRP), and type and duration of antibiotics used. Comorbidities included cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus. Diagnosis of AUD was based on CT scan. In cases of missing data, the corresponding author of the study was contacted by e-mail.

Statistical analysis

Statistical analysis was undertaken using RevMan 5.3. Data were pooled and the risk ratio (RR) for dichotomous data and the standard mean difference for continuous data with their corresponding 95% confidence intervals were calculated. The random effects model was used as the effects were expected to be heterogeneous due to the variety of study populations and study design included in the analysis [10]. A P value of less than

0.05 was considered statistically significant. The I^2 statistic was used to estimate the inconsistencies between included studies. $I^2 > 50\%$ is indicative of significant heterogeneity.

Quality assessment

The Methodological Index of Nonrandomized Studies (MINORS) [11] was used to evaluate the methodological quality of and the potential bias within the studies selected for this review. For randomized studies, the Jadad score was used [12].

Results

Description of included studies

The search resulted in a total of 520 articles, of which 404 were excluded due to duplication. The remaining 116 articles were then reviewed by title screen and, following exclusion of review articles, letters, case reports, non-English language studies and studies reporting inappropriate outcome measures, 11 studies were taken forward to abstract review (Fig. 1). A further three studies were excluded and the remaining eight studies [13–20] were included in this review. Of these eight articles, there were two randomized controlled trials (RCTs) [13,16] and three retrospective studies [15–17], one prospective case-controlled study [18] and two prospective single-arm studies [19,20] (Table 1).

Study and patient characteristics

A total of 2469 patients were included in the study; 1626 patients were in the non-antibiotic group (NAb) and 843 in the antibiotic group (Ab). The mean age was reported in all eight studies [13–20] and ranged from 56 to 61 years in the NAb group and from 56.3 to 63 years in the Ab group. Median body mass index was reported in two studies [13,14] with a range of 26.4–28.2 kg/m^2 and 27.2–27.9 kg/m^2 in the NAb and Ab groups respectively. WCC and CRP on admission were reported in all eight studies [13–20]. The WCC in the NAb group ranged from 10.2 to 12.5 $\times$ 10^9/l and from 11.7 to 13 $\times$ 10^9/l in the Ab group. CRP in the NAb group ranged from 73 to 99 mg/l and from 82.7 to 119 mg/l in the Ab group. Comorbidities were reported in six studies [13,15,16,18–20]. The type and duration of antibiotics used in the treatment of diverticulitis were specified in four studies [13,16–18]. Mean follow-up was reported in all the included studies with a range of 12–50 months. Mortality was reported in five studies [13,16,17,19,20].

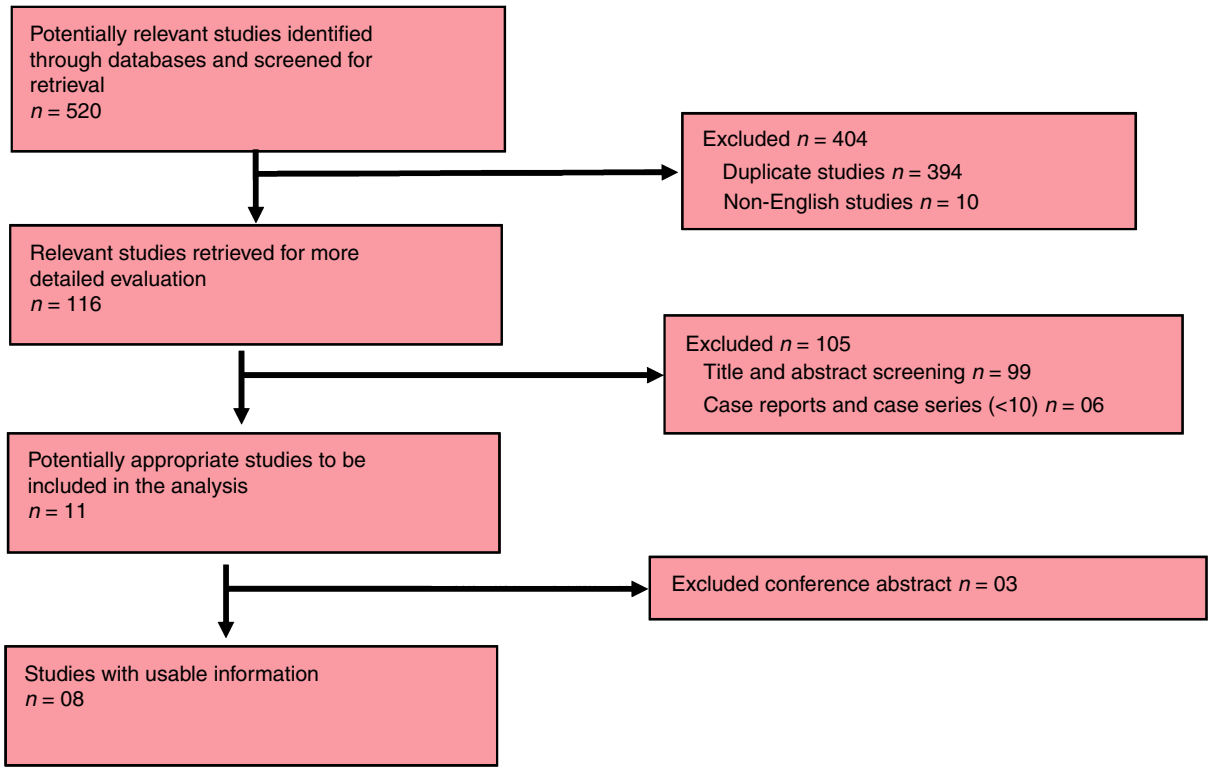

Figure 1 PRISMA diagram detailing study selection for the review.

Table 1 Patient characteristics, study type and quality scoring.

Reference	Year	Study type	Number of patients			Mean age in years (SD)		Mean WCC on admission (SD)		Mean CRP on admission (SD)		MINORS score
			Total (M:F)	Ab	NAb	Ab	NAb	Ab	NAb	Ab	NAb	
Daniels *et al.* [13]	2017	RCT	528 (267:261)	266	262	56.3 (48.5–63.8)*	57.4 (48.5–64.6)*	12.0 (10.0–14.2)*	12.5 (10.2–14.8)*	82.7 (42.0–128.3)*	73.0 (44.5–125.5)*	N/A
Brochmann *et al.* [14]	2016	Retrospective	224 (73:151)	47	177	65.9 (13.21)	60.3 (13.01)	11 (6.5)	10.5 (3)	112 (82)	93 (54)	14
Isacson *et al.* [15]	2014	Retrospective	195 (77:118)	17	178	60 (17)	60 (14)	13 (3)	11 (3)	115 (109)	85 (57)	10
Chabok *et al.* [16]	2012	RCT	623 (220:403)	314	309	57.4 (12.8)	57.1 (13.2)	12.6 (3.1)	12.3 (3.3)	100 (62)	91 (61)	N/A
de Korte *et al.* [17]	2012	Retrospective	272 (85:187)	81	191	63 (range 34–94)	61 (range 27–92)	12.9 (5.1)*	12.4 (4.7)*	109 (96)*	99 (108)*	11
Hjern *et al.* [18]	2007	Prospective	311 (111:200)	118	193	60	59	11.7 (range 5.8–28.1)	10.2 (range 4.3–19.6)	119 (range 7–421)	87 (range 4–231)	17
Isacson *et al.* [20]	2015	Prospective single arm	155 (54:101)	–	–	57 (12)		10.5 (2.9)		73 (50)		11
Mali *et al.* [19]	2016	Prospective single arm	161 (63:101)	–	–	56 (range 25–86)		11.2 (3.0)		94 (51)		11

RCT, randomized controlled trial; Ab, antibiotics given; NAb, no antibiotics; WCC, white cell count ($\times 10^9$/l); CRP, C-reactive protein (mg/l).
*Values are median and interquartile range.

Primary outcome

Complications related to diverticulitis

Complications including colonic perforation, intra-peritoneal abscess, large bowel obstruction, bleeding and colovesical fistula were reported in six studies [13–18]. The pooled results from the studies demonstrated a slightly higher complication rate in the Ab group; however, this difference was not significant [1.9% (25/1310) *vs* 2.6% (22/843)] with a combined RR of 0.63 (95% CI 0.25–1.57, $P = 0.32$). Heterogeneity was 49% (Fig. 2).

Secondary outcomes

Readmission to hospital due to either recurrence of symptoms or complications

Readmission to hospital was reported in six studies [13–18] with rates ranging from 3% to 26.7% in the NAb group and from 6% to 27.1% in the Ab group. There was no significant difference noted in readmission rate between the NAb and Ab groups [13.2% (171/1291) *vs* 14.9% (123/821)] with a combined RR of 1.01 (95% CI 0.75–1.37, $P = 0.94$). Heterogeneity in these studies was 37% (Fig. 3).

Recurrence of diverticulitis

The recurrence of diverticulitis after index intervention was reported in six studies [13–18] with a range of 3.4–27.7% in the NAb group and 3–28% in the Ab group. The difference was not statistically significant [11.8% (152/1291) *vs* 13.2% (108/821)] with a combined RR of 0.82 (95% CI 0.61–1.11, $P = 0.20$). The heterogeneity in the studies was 27% (Fig. 4).

Mean hospital stay

The mean hospital stay ranged from 1.5 to 7 days in the NAb group and from 2.5 to 7 days in the Ab

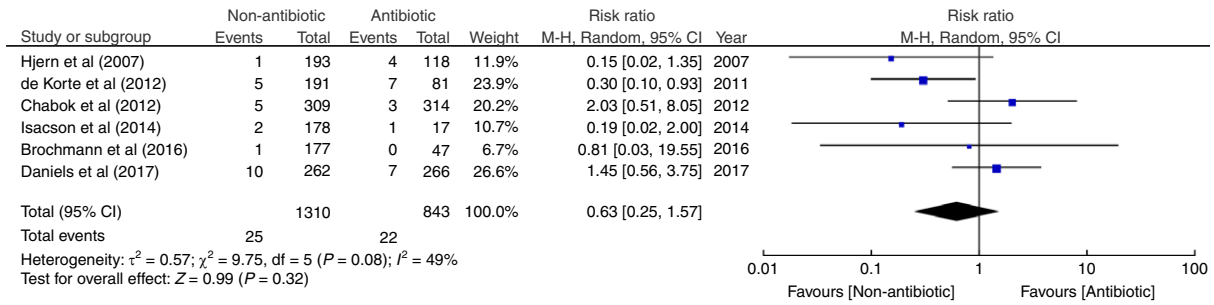

Figure 2 Forest plot comparing complication rates in the non-antibiotic group and the antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

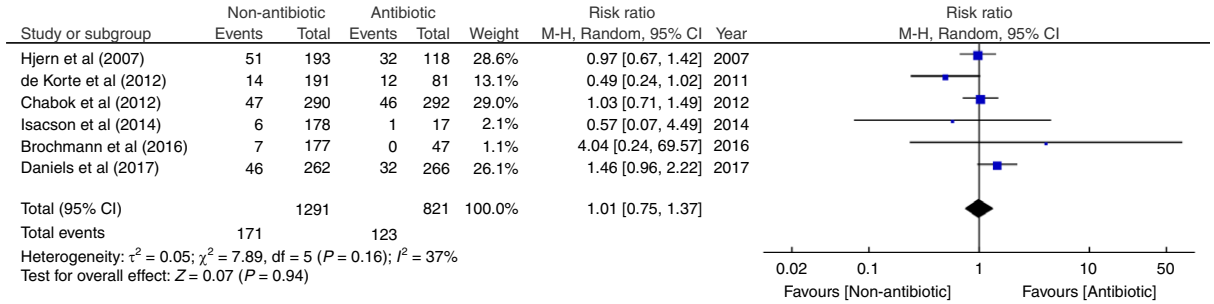

Figure 3 Forest plot comparing readmission rates between non-antibiotic group and antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

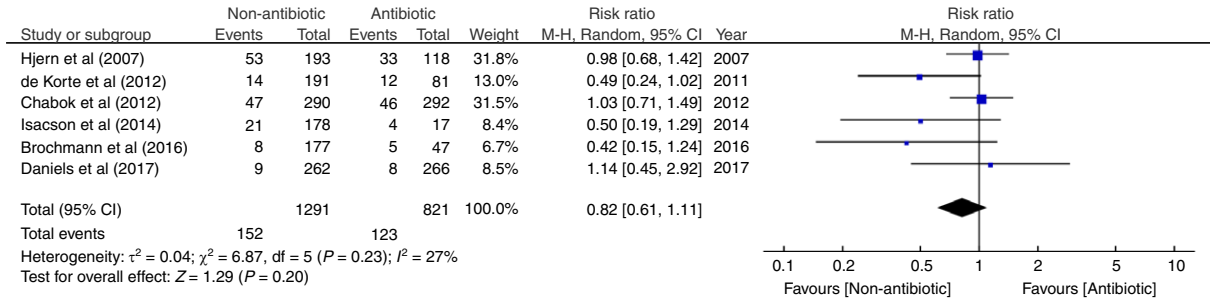

Figure 4 Forest plot comparing rates of recurrence of diverticulitis between non-antibiotic group and antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

group [13–18]. The mean hospital stay was slightly lower in the NAb group [standard mean difference −1.18 (95% CI −2.34 to −0.03, $P = 0.04$)] (Fig. 5). However, the heterogeneity in the studies was high at 99%.

Requirement of surgery during follow-up after completing index treatment

There was no significant difference noted in the requirement of surgical intervention between the NAb and Ab groups [1.9% (25/1310) *vs* 2.1% (18/843)] with a combined RR of 0.89 (95% CI 0.44–1.80, $P = 0.75$). Heterogeneity in the studies was 16% (Fig. 6).

Requirement for percutaneous drainage of intra-peritoneal abscess

The requirement of percutaneous drainage of diverticular abscesses was reported by three studies [13,16,17]. There was no significant difference noted in the requirement of percutaneous drainage of diverticular abscesses between the NAb and Ab groups [1.0% (8/762) *vs* 0.5% (3/661)] with a combined RR of 1.52 (95% CI 0.16–14.46, $P = 0.75$). The heterogeneity in the studies was 57% (Fig. 7).

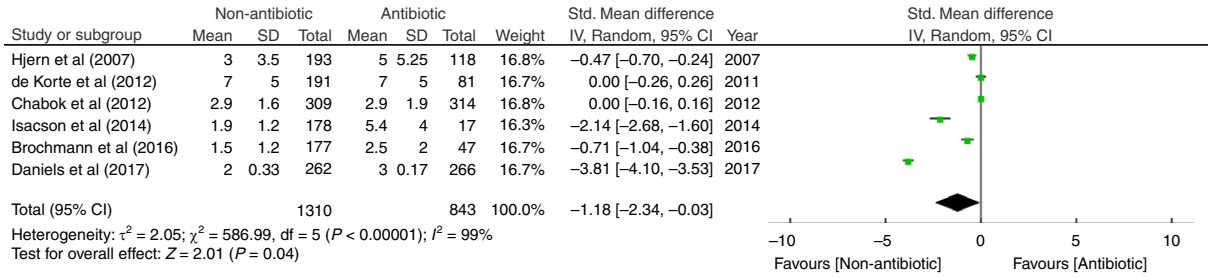

Figure 5 Forest plot comparing mean hospital stay of non-antibiotic group and antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

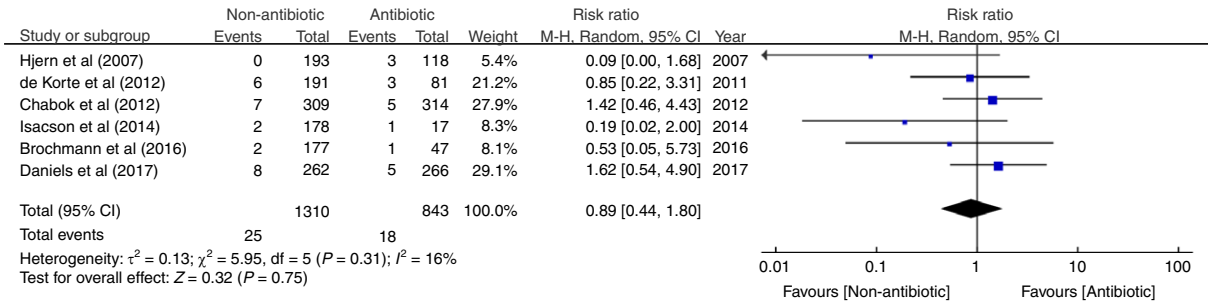

Figure 6 Forest plot comparing requirement of surgery during follow up for non-antibiotic group and antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

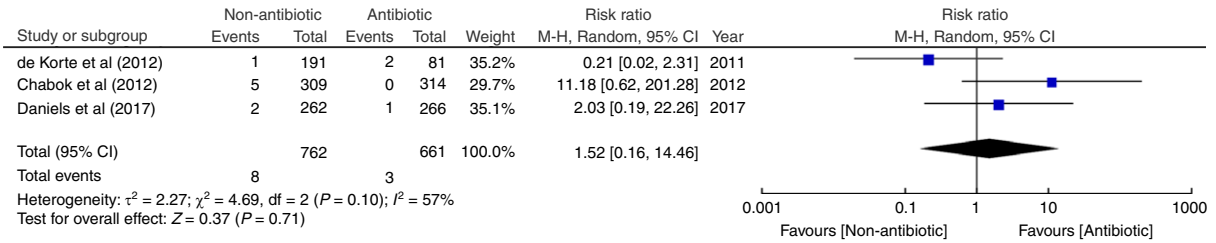

Figure 7 Forest plot comparing requirement of percutaneous drainage for non-antibiotic group and antibiotic group. A random effect model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

Quality of studies

The quality of the non-randomized studies was evaluated using the MINORS criteria. None of the studies in this review reached the minimum global score of 16 for non-comparative studies and 24 for comparative studies. The maximum score achieved was 17 [18] for comparative studies and 11 [19,20] for non-comparative studies (Table 1). The randomized studies were compared with the Jadad score [12] with both achieving a score of 3 (Table 2).

Discussion

The surgical dogma of routine antibiotic use in the management of AUD is long standing and lacks a clear evidence base.

This systematic review has examined whether a watch and wait approach without antibiotics is as safe or effective as treatment with antibiotics in AUD. The overall finding is that the initial management of AUD without antibiotics appears to be of equivalent safety to treating with antibiotics. Certainly, the studies included in this review have failed to demonstrate any significant benefit to routine antibiotic use in AUD [13–20]. There were no differences between the groups in terms of recurrence rate, readmission rate, requirement of surgery during follow-up or the need for percutaneous drainage. There was a lower mean length of hospital stay in the NAb group, as would be expected; however, this was in a very heterogeneous group of studies. These findings suggest that AUD could be managed without

Table 2 Quality assessment of the randomized studies.

Study	Randomization process used	Blinding			Loss to follow-up/ discontinued participation			Jadad score	Comments
		Patient	Clinician	Data analyser	Ab	NAb	Total		
Daniels *et al.* 2017 [13]	Computerized, varying block size of two to four patients, stratified by Hinchey classification + centre	No	N/S	Yes	23 (8%)	28 (11%)	51	3/5	Multicentre, inclusion and exclusion criteria documented, Hinchey 1b included
Chabok *et al.* 2012 [16], AVOD study	Sealed envelope, blocks of four and stratified by centre	No	No	N/S	22 (7%)	19 (6%)	41	3/5	Multicentre, inclusion and exclusion criteria documented

N/S, not stated.

routine antibiotics for the majority of patients, at least in the first instance. There are of course some notable exceptions to this approach; in particular patients who are immunocompromised or those displaying overt signs of systemic sepsis or peritonitis, regardless of the CT findings, should be treated with intravenous antibiotics to prevent septic complications. This review has demonstrated that the evidence base remains weak for decision-making regarding antibiotic use in AUD. Indeed, a recent Delphi study by O'Leary and colleagues failed to reach consensus regarding the use of antibiotics in AUD [21]. This is also reflected in the mixed messages in the currently available practice guidelines for the management of colonic diverticular disease [22–26]. However, the most recent guidelines and updates have addressed the problem in more detail, suggesting a selective approach to antibiotic administration in AUD [23,24].

In a recent Swiss study, von Strauss Und Torney *et al.* [27] performed a cross-sectional analysis of patients presenting with AUD at two different time periods and assessed trends in the surgical management of AUD. They found that the crude resection rate decreased from 40% to 34% between May 2004 and November 2010. Optimization of the conservative management of AUD may help to reduce the resection rates further.

For an episode of acute diverticulitis to be considered 'uncomplicated' there must be evidence of the lack of perforation, abscess or free intra-peritoneal fluid [3]. CT scanning is widely regarded as the key diagnostic investigation for AUD [28,29]. If the shift towards non-antibiotic management of AUD were to continue in the National Health Service (NHS) setting, we would suggest caution in initiating this management unless the CT has been reviewed and reported by a radiologist with the appropriate expertise, in order not to miss any soft signs of perforation such as small gas bubbles or free fluid, which might necessitate the initiation of antibiotic therapy. That being said, a recent re-evaluation by Thorisson *et al.* [30] of the CT imaging in the RCT by Chabok *et al.* [16] has demonstrated that 7% of the CT scans had missed complications such as abscess or free air. Of these, four patients underwent surgical management, two from each group. Furthermore, we recognize that the RCT by Daniels *et al.* [13] included some Hinchey 1b patients. This would suggest that further work in this field is required to give a definitive answer as to what grade of acute diverticulitis can be safely managed without antibiotics.

Indeed, CT alone is not the only tool in the armamentarium to aid decision-making in the treatment of acute diverticulitis. It is vital that the clinician take into account the patient's entire clinical status, including signs of sepsis such as the presence of tachycardia, hypotension and fever. A clinical examination revealing peritonitis should also prompt close in-patient observation with a low threshold for administration of antibiotics even if the CT scan shows no signs of peritoneal irritation. Finally, serological markers of inflammation such as WCC and CRP should also be considered. A recent study by Buchs *et al.* [31] has shown that raised CRP on admission is strongly associated with early recurrence within 6 months. With all these parameters taken into account, and with the help of larger prospective trials, a scoring system might be developed to guide decision-making in the use of antibiotics for AUD. Indeed, in their recent guidelines [23], the American Gastroenterological Association has stated that 'identifying patients who will benefit from antibiotics and those

in whom it can be safely withheld' is a key area for future research.

The over-use or inappropriate use of antibiotics is a multifaceted problem with both patient-centred and service provision issues. First, exposing patients to unnecessary antibiotics clearly exposes them to the risks of adverse drug reactions, gastrointestinal side effects, *Clostridium difficile* infection etc., and to the wider issue of drug resistance both on an individual level and a population level. In the UK there has been a 6.5% increase in the prescribing of antibiotics between 2011 and 2014 alone and clinicians have a duty of antibiotic stewardship in order to reduce risk to patients and tackle the problem of antibiotic resistance [32].

From an organizational point of view, at a trust and local health authority level, there are cost implications with the unnecessary use of antibiotics and over-treatment of AUD. In the USA in 2008, data suggest an average cost of $9594 per patient for the management of diverticular disease [33]. Management of AUD with intravenous antibiotics requires hospital admission for at least one night, with data from 1999 to 2006 suggesting median inpatient stay in England of 6 days for all manifestations of diverticular disease [34]. There is a potential to free up bed space and reduce avoidable expenditure in the NHS if some of those patients, particularly those with AUD, could be managed without antibiotics [15] or as outpatients [35].

As the non-antibiotic management of AUD gains popularity, stringent follow-up practices must be agreed upon and entered into the guidelines. The current Association of Coloproctology of Great Britain and Ireland guidelines recommend colonic investigation (in the form of endoscopy, barium enema or CT colonography) after the acute flare up has settled [25]. Patients in the studies analysed in this paper were all followed up for at least 12 months to allow evaluation of recurrence of disease or other complication [13–20].

There are limitations associated with this study. This meta-analysis has been undertaken using both non-randomized studies and RCTs, as there is a dearth of RCTs on the subject. The inclusion of non-randomized studies in meta-analyses has been a matter of continuing debate for some time now [36]. While RCTs are considered to be the gold standard for evidence-based practice, both non-randomized studies as well as RCTs are associated with unique strengths and weaknesses [37]. RCTs, due to the nature of their design, can be restrictive in their selection criteria. On the other hand, non-randomized studies tend to be more representative of patient populations routinely seen in clinical practice [38]. The approach of analysing non-randomized studies in a systematic manner through a meta-analysis is becoming increasingly prevalent nowadays as the resulting information can play an important role in informing practice and further investigation [39,40]. Another limitation of this review relates to the quality of the included studies, with none of the non-randomized studies meeting the minimal MINORS criteria [11] score of 16, and neither of the randomized trials reaching a Jadad score [12] of greater than 3. There was variable heterogeneity in the studies, in particular relating to complications (49%), mean hospital stay (99%) and requirement for percutaneous drainage of abscess (57%), with any value over 50% suggested to have a moderate degree of heterogeneity [11]. These factors should be borne in mind when interpreting the results of this study. There is a need for large, well-designed, multi-centred, trials in the area before cast-iron recommendations can be made.

Conclusions

The treatment of AUD without antibiotics may be feasible with outcomes that are comparable to its treatment with antibiotics and with potential significant benefits for patients and the NHS. However, there is a need for large, well-designed, multi-centred trials to be undertaken, prior to adopting this approach routinely in the management of AUD.

Author contributions

AL: conceptual design, data collection, analysis and interpretation. VLF: drafting and critical revision of article. QMN: conceptual design, data collection, analysis and interpretation. PSR: senior advice and review at all points of the project including final approval of the submitted article.

Funding

None.

Conflicts of interest

None.

References

1 Jaung R, Robertson J, Vather R, Rowbotham D, Bissett IP. Changes in the approach to acute diverticulitis. *ANZ J Surg* 2015; **85:** 715–9.
2 Nguyen GC, Sam J, Anand N. Epidemiological trends and geographic variation in hospital admissions for diverticulitis

in the United States. *World J Gastroenterol* 2011; **17:** 1600–5.
3 Sartelli M, Moore FA, Ansaloni L *et al.* A proposal for a CT driven classification of left colon acute diverticulitis. *World J Emerg Surg* 2015; **10:** 3.
4 Horesh N, Wasserberg N, Zbar AP *et al.* Changing paradigms in the management of diverticulitis. *Int J Surg* 2016; **33 (Pt A):** 146–50.
5 Vennix S, Morton DG, Hahnloser D, Lange JF, Bemelman WA. Research Committee of the European Society of Coloproctocology. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. *Colorectal Dis* 2014; **16:** 866–78.
6 Peery AF. Recent advances in diverticular disease. *Curr Gastroenterol Rep* 2016; **18:** 37.
7 Salem L, Flum DR. Primary anastomosis or Hartmann's procedure for patients with diverticular peritonitis? *A systematic review*. *Dis Colon Rectum* 2004; **47:** 1953–64.
8 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151:** W65–94.
9 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54:** 1046–55.
10 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.
11 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; **73:** 712–6.
12 Jadad AR, Moore RA, Carroll D *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.
13 Daniels L, Unlu C, de Korte N *et al.* Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. *Br J Surg* 2017; **104:** 52–61.
14 Brochmann ND, Schultz JK, Jakobsen GS, Oresland T. Management of acute uncomplicated diverticulitis without antibiotics: a single-centre cohort study. *Colorectal Dis* 2016; **18:** 1101–7.
15 Isacson D, Andreasson K, Nikberg M, Smedh K, Chabok A. No antibiotics in acute uncomplicated diverticulitis: does it work? *Scand J Gastroenterol* 2014; **49:** 1441–6.
16 Chabok A, Pahlman L, Hjern F, Haapaniemi S, Smedh K. AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. *Br J Surg* 2012; **99:** 532–9.
17 de Korte N, Kuyvenhoven JP, van der Peet DL, Felt-Bersma RJ, Cuesta MA, Stockmann HB. Mild colonic diverticulitis can be treated without antibiotics. A case–control study. *Colorectal Dis* 2012; **14:** 325–30.
18 Hjern F, Josephson T, Altman D *et al.* Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? *Scand J Gastroenterol* 2007; **42:** 41–7.
19 Mali JP, Mentula PJ, Leppaniemi AK, Sallinen VJ. Symptomatic treatment for uncomplicated acute diverticulitis: a prospective cohort study. *Dis Colon Rectum* 2016; **59:** 529–34.
20 Isacson D, Thorisson A, Andreasson K, Nikberg M, Smedh K, Chabok A. Outpatient, non-antibiotic management in acute uncomplicated diverticulitis: a prospective study. *Int J Colorectal Dis* 2015; **30:** 1229–34.
21 O'Leary DP, Lynch N, Clancy C, Winter DC, Myers E. International, expert-based, consensus statement regarding the management of acute diverticulitis. *JAMA Surg* 2015; **150:** 899–904.
22 Feingold D, Steele SR, Lee S *et al.* Practice parameters for the treatment of sigmoid diverticulitis. *Dis Colon Rectum* 2014; **57:** 284–94.
23 Stollman N, Smalley W, Hirano I; Committee AGAICG. American Gastroenterological Association Institute guideline on the management of acute diverticulitis. *Gastroenterology* 2015; **149:** 1944–9.
24 Sartelli M, Catena F, Ansaloni L *et al.* WSES guidelines for the management of acute left sided colonic diverticulitis in the emergency setting. *World J Emerg Surg* 2016; **11:** 37.
25 ACPGBI. Association of Coloproctology of Great Britain and Ireland and Royal College of Surgeons Commissioning Guide for Colinic Diverticular Disease. 2014. https://www.acpgbi.org.uk/content/uploads/2017/02/Commissioning-guide-colonic-diverticular-disease-RCS-2014.pdf (accessed April 2017).
26 Floch MH, Longo WE. United States guidelines for diverticulitis treatment. *J Clin Gastroenterol* 2016; **50(Suppl 1):** S53–6.
27 von Strauss Und Torney M, Thommen S, Dell-Kuster S *et al.* Surgical treatment of uncomplicated diverticulitis in Switzerland: comparison of population-based data over two time periods. *Colorectal Dis* 2017; **19:** 840–50.
28 Sartelli M, Binda GA, Brandara F *et al.* IPOD Study: Management of acute left colonic diverticulitis in Italian surgical departments. *World J Surg* 2017; **41:** 851–9.
29 Laméris W, van Randen A, Bipat S, Bossuyt PMM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. *Eur Radiol* 2008; **18:** 2498–511.
30 Thorisson A, Smedh K, Torkzad MR, Pahlman L, Chabok A. CT imaging for prediction of complications and recurrence in acute uncomplicated diverticulitis. *Int J Colorectal Dis* 2016; **31:** 451–7.
31 Buchs NC, Konrad-Mugnier B, Jannot AS, Poletti PA, Ambrosetti P, Gervaz P. Assessment of recurrence and complications following uncomplicated diverticulitis. *Br J Surg* 2013; **100:** 976–9; discussion 979.
32 NICE. Guidance and guidelines–antimicrobial stewardship. 2016. https://www.nice.org.uk/guidance/qs121 (accessed April 2017).
33 Reddy VB, Longo WE. The burden of diverticular disease on patients and healthcare systems. *Gastroenterol Hepatol (NY)* 2013; **9:** 21–7.

34 Jeyarajah S, Faiz O, Bottle A *et al.* Diverticular disease hospital admissions are increasing, with poor outcomes in the elderly and emergency admissions. *Aliment Pharmacol Ther* 2009; **30:** 1171–82.
35 Biondo S, Golda T, Kreisler E *et al.* Outpatient versus hospitalization management for uncomplicated diverticulitis: a prospective, multicenter randomized clinical trial (DIVER Trial). *Ann Surg* 2014; **259:** 38–44.
36 Shrier I, Boivin JF, Steele RJ *et al.* Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol* 2007; **166:** 1203–9.
37 Faber T, Ravaud P, Riveros C, Perrodeau E, Dechartres A. Meta-analyses including non-randomized studies of therapeutic interventions: a methodological review. *BMC Med Res Methodol* 2016; **16:** 35.
38 Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; **342:** 1878–86.
39 Tandon A, Pathak S, Lyons NJ, Nunes QM, Daniels IR, Smart NJ. Meta-analysis of closure of the fascial defect during laparoscopic incisional and ventral hernia repair. *Br J Surg* 2016; **103:** 1598–607.
40 Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283:** 2008–12.

Top cited papers, *Colorectal Disease*

In each issue of this 20th anniversary year, we present the abstract of the most cited papers published in *Colorectal Disease* over the past years. In this issue we present the abstract of the most cited paper published in 2007.

Consequences and complications of peritoneal adhesions
H Van Goor
Colorectal Disease, 9: 25–34. doi:10.1111/j.1463-1318.2007.01358.x

Consequences and complications of postsurgical intra-abdominal adhesion formation not including small bowel obstruction and secondary infertility are substantial but are under-exposed in the literature. Inadvertent enterotomy during reopening of the abdomen or subsequent adhesion dissection is a feared complication of surgery after previous laparotomy. The incidence can be as high as 20% in open surgery and between 1% and 100% in laparoscopy depending on the underlying disease. Delayed postoperative detection of enterotomy is a particular feature of laparoscopy associated with significant morbidity and mortality. Adhesions to the ventral abdominal wall are responsible for the majority of trocar injuries. Both trocar injuries and inadvertent enterotomies result in conversion from laparoscopy to laparotomy in almost 100% of cases. There is a paucity of data on other organ injury, such as liver laceration or bladder perforation. Dissecting adhesions before executing the planned operation takes on average 20 min, being one-fifth of the total operating time in patients having had previous open colorectal surgery. There is some evidence that postoperative morbidity and mortality of patients who need adhesiolysis is higher than that of patients with a virgin abdomen. The necessity to dissect adhesions is associated with increased hospital stay. Postsurgical adhesions are considered a main reason for conversion from laparoscopy to laparotomy in many types of procedures including laparoscopic colonic resection. Adhesion formation is part of the innate peritoneal defence mechanism in peritonitis. Abscess formation and bleeding, organ injury and fistula formation at 'on demand' relaparotomies are well-known complications after surgery for intra-abdominal sepsis associated with fibrinous adhesions. The clinical magnitude hereof is poorly researched. Postsurgical adhesions may cause pain as evidenced by pain mapping clinical experiments. Filmy adhesions between movable organs and the peritoneum appear to be worse in terms of generating pain. The high caseload of gynaecological and some colorectal practices suggest an enormous impact of adhesion-related chronic abdominal and pelvic pain on patient's wellbeing and socio-economic costs. The significant risk of inadvertent enterotomy, conversion to laparotomy and trocar injury, and the associated postoperative morbidity and mortality and increased length of hospital stay warrant routine informed consent of adhesiolysis related complications in patients scheduled for abdominal or pelvic reoperation.