National Institute for Health and Care Excellence

Consultation

Diverticular Disease

H. Evidence review for non-surgical management of acute diverticulitis

NICE guideline

Intervention evidence review

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What are the most clinically and cost-effective non-surgical treatments for acute diverticulitis??

1.2 Introduction

The purpose of this review is to identify the clinical and cost effective non-surgical treatments for people with acute diverticulitis. Treatments are aimed at reducing symptoms, for example pain. For patients treated in the community the main stay of treatment has been bowel rest and oral antibiotics with subsequent review. For patients referred to secondary care the standard treatment for patients with acute diverticulitis has been to advise bowel rest, rehydrate with intravenous fluids and administer antibiotics however recent evidence has suggested that these treatments may not be indicated in all cases. There is also considerable uncertainty regarding how to manage people with recurrent episodes of acute diverticulitis particularly in regards to preventing recurrent episodes.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over with acute diverticulitis
Interventions	• Bowel rest (clear fluids only) • Antibiotics (antibiotic or no antibiotic, choice of antibiotic, route of administration and length of treatment) • Analgesia (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opiates, and nefopam) • IV fluids • Aminosalycilates
Comparisons	• Each other • No treatment • Placebo • Dosing strategies
Outcomes	Critical outcomes: • Progression of disease • Hospitalisation • Need for surgery • Complications (infections, abscesses, perforation, stricture, fistula) • Recurrence rates of acute diverticulitis (minimum 1year) • Quality of life Important outcomes: • Mortality • Symptom control (pain relief) • Side effects of

	○ Antibiotics: nausea and vomiting, diarrhoea, infections related to antibiotics ○ Analgesics: nausea and vomiting, constipation
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies. • Confounders: age, gender

1.4 Clinical evidence

1.4.1 Included studies

Seven randomised controlled trials (from 8 papers) were included in the review[5, 11, 18, 55, 56, 62, 66, 80]; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Biondo 2014[5]	**IV antibiotic:** After the first dose of antibiotic, patients were admitted to the ward and administered intravenous antibiotics (amoxicillin 1g and clavulanic acid 125mg) and fluids every 8 hours for at least 36 to 48 hours, up to 10 days until oral feeding was tolerated. n=66 **Oral antibiotic:** After the first dose of antibiotic, patients were discharged and administered oral antibiotics (amoxicillin 875mg and clavulanic acid 125mg) every 8 hours for 10 days. n=66	Patients aged 18 years and over with uncomplicated diverticulitis defined as pericolic phlegmon. Confirmed by CT scan. Mean age: 56.3±13 Spain	• Quality of life • Readmission Followed up at 60 days	First dose of antibiotic was given intravenously in the emergency department.
Chabok 2012[11]	**Antibiotic:** Orally administered antibiotics such as ciprofloxacin or cefadroxil combined with metronidazole were initiated subsequently on the ward or at discharge. n=335 **Control:** Treatment with	Adults acute lower abdominal pain with tenderness, body temp ≥38C, raised WBC and C-reactive protein level, signs of diverticulitis on CT Mean age: 57.3±13	• Complication: abscess • Complication: perforation • Need for surgery: sigmoid resection • Recurrent diverticulitis • Symptom: abdominal pain Followed up at 12 months	All patients received an initial treatment of IV fluids/antibiotics.

Study	Intervention and comparison	Population	Outcomes	Comments
	intravenous fluids only (no-antibiotic group) n=334	Sweden/Iceland		
Daniels 2017[18] and Van Dijk 2018[80]	**Antibiotic:** Amoxicillin–clavulanic 1200mg four times daily for at least 48 hr, after which the route could be switched, if tolerated, to oral administration of 625mg three times daily. 10-day regimen. n=287 **Control:** Patients allocated to observational treatment treated directly in an outpatient setting. n=283	Adults with a first episode of left-sided, uncomplicated, acute diverticulitis, confirmed by CT. Mean age: 57.3±13 Netherlands	• Complication: abscess • Complication: perforation • Complication: fistula • Need for surgery: sigmoid resection • Recurrent diverticulitis • Hospitalisation • Mortality Followed up at 24 months	Control group treated with antibiotics if symptoms of diverticulitis deteriorated. Considered as treatment failure.
Ribas 2010[55]	**IV antibiotic:** IV administered amoxicillin plus clavulanic acid 1 g every 8 hr for 8-9 days. At the point of discharge, the patient took oral antibiotic for 5 more days. n=25 **Oral antibiotic:** Upon symptomatic improvements at 24-48 hours, initiated orally administered amoxicillin plus clavulanic acid 1 g every 8 hr in place of IV antibiotics. Advised	Patients with a clinical diagnosis of uncomplicated acute diverticulitis, which was confirmed by a computed tomography (CT) scan within 24-48 hours of admission. Mean age: 53.5 Spain	• Readmission • Symptoms: abdominal pain Followed up at 2 months	All patients received an initial treatment of IV antibiotics.

Study	Intervention and comparison	Population	Outcomes	Comments
	to continue treatment for 10 days. n=25			
Ridgway 2009[56]	**IV antibiotic:** Ciprofloxacin 400mg BD / Metronidazole 500mg TDS. Fasted on entry for 24 hours, IV fluids only. Progressed onto oral intake/ oral antibiotics according to attending physicians' daily examination until discharge. n=38 **Oral antibiotic:** Ciprofloxacin 400mg BD / Metronidazole 500mg TDS until discharge. n=25	Patients who presented with a clinical syndrome of left iliac fossa pain and local tenderness, symptomatic of diverticulitis. CT diagnosis was not available for participants. Mean age (range): 67 (31-86) Canada	• Symptoms: abdominal pain Followed up at 3 days	Inclusion of all left iliac fossa pain syndromes, the majority of whom would be expected to have diverticulitis. IV antibiotic patients progressed onto oral antibiotics.
Schug-pass 2010[62]	**Antibiotic(4-days):** Ertapenem (a 1-ß-carbapenem, available as an intravenous broad-spectrum antibiotic) 1g/d n=50 **Antibiotic(7-days):** Ertapenem (a 1-ß-carbapenem, available as an intravenous broad-spectrum antibiotic) 1g/d n=56	Adult patients admitted to hospital because of a diagnostically confirmed acute episode of sigmoid diverticulitis and the necessity of an inpatient treatment with parenteral nutrition. Mean age: 59.4±12.1 Germany	• Complication: abscess • Complication: fistula • Need for surgery: elective surgery • Recurrent diverticulitis Followed up at 1 year	
Stollman 2013[66]	**Aminosalicylate + probiotic:**	Patients with a clinical	• Recurrent diverticulitis	Probiotic/probiotic placebo

Study	Intervention and comparison	Population	Outcomes	Comments
	Mesalamine (Asacol) 400mg 6 times daily + probiotic (Align) B. infantis 35624, 1billion units, once daily for 12 weeks. n=36 **Aminosalicylate:** Mesalamine (Asacol) 400mg 6 times daily for 12 weeks. n=40 **Placebo:** Placebo 6 times daily for 12 weeks. n=41	diagnosis of acute diverticulitis confirmed by CT scan. Mean age(range): 58 (35-83) USA	• Symptoms: total Followed up at 12 months	introduced after 14 days

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Chabok 2012[11]	Antibiotic vs control	Symptom: abdominal pain at 12 months (VAS)	NA	335	NA	334	High
			There were no differences between groups for pain (VAS): P=0.253-0.886				
Stollman 2013[66]	Aminosalicylate + probiotic vs Aminosalicylate	Symptom: Global Symptom Score	NA	27	NA	32	High

Study	Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
	Aminosalicylate + probiotic vs Placebo		NA	27	NA	29	
	Aminosalicylate vs placebo		NA	32	NA	29	
			The difference between groups did not reach statistical significance at the end of the 12 week intervention period, or at any of the 9 month follow up visits.				

Table 4: Clinical evidence summary: Antibiotic compared to control for acute diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antibiotic (95% CI)
Complication: perforation	1091 (2 studies) 12-24 months	⊕⊕⊖⊖ LOW[b,c] due to risk of bias, imprecision	OR 0.28 (0.08 to 0.99)	Moderate	
				16 per 1000	10 fewer per 1000 (from 20 fewer to 0 more)[a]
Complication: abscess	1091 (2 studies) 12-24 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.16 (0.36 to 3.78)	Moderate	
				9 per 1000	1 more per 1000 (from 6 fewer to 25 more)
Complication: fistula	468 (1 study) 24 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	OR 0.94 (0.06 to 15.12)	Moderate	
				4 per 1000	0 fewer per 1000 (from 4 fewer to 53 more)
Sigmoid resection	1085 (2 studies) 12-24 months	⊕⊕⊖⊖ LOW[b,c] due to risk of bias,	RR 0.59 (0.33 to 1.07)	Moderate	
				56 per 1000	23 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antibiotic (95% CI)
		imprecision			(from 38 fewer to 4 more)
Recurrent diverticulitis	1050 (2 studies) 12-24 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.97 (0.73 to 1.29)	Moderate	
				158 per 1000	5 fewer per 1000 (from 43 fewer to 46 more)
Hospitalisation	528 (1 study) 6 months	⊕⊕⊕⊖ MODERATE[c] due to imprecision	RR 0.69 (0.45 to 1.04)	Moderate	
				176 per 1000	55 fewer per 1000 (from 97 fewer to 7 more)
Mortality	472 (1 study) 24 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	OR 0.35 (0.05 to 2.48)	Moderate	
				13 per 1000	8 fewer per 1000 (from 12 fewer to 19 more)

[a]Absolute effect value calculated manually using risk difference as event rate <1% and zero events in one arm of at least one study
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence summary: Antibiotic (IV) compared to antibiotic (oral) for acute diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Antibiotic (oral)	Risk difference with Antibiotic (IV) (95% CI)
Hospitalisation	161 (2 studies) 30-60 days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.31 (0.31 to 5.63)	Moderate	
				24 per 1000	7 more per 1000 (from 17 fewer to 111 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Antibiotic (oral)	Risk difference with Antibiotic (IV) (95% CI)
Quality of life: SF-12 (physical) Scale from: 0 to 100.	127 (1 study) 60 days	⊕⊕⊕⊖ MODERATE[a] due to risk of bias		The mean quality of life: sf-12 (physical) in the control groups was 50.3 SF-12	The mean quality of life: sf-12 (physical) in the intervention groups was 0.7 lower (3.48 lower to 2.08 higher)
Quality of life: SF-12 (mental) Scale from: 0 to 100.	127 (1 study) 60 days	⊕⊕⊕⊖ MODERATE[a] due to risk of bias		The mean quality of life: sf-12 (mental) in the control groups was 53 SF-12	The mean quality of life: sf-12 (mental) in the intervention groups was 0.4 lower (3.55 lower to 2.75 higher)
Symptom: abdominal pain Scale from: 0 to 4.	79 (1 study) 3 days	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean symptom: abdominal pain in the control groups was 1.26	The mean symptom: abdominal pain in the intervention groups was 0.06 lower (0.5 lower to 0.38 higher)
Symptom: abdominal pain	44 (1 study) 2 months	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.07 to 15)	Moderate	
				46 per 1000	0 fewer per 1000 (from 43 fewer to 644 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence summary: Antibiotic (long course) compared to antibiotic (short course) for acute diverticulitis

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Antibiotic (short course[c])	Risk difference with Antibiotic (long course[c]) (95% CI)
Complication: abscess	91 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0 to 6.11)	Moderate	
				23 per 1000	20 fewer per 1000 (from 23 fewer to 103 more)
Complication: fistula	91 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.12 (0 to 6.11)	Moderate	
				23 per 1000	20 fewer per 1000 (from 23 fewer to 103 more)
Recurrent diverticulitis	88 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.39 (0.35 to 5.46)	Moderate	
				75 per 1000	29 more per 1000 (from 49 fewer to 335 more)
Surgery	91 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.18 (0.71 to 1.95)	Moderate	
				372 per 1000	67 more per 1000 (from 108 fewer to 353 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[c]In this study, long and short course antibiotics referred to a 7-day and 4-day course of antibiotics, respectively.

Table 7: Clinical evidence summary: Aminosalicylate + probiotic compared to Aminosalicylate for acute diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate	Risk difference with Aminosalicylate + probiotic (95% CI)
Recurrent diverticulitis	59	⨁⨁⊖⊖	RR 1.32	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate	Risk difference with Aminosalicylate + probiotic (95% CI)
	(1 study) 1 years	LOW[a] due to imprecision	(0.63 to 2.76)	281 per 1000	90 more per 1000 (from 104 fewer to 495 more)

[a]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 8: Clinical evidence summary: Aminosalicylate + probiotic compared to Placebo for acute diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate + probiotic (95% CI)
Recurrent diverticulitis	56 (1 study) 1 years	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 1.19 (0.57 to 2.48)	Moderate	
				310 per 1000	59 more per 1000 (from 133 fewer to 459 more)

[a]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 9: Clinical evidence summary: Aminosalicylate compared to Placebo for acute diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (95% CI)
Recurrent diverticulitis	61 (1 study) 1 years	⨁⨁⨀⨀ LOW[a] due to imprecision	RR 0.91 (0.42 to 1.97)	Moderate	
				310 per 1000	28 fewer per 1000 (from 180 fewer to 301 more)

[a]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review. [5] This is summarised in the health economic evidence profile below (Table 10) and the health economic evidence table in appendix H.

1.5.2 Excluded studies

One economic study relating to this review question was excluded as it was not applicable. [40] Two economic studies were excluded as they had very serious limitations. [35] [43] One economic study relating to this review question was selectively excluded due to the availability of evidence of a greater methodological quality. [52] These are listed in appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

1.5.3 Summary of studies included in the economic evidence review

Table 10: Health economic evidence profile: IV antibiotics versus oral antibiotics

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Biondo 2014 [5] (Spain)	Partially applicable [(a)]	Potentially serious limitations[(b)]	Within-trial cost consequences analysis of multicentre RCT (DIVER) comparing hospitalisation with outpatient treatment in people with uncomplicated acute diverticulitis. Hospitalised patients received intravenous amoxicillin and clavulanic acid and outpatients received oral antibiotics. 60 day follow-up.	+£1,112 [(c)]	SF-12 (physical) 0.7 lower SF-12 (mental) 0.4 lower	Oral antibiotics dominates	NA

Abbreviations: RCT: randomised controlled trial; NA: not applicable; SF-12: 12-item short from health survey

(a) Within-trial analysis of DIVER multi-centre RCT. Spanish hospital perspective. Population limited to people with uncomplicated acute diverticulitis who responded to first treatment with antibiotics and analgesia

(b) Treatment effect from DIVER trial only. High numbers of eligible patients refused to be included in the trial. Costs were reported interchangeably as per patient and per episode. Cost year not reported. Costs were calculated in one centre (Bellvitge University Hospital) whereas quality of life assessment was conducted five centres. Local factors could have influenced delivery of the two interventions. No conflicts of interest reported.

(c) Converted using 2011 purchasing power parities [49]

1.5.4 Unit costs

The unit costs below were presented to the Committee, to aid consideration of cost effectiveness.

Table 11: UK costs of laxatives, antibiotics, analgesia, antispasmodics, aminosalicylates, probiotics and prebiotics

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Laxatives				
Isphagula husk 3.5g effervescent granules sachets	2 x 3.5g sachets [5-10g once daily]	£0.09	£5.52	NHS Drug Tariff
Methylcellulose 500mg	2 x 500mg tablets daily [3-6 x 500mg tablets twice daily]	£0.05	£2.89	NHS Drug Tariff
Sterculia 62% granules 7g sachets	2 x 7g sachets twice daily [1-2 sachets 1-2 times a day]	£0.11	£13.53	NHS Drug Tariff
Bisacodyl 5mg gastro-resistant tablets	2 x5mg tablets [5-10mg once daily increased if necessary up to 20mg once daily]	£0.21	£12.66	NHS Drug Tariff
Sodium picosulfate 5mg/5ml oral solution	2 x 5mg/ml solutions [5-10mg once daily]	£0.12	£7.20	NHS Drug Tariff
Senna 7.5mg tablets	2 x 7.5mg tablets [7.5-15mg daily (maximum dose 30 mg daily)]	£0.03	£1.67	NHS Drug Tariff
Lactulose 3.1g-3.7g/5ml oral solution	6 x 3.1g-3.7g/5ml oral solution [Initially 15ml twice daily, adjusted according to response]	£0.02	£4.13	NHS Drug Tariff
Macrogol 3350 oral powder 8.5g sachets	2 sachets [2 sachets once daily usually for up to 2 weeks]	£0.14	£3.89[c]	NHS Drug Tariff
Docusate sodium 100mg capsules (by mouth)	5 x 100mg capsules [Up to 500mg daily in divided doses, adjusted according to response]	£0.07	£10.60	NHS Drug Tariff
Glycerol (by rectum) 4g suppositories	1 x 4g suppository [4g, as required]	£0.10	£2.94	NHS Drug Tariff
Micralax (sodium citrate 90mg/ml) 5ml micro-enema	1 enema [1 enema per dose]	£0.41	£12.35	British National Formulary

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Arachis oil 130ml enema	1 x 130ml enema [130ml, as required]	£47.50	£95[d]	NHS Drug Tariff
Antibiotics (Intravenous)				
Co-Amoxiclav 1000mg/200mg powder for solution for injection	1000mg/ 200mg every 8 hours by intravenous infusion	£1.06	£6.36[d] - £31.80[e]	BNF NHS Indicative price
Ciprofloxacin 400mg/200ml solution for infusion bottles	2x 400mg daily by intravenous infusion	£2.08	£29.12[f]	BNF NHS Indicative price
Metronidazole500mg/100ml infusion 100ml bags	3 x 500mg daily by intravenous infusion	£3.19	£66.99[f]	BNF NHS Indicative price
Ertapenem sodium 1g powder for solution for infusion vials	1g daily by intravenous infusion	£31.86	£127.44[g]- £223.02[f]	BNF NHS Indicative Price
Piperacillin 2g/ Tazobactam 250mg powder for solution for injection vials	4.5g every 8 hours by intravenous infusion	£7.65	£321.30[f]	NHS Drug Tariff
Cefuroxime 750mg powder for solution for injection vials	1.5g every 8 hours; by intravenous infusion [750mg every 6-8 hours; increased if necessary up to 1.5g every 6-8 hours]	£2.52	£45.36[h]	BNF NHS Indicative Price
Amoxicillin 500mg powder for solution for injection vials	3x 500mg daily by intravenous infusion	£0.55	£11.51[f]	NHS Drug Tariff
Gentamicin 240mg/80ml infusion bags	5-7mg/kg daily	£6.13	£85.80[f]	NHS Drug Tariff
Antibiotics (Oral)				
Co-Amoxiclav 500mg/125mg tablets (oral)	3 x 500mg/125mg tablets daily	£0.08	£2.36[e]	NHS Drug Tariff
Ciprofloxacin 500 mg tablets (oral)	2x 500mg tablets daily	£0.08	£1.15[f]	NHS Drug Tariff
Metronidazole 400mg tablets (oral)	3 x 400mg daily	£0.25	£5.18[f]	NHS Drug Tariff
Cefadroxil 500mg capsules (oral)	2 x 1g daily	£0.32	£9.03[f]	NHS Drug Tariff
Cefuroxime 125mg tablets	4 x 125mg tablets daily	£0.33	£3.91[h]	NHS Drug Tariff
Cephalexin 500mg tablets	500mg every 8 hours	£0.08	£1.71[f]	NHS Drug Tariff
Trimethoprim 200mg tablets	2x 200mg daily	£0.07	£0.93[f]	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Analgesia				
Paracetamol 500mg (by mouth)	2 x 500mg tablets every 6 hours [0.5-1g every 4-6 hours (maximum 4g per day)]	£0.02	£3.87	NHS Drug Tariff
Ibuprofen 400mg tablets	1 x 400mg tablet 4 times a day [Initially 300-400mg 3-4 times a day; increased if necessary to up to 600mg 4 times a day; maintenance 200-400mg 3 times a day, may be adequate]	£0.03	£3.25	NHS Drug Tariff
Naproxen 250mg tablets	5 x 250mg tablets [Initially 500mg, then 250mg every 6-8 hours as required (maximum dose after the first day 1.25g daily)]	£0.03	£4.24	NHS Drug Tariff
Oxycodone 5mg capsules	6 x 5mg capsules daily [5 mg every 4–6 hours, dose to be increased if necessary. Maximum 400mg daily]	£0.20	£37.28	NHS Drug Tariff
Oxycodone 10mg/ml solution for injection ampoules	10mg every 4 hours as required by slow intravenous injection	£1.60	£292.20	NHS Drug Tariff
Tramadol hydrochloride 50mg capsules	100mg every 6 hours [Initially 100mg, then 50-100mg every 4-6 hours]	£0.02	£2.76	BNF NHS Indicative Price
Morphine sulfate 10mg/ml solution for injection ampoules	Initially 10mg every 4 hours by subcutaneous injection	£0.94	£170.94	NHS Drug Tariff
Morphine sulfate 10mg/5ml oral solution	Initially 10mg every 4 hours	£0.09	£16.59	NHS Drug Tariff
Nefopam 30mg tablets	6 x 30mg tablets [Initially 60mg, 3 times a day, adjusted according to response; usual dose 30-90mg, 3 times a day]	£0.21	£38.90	NHS Drug Tariff
Hyoscine butylbromide 10mg tablets	3 x 10mg tablets [3 x 10mg tablets daily;	£0.05	£4.89	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
	increased if necessary up to 20mg 4 times a day]			
Antispasmodics				
Atropine sulfate 600 microgram tablets	2 x 600µg tablets [600-1200µg daily]	£1.89	£115.05	NHS Drug Tariff
Aminosalicylates				
Mesalazine (Octasa®) 800mg gastro-resistant tablets	3 x 800mg tablets daily [2.4-4.8g daily]	£0.45	£40.96	NHS Drug Tariff
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets	1 x 4.4g sachet daily	£1.15	£34.86	BNF (NHS indicative price)

(a) Dosages for adults, British National Formulary
(b) Depending on number of units taken
(c) Cost per 14 day course; not per month
(d) Cost when dose taken for 2 days
(e) Cost when dose taken for 10 days
(f) Cost when dose taken for 7 days
(g) Cost when dose taken for 4 days
(h) Cost when dose taken for 3 days

Table 12: Example UK costs to people with diverticular disease for items not prescribed on the NHS

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets (non-prescribed)	1 x 4.4g sachet daily	£2.35	£71.47	Retail price from stockist[e]
Vivomixx (450 billion live bacteria per sachet) 4.4g sachets	1 x 4.4g sachet daily	£1.48	£45.02	Retail price from stockist[e]
Lactobacillus casei: Probio 10 (containing *L. casei* 5x10^7 viable cells, among 10 different species of micro-organisms)	1 capsule daily	£0.08	£2.53	Not available in BNF; Retail price from stockist[d]
Symprove™	1ml/kg	£0.03/ml	£75.14[c]	Not available in BNF; Retail price from stockist[f]

Sources: Amazon.co.uk, Holland and Barrett, shop.symprove.com
(a) Dosages for adults
(b) Depending on number of units taken
(c) Cost exclusive of VAT for a weight of 75kg calculated from the average BMI (BMI 27.7) reported in Kvasnovsky 2017[32]

(d) Retail price obtained from Holland and Barrett
(e) Retail price obtained from Amazon.co.uk
(f) Retail price obtained from shop.symprove.com

1.6 Evidence statements

1.6.1 Clinical evidence statements

- Antibiotics

Antibiotics versus control

Evidence from 2 randomised trials demonstrated no clinically important difference for hospitalisation, perforation, abscess, fistula, sigmoid resection, recurrent diverticulitis or mortality (moderate to very low quality). Despite none of the outcomes reaching the threshold to be considered a clinically important difference, the absolute risk difference for the hospitalisation outcome at 6 months was larger than that of the other listed outcomes and favoured antibiotics over no antibiotics.

Antibiotics versus antibiotics

Randomised controlled evidence showed no clinically important difference between IV and oral antibiotics in people with acute diverticulitis on hospitalisation, quality of life (physical), quality of life (mental) or abdominal pain (moderate to very low quality).

Randomised controlled evidence showed no clinically important difference between long course and short course antibiotics in people with acute diverticulitis on the outcomes abscess, fistula, recurrent diverticulitis or surgery (very low quality).

- Aminosalicylates

Single randomised trials found no clinically important difference between aminosalicylate plus probiotics when compared to either aminosalicylate alone (n=59, low quality) or placebo (n=56, low quality) in people with acute diverticulitis for the outcome recurrent diverticulitis.

One randomised controlled trial found no clinically important difference of aminosalicylates on recurrent diverticulitis when compared to placebo in people with acute diverticulitis (n=61, low quality).

1.6.2 Health economic evidence statements

- A cost-consequences analysis found that outpatient oral antibiotics was cost saving (-£1,100 per patient) compared to inpatient intravenous antibiotics for people with uncomplicated diverticulitis. This study was rated as partially applicable with potentially serious limitations.

1.7 Recommendations

H1. Consider a no antibiotic prescribing strategy (with watchful waiting) for people with acute diverticulitis if the person is systemically well.

H2. Offer an antibiotic prescribing strategy if the person with acute diverticulitis is systemically unwell, is immunosuppressed or has significant comorbidity.

H3. For guidance on the management of suspected sepsis see the NICE guideline on sepsis.

H4. Offer intravenous antibiotics to people admitted to secondary care with suspected complicated acute diverticulitis.

H5. Review intravenous antibiotics within 48 hours or after scanning if sooner (see recommendation G3, Chapter G) and consider stepping down to oral antibiotics where possible.

H6. If the person has CT-confirmed uncomplicated acute diverticulitis, review the need for antibiotics and discharge them depending on any co-existing medical conditions.

H7. When prescribing an antibiotic for suspected or confirmed acute diverticulitis, follow the advice in table 13..

Table 13: Antibiotics for adults aged 18 years and over with suspected or confirmed acute diverticulitis

Antibiotic[1]	Dosage and course length[2]
First-choice oral antibiotic for suspected or confirmed uncomplicated acute diverticulitis	
Co-amoxiclav	500/125 mg three times a day for 5 days
Alternative first-choice oral antibiotics if penicillin allergy or co-amoxiclav unsuitable	
Cefalexin **with**	500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infection) for 5 days
Metronidazole	400 mg three times a day for 5 days
Trimethoprim **with**	200 mg twice a day for 5 days
Metronidazole	400 mg three times a day for 5 days
First- choice intravenous antibiotics[3] for suspected or confirmed complicated acute diverticulitis	
Co-amoxiclav	1.2 g three times a day
Cefuroxime **with**	750 mg three or four times a day (increased to 1.5 g three or four times a day if severe infection)
Metronidazole	500 mg three times a day
Amoxicillin **with**	500 mg three times a day (increased to 1 g four times a day if severe infection)
Gentamicin **and**	Initially 5 to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration[4]
Metronidazole	500 mg three times a day
Ciprofloxacin[5] **with**	400 mg twice or three times a day
Metronidazole	500 mg three times a day
Alternative intravenous antibiotics	
Consult local microbiologist	

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.

[2] A longer course may be needed based on clinical assessment. Continue antibiotics for up to 14 days in people with CT confirmed diverticular abscess.

[3] Review intravenous antibiotics within 48 hours or after scanning if sooner and consider stepping down to oral antibiotics where possible.

[4] Therapeutic drug monitoring and assessment of renal function is required (BNF, May 2019).

[5] Only in people with allergy to penicillins and cephalosporins. See MHRA advice for restrictions and precautions for using fluoroquinolones due to very rare reports of disabling and potentially long-lasting or irreversible side effects (March 2019).

1.7.1 Research recommendations

What is the clinical and cost effectiveness of antibiotics for the management of acute complicated diverticulitis in primary care?

1.8 Rationale and impact

1.8.1 Why the committee made the recommendations

For people with suspected acute diverticulitis who are not referred for urgent same-day hospital assessment, the committee agreed watchful waiting is an option if the person is systemically well and has no co-morbidities that increase the risk of infection. This decision would be in the context of shared decision making. Oral antibiotics are appropriate if the person is systemically unwell but does not meet the criteria for referral with suspected complicated acute diverticulitis.

The evidence supports current practice of treating an acute episode of diverticulitis with intravenous antibiotics in secondary care. If CT confirms uncomplicated acute diverticulitis, switching to oral antibiotics does not affect outcomes. The committee recommended antibiotics for this group because they were aware of evidence that watchful waiting could increase recurrence rates and the probability of further surgery. In support of antibiotic stewardship and to avoid antibiotic resistance the committee recommended that the person should be reassessed if necessary and the need for antibiotic therapy should be reviewed.

The need for intravenous antibiotics should be reviewed by 48 hrs in line with current good practice on antibiotic prescribing or after the CT scan. The CT will confirm if the person has an abscess or not. The total course of antibiotic treatment should be for a maximum of 7 days and then reviewed. The duration of antibiotics used in the studies was variable and 7 days was based on current clinical practice and the knowledge and expertise of the committee.

In light of the lack of evidence on this topic, and the need to prevent antibiotic resistance, the committee considered this an important area for research. It made research recommendations on antibiotics for people with acute diverticulitis managed in primary care.

1.8.2 Impact of the recommendations on practice

The recommendation to offer an initial treatment of intravenous antibiotics before CT scanning for confirmation reflects current practice, so the committee agreed there should be no change in practice. Using oral antibiotics beyond this point in place of intravenous antibiotics may reduce the resource requirement in caring for people with acute diverticulitis.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee identified quality of life, recurrence of diverticulitis, progression of disease, hospitalisation, surgery or complications (infections, abscesses, perforation, stricture and

fistula) as the critical outcomes. The following outcomes were identified as important for management of diverticulitis; mortality, symptom control, and side effects of treatments.

Mortality was only considered to be an important outcome as it is accepted that the outcome would be unlikely to occur as a result of diverticulitis.

1.9.1.2 The quality of the evidence

The quality of evidence ranged from very low to moderate. The majority of the evidence was graded at low or very low quality. This was mostly due to selection and performance bias, resulting in a high risk of bias rating, and imprecision.

All evidence was obtained from randomised controlled trial studies published within the past 10 years. Observational studies were considered, although no studies were identified for comparisons not already addressed by RCTs.

No evidence was found for the interventions of bowel rest or analgesia.

1.9.1.3 Benefits and harms

The committee discussed the evidence on the non-surgical management of acute diverticulitis.

The committee noted that there was little difference in outcomes between people receiving IV and then oral antibiotics and those only receiving an initial dose of IV antibiotics at hospital admission and then being treated as an outpatient without further antibiotics. The committee agreed that watchful waiting is an option if the watchful waiting is an option if the person is systemically well and has no co-morbidities that increase the risk of infection. This decision would be in the context of shared decision making.. The committee noted that some people with uncomplicated acute diverticulitis might require admission for example due to uncontrollable pain. The committee noted that some people can be treated as outpatients with no antibiotic therapy beyond initial IV treatment, but in the studies reflecting this, the population was those with CT-confirmed diverticulitis without complications. However,

There was no clinical difference in hospitalisation, quality of life, and pain in those who received IV antibiotics and those who switched to oral antibiotics after the initial IV dose. The committee also agreed that patients should be allowed to eat and drink if tolerated, and should at this point be taken off IV fluids (and IV antibiotics) once a diagnosis of non-complicated acute diverticulitis had been confirmed.

The committee discussed the evidence from one study comparing a 7-day course of antibiotic to a 4-day course. No clinical difference was seen between treatment durations in complications, recurrence of diverticulitis, or need for surgery. As such, the GC noted that there was no evidence to support a long course of antibiotics. The committee also highlighted that treatment duration longer than necessary could facilitate antibiotic resistance. See Table 13 for details of the antibiotic prescribing strategy.

The committee agreed that there was no evidence of notable effect of aminosalicylates on the management of acute diverticulitis.

1.9.2 Cost effectiveness and resource use

One cost-consequences study was included comparing inpatient with outpatient antibiotics for uncomplicated diverticulitis. This review question was also prioritised for original health

economic modelling incorporating evidence from the randomised controlled trials identified in the clinical review.

The committee noted that there is no clinical or health economic evidence for non-surgical management strategies for acute diverticulitis in the primary care setting. The committee made a consensus recommendation that a short course of oral antibiotics should be considered in those with suspected acute diverticulitis who do not meet referral criteria for hospital admission. The clinical review suggests that antibiotics are highly cost-effective compared with no antibiotics – they are cheap, effective and there appears to be a reduction in hospitalisation (although this was not statistically significant).

The committee felt that people presenting with acute diverticulitis in the hospital setting should be given an initial dose of intravenous antibiotics, as indicated by the clinical evidence and established trial protocols and according to current practice.

The higher costs of strategies requiring hospital admissions compared with interventions delivered in outpatient settings are reflected in the results of a published cost consequence analysis with a Spanish hospital perspective, which estimated that treatment with oral antibiotics in an outpatient setting saved £1,112 per patient compared with inpatient treatment with intravenous antibiotics. The study found no difference in mental or physical quality of life, measured using the SF-12 questionnaire.

An original cost analysis (see Chapter G and Appendix 1, both separate documents) for people with suspected severe or complicated diverticulitis compared:

- IV antibiotics and no CT
- Initial IV antibiotics and CT. Then discharge with oral antibiotics if uncomplicated
- Initial IV antibiotics and CT. Then discharge with no antibiotics if uncomplicated

The lowest cost strategy was ‘CT and then discharge with oral antibiotics if uncomplicated’. Discharging with no antibiotics was more costly because of increased rehospitalisation. These results were robust to sensitivity analysis. The analysis did not consider the long-term consequences in terms of antimicrobial resistance, which would favour no antibiotics. However, neither does it include other outcomes that trended towards favouring oral antibiotics, including sigmoid resection and death. Overall, the committee felt that stepping down to oral antibiotics for uncomplicated diverticulitis was a safe and efficient strategy and that for some patients ceasing all antibiotics would be reasonable.

Given these findings and on the basis that that the clinical evidence found no difference in effectiveness compared with IV antibiotics, the committee felt that people with acute diverticulitis can be discharged with oral antibiotics, following confirmation by CT that their diverticulitis is not complicated.

1.9.3 Other factors the committee took into account

The committee noted that in all but one of the studies included in this review the population had a CT confirmation of diverticulitis. While the committee agreed that this was good practice, it was commented that this may not always be available in current practice. The AVOD and DIABOLO studies both report no difference in outcomes for those patients with CT confirmed acute diverticulitis treated with or without antibiotics. However, longer term results suggest a possible increase in recurrent attacks and the need for surgical resection.

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78. Urushidani S, Kuriyama A, Matsumura M. 5-aminosalicylic acid agents for prevention of recurrent diverticulitis: a systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. 2017; 33(1):12-9
79. van Dijk ST, Bos K, de Boer MGJ, Draaisma WA, van Enst WA, Felt RJF et al. A systematic review and meta-analysis of outpatient treatment for acute diverticulitis. International Journal of Colorectal Disease. 2018; 33(5):505-512
80. van Dijk ST, Daniels L, Unlu C, de Korte N, van Dieren S, Stockmann HB et al. Long-Term Effects of Omitting Antibiotics in Uncomplicated Acute Diverticulitis. American Journal of Gastroenterology. 2018; 113(7):1045-1052
81. Van Ooteghem G, El-Mourad M, Slimani A, Margos W, El Nawar A, Patris A et al. Is early enteral nutrition dangerous in acute non surgical complicated diverticulitis? About 25 patients fed with oral fiber free energetic liquid diet. Acta Gastroenterologica Belgica. 2013; 76(2):235-40
82. Vetter D, Schuurmans MM, Benden C, Clavien PA, Nocito A. Long-term follow-up of lung transplant recipients supports non-operative treatment of uncomplicated diverticulitis. Clinical Transplantation. 2016; 30(10):1264-1270
83. Weisberger L, Jamieson B. How can you help prevent a recurrence of diverticulitis? Journal of Family Practice. 2009; 58(7):381-382

Appendices

Appendix A: Review protocols

Table 14: Review protocol: Review protocol for non-surgical treatments for acute diverticulitis

Field	Content
Review question	What are the most clinically and cost-effective non-surgical treatments for acute diverticulitis?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To find the most effective non-surgical treatments for acute diverticulitis
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with acute diverticulitis
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Bowel rest (clear fluids only) • Antibiotics (antibiotic or no antibiotic, choice of antibiotic, route of administration and length of treatment) • Analgesia (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opiates, and nefopam) • IV fluids • Aminosalycilates
Eligibility criteria – comparator(s) / control or reference (gold) standard	Each other No treatment Placebo
Outcomes and prioritisation	Critical outcomes: • Progression of disease • Hospitalisation • Need for surgery • Complications (infections, abscesses, perforation, stricture, fistula) • Recurrence rates of acute diverticulitis (minimum 1year) • Quality of life Important outcomes: • Mortality • Symptom control (pain relief) • Side effects of ○ Antibiotics: nausea and vomiting, diarrhoea, infections related to antibiotics ○ Analgesics: nausea and vomiting, constipation
Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies.

	Confounders: age, gender
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger
Proposed sensitivity / subgroup analysis, or meta-regression	Strata: • Hospitalised and non-hospitalised (community) patients Subgroups: • people of Asian family origin as they are known to develop right-sided diverticula • Age <50 years and >50 years • Male and female • Transplant patients/ immunocompromised
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in	For details please see sections 6.4 and 9.1 of Developing NICE

cumulative evidence	guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 15: Health economic review protocol**

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[46] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic

evidence table will not be completed and it will not be included in the health economic evidence profile.

- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 16: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 11 of 12 CENTRAL to 2018 Issue 11 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Table 17: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/

19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	randomized controlled trial.pt.
23.	controlled clinical trial.pt.
24.	randomi#ed.ti,ab.
25.	placebo.ab.
26.	randomly.ti,ab.
27.	Clinical Trials as topic.sh.
28.	trial.ti.
29.	or/22-28
30.	Meta-Analysis/
31.	exp Meta-Analysis as Topic/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/50-59
41.	Epidemiologic studies/
42.	Observational study/
43.	exp Cohort studies/
44.	(cohort adj (study or studies or analys* or data)).ti,ab.
45.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
46.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
47.	Controlled Before-After Studies/
48.	Historically Controlled Study/
49.	Interrupted Time Series Analysis/
50.	(before adj2 after adj2 (study or studies or data)).ti,ab.
51.	or/30-39
52.	exp case control study/
53.	case control*.ti,ab.
54.	or/41-42
55.	40 or 43
56.	Cross-sectional studies/
57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/45-46
59.	40 or 47

60.	40 or 43 or 47
61.	21 and (29 or 40 or 60)

1

2 **Table 18: Embase (Ovid) search terms**

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	random*.ti,ab.
21.	factorial*.ti,ab.
22.	(crossover* or cross over*).ti,ab.
23.	((doubl* or singl*) adj blind*).ti,ab.
24.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
25.	crossover procedure/
26.	single blind procedure/
27.	randomized controlled trial/
28.	double blind procedure/
29.	or/20-28
30.	systematic review/
31.	meta-analysis/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/30-39
41.	Clinical study/
42.	Observational study/
43.	family study/
44.	longitudinal study/
45.	retrospective study/
46.	prospective study/
47.	cohort analysis/
48.	follow-up/
49.	cohort*.ti,ab.
50.	48 and 49
51.	(cohort adj (study or studies or analys* or data)).ti,ab.
52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	(before adj2 after adj2 (study or studies or data)).ti,ab.
55.	or/41-47,50-54
56.	exp case control study/
57.	case control*.ti,ab.
58.	or/56-57
59.	55 or 58
60.	cross-sectional study/
61.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	or/60-61
63.	55 or 62
64.	55 or 58 or 62
65.	19 and (29 or 40 or 64)

Table 19: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Diverticular Disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 November 2018 NHSEED - Inception to March 2015	None

1 **Table 21: Medline (Ovid) search terms**

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	Economics/
23.	Value of life/
24.	exp "Costs and Cost Analysis"/
25.	exp Economics, Hospital/
26.	exp Economics, Medical/
27.	Economics, Nursing/
28.	Economics, Pharmaceutical/

29.	exp "Fees and Charges"/
30.	exp Budgets/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/22-37
39.	exp models, economic/
40.	*Models, Theoretical/
41.	markov chains/
42.	monte carlo method/
43.	exp Decision Theory/
44.	(markov* or monte carlo).ti,ab.
45.	econom* model*.ti,ab.
46.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
47.	Models, Organizational/
48.	*models, statistical/
49.	*logistic models/
50.	models, nursing/
51.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
52.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
53.	(SSM or SODA).ti,ab.
54.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
55.	soft systems method*.ti,ab.
56.	(Meta-heuristic* or Metaheuristic*).ti,ab.
57.	(dynamic* adj2 (model* or system*)).ti,ab.
58.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
59.	(microsimulation* or "micro* simulation*").ti,ab.
60.	((flow or core) adj2 model*).ti,ab.
61.	(data adj2 envelopment*).ti,ab.
62.	system* model*.ti,ab.
63.	or/41-64
64.	quality-adjusted life years/
65.	sickness impact profile/
66.	(quality adj2 (wellbeing or well being)).ti,ab.
67.	sickness impact profile.ti,ab.
68.	disability adjusted life.ti,ab.
69.	(qal* or qtime* or qwb* or daly*).ti,ab.
70.	(euroqol* or eq5d* or eq 5*).ti,ab.
71.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

72.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
73.	(hui or hui1 or hui2 or hui3).ti,ab.
74.	(health* year* equivalent* or hye or hyes).ti,ab.
75.	discrete choice*.ti,ab.
76.	rosser.ti,ab.
77.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
78.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
79.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
80.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
81.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
82.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
83.	or/22-40
84.	21 and (38 or 63 or 83)

Table 22: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	Economics/
21.	Value of life/
22.	exp "Costs and Cost Analysis"/
23.	exp Economics, Hospital/
24.	exp Economics, Medical/
25.	Economics, Nursing/
26.	Economics, Pharmaceutical/

27.	exp "Fees and Charges"/
28.	exp Budgets/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/20-35
37.	statistical model/
38.	*theoretical model/
39.	nonbiological model/
40.	stochastic model/
41.	decision theory/
42.	decision tree/
43.	exp nursing theory/
44.	monte carlo method/
45.	(markov* or monte carlo).ti,ab.
46.	econom* model*.ti,ab.
47.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
48.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
49.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
50.	(SSM or SODA).ti,ab.
51.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
52.	soft systems method*.ti,ab.
53.	(Meta-heuristic* or Metaheuristic*).ti,ab.
54.	(dynamic* adj2 (model* or system*)).ti,ab.
55.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
56.	(microsimulation* or "micro* simulation*").ti,ab.
57.	((flow or core) adj2 model*).ti,ab.
58.	(data adj2 envelopment*).ti,ab.
59.	system* model*.ti,ab.
60.	or/39-61
61.	quality adjusted life year/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.

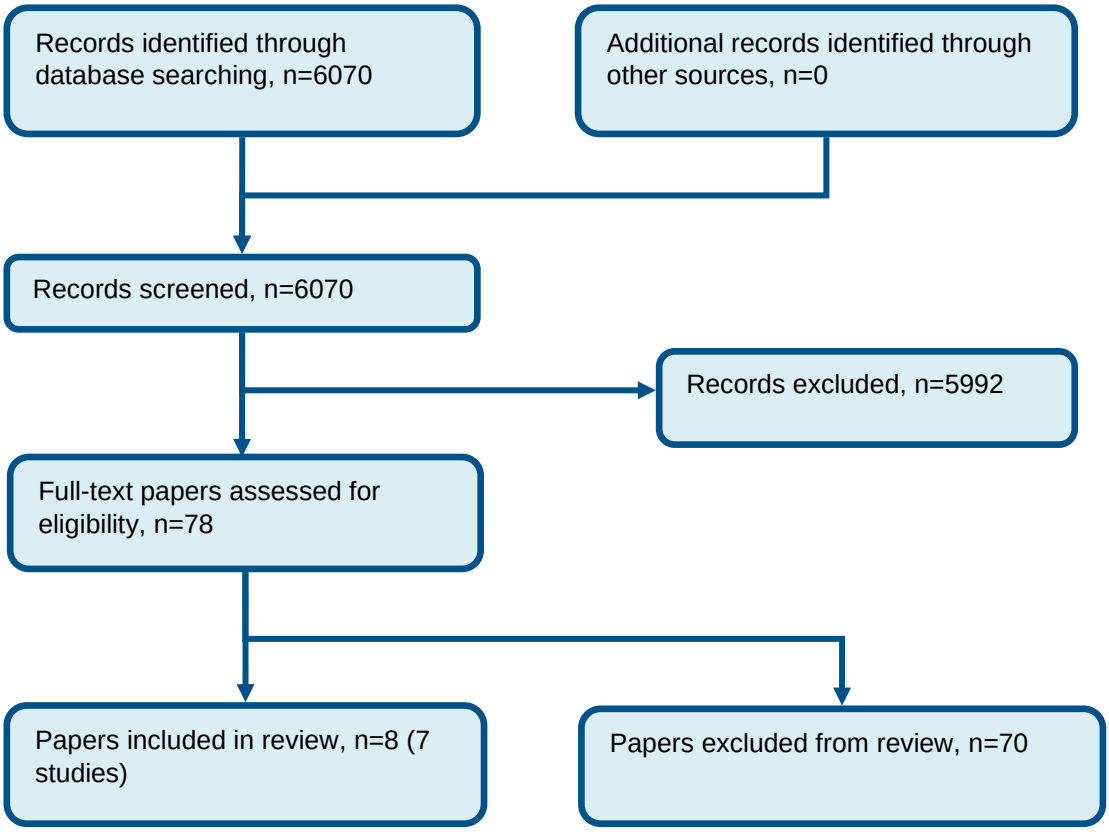
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/20-40
83.	19 and (36 or 60 or 82)

Table 23: NHS EED and HTA (CRD) search terms

#1.	diverticul*

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of non-surgical treatments for acute diverticulitis



Appendix D: Clinical evidence tables

Table 24: Clinical evidence tables

Study	Biondo 2014[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=132)
Countries and setting	Conducted in Spain; Setting: 5 tertiary care university hospitals in Spain.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 60 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by CT scan
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years and over with uncomplicated diverticulitis defined as pericolic phlegmon.
Exclusion criteria	Complicated colonic diverticulitis, absence of symptom relief, pregnancy or breastfeeding, intake of antibiotics for colonic diverticulitis in the month previous to diagnosis, colorectal cancer suspicion, immunosuppression, chronic renal failure with haemodialysis.
Recruitment/selection of patients	Recruited from emergency department of hospitals
Age, gender and ethnicity	Age - Mean (SD): 56.3 (13). Gender (M:F): 72/60. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Antibiotics - IV antibiotics. Inpatient: After the first dose of antibiotic, patients were admitted to the ward and administered intravenous antibiotics (amoxicillin and clavulanic acid, 1g per

	125mg) and fluids every 8 hours for at least 36 to 48 hours until oral feeding was tolerated. . Duration 10 days. Concurrent medication/care: First dose of antibiotic was given intravenously in the emergency department. . Indirectness: No indirectness (n=66) Intervention 2: Antibiotics - Oral antibiotics. Outpatient: After the first dose of antibiotic, patients were discharged and administered oral antibiotics (amoxicillin and clavulanic acid, 875mg per 125mg) every 8 hours. . Duration 10 days. Concurrent medication/care: First dose of antibiotic was given intravenously in the emergency department. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ANTIBIOTICS versus ORAL ANTIBIOTICS Protocol outcome 1: Quality of life at Define - Actual outcome: SF-12: Physical at 60 days; Group 1: mean 49.6 (SD 8.7); n=64, Group 2: mean 50.3 (SD 7.2); n=63; S5-12: Pysical 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3 - Actual outcome: SF-12: Mental at 60 days; Group 1: mean 52.6 (SD 9.5); n=64, Group 2: mean 53 (SD 8.6); n=63; SF-12 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3 Protocol outcome 2: Hospitalisation at Define - Actual outcome: Readmitted because of failure of medical treatment. at 60 days; Group 1: 4/64, Group 2: 3/63 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3	
Protocol outcomes not reported by the	Need for surgery at Define; Symptom control (pain relief) at Define; Mortality at Define; Side effects of

study	antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Recurrence rates of acute diverticulitis at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Chabok 2012[11]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=623)
Countries and setting	Conducted in Iceland, Sweden; Setting: 10 surgical departments in Sweden and one in Iceland.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged ≥18 years, acute lower abdominal pain with tenderness, body temp ≥38C at admission or during the last 12 hours before admission, raised WBC and C-reactive protein level, signs of diverticulitis on CT
Exclusion criteria	Signs of complicated diverticulitis on CT with abscess, fistula or free air in abdomen or pelvis, signs of other diagnosis on CT, receiving immunosuppressive therapy, pregnancy, ongoing antibiotic therapy.
Recruitment/selection of patients	Recruited from hospitals.
Age, gender and ethnicity	Age - Mean (SD): 57.3 (13). Gender (M:F): 220/403. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=335) Intervention 1: Antibiotics. Orally administered antibiotics such as ciprofloxacin or cefadroxil combined with metronidazole were initiated subsequently on the ward or at discharge. . Duration At least 7 days. Concurrent medication/care: All patients received an initial treatment of IV fluids.. Indirectness: No indirectness (n=334) Intervention 2: No intervention/placebo - No intervention. Treatment with intravenous fluids only (no-antibiotic group). Duration NA. Concurrent medication/care: NA. Indirectness: No indirectness

Funding	Academic or government funding (Uppsala and Orebro Regional Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANTIBIOTICS versus NO INTERVENTION

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Sigmoid resection at 12 months; Group 1: 5/309, Group 2: 7/314
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 19

Protocol outcome 2: Symptom control (pain relief) at Define
- Actual outcome: Abdominal pain at 12 months; There were no differences between groups for pain (VAS): P=0.253-0.886;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 19

Protocol outcome 3: Complications (abscesses) at Define
- Actual outcome: Complications: abscess at 12 months; Group 1: 0/314, Group 2: 3/309
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 19
- Actual outcome: Complications: perforation at 12 months; Group 1: 3/314, Group 2: 3/309
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 19

Protocol outcome 4: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrent diverticulitis at 12 months; Group 1: 46/292, Group 2: 47/290
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 19

Protocol outcomes not reported by the	Quality of life at Define; Hospitalisation at Define; Mortality at Define; Side effects of antibiotics: nausea and

study	vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (perforation) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study (subsidiary papers)	Daniels 2017[18] (Van dijk 2018[80])
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=528)
Countries and setting	Conducted in Netherlands; Setting: 22 clinical sites in the Netherlands
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT diagnosed AD
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible if they had a first episode of left-sided, uncomplicated, acute diverticulitis, confirmed within 24 h by CT.
Exclusion criteria	Previous radiologically proven diverticulitis, higher modified Hinchey stages or Ambrosetti's 'severe' diverticulitis stage plus sepsis as defined by the American College of Chest Physicians/Society of Critical Care Medicine antibiotic use in the previous 4 weeks.

Recruitment/selection of patients	Recruited from clinical site
Age, gender and ethnicity	Age - Mean (range): 56.8 (48.5-64.6). Gender (M:F): 267/261. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=287) Intervention 1: Antibiotics. Amoxicillin–clavulanic acid was chosen as broad-spectrum antibiotic treatment. The regimen consisted of a 10-day course, with intravenous administration of 1200mg four times daily for at least 48 hr, after which the route could be switched, if tolerated, to oral administration of 625mg three times daily.. Duration 10 days. Concurrent medication/care: CT was repeated in the event of clinical deterioration. In the event of an allergy, a switch made to the combination of ciprofloxacin and metronidazole.. Indirectness: No indirectness (n=283) Intervention 2: No intervention/placebo - No intervention. Patients allocated to observational treatment could be treated directly in an outpatient setting when the following criteria were met: toleration of a normal diet (solid food and more than 1 litre oral fluids), temperature less than 38°C, pain score measured on a visual analogue scale (VAS) below 4 (with paracetamol at the most), capable of self-support at same level as before illness, and patient acceptance.. Duration NA. Concurrent medication/care: CT was repeated in the event of clinical deterioration. Deterioration, proven subsequent complicated diverticulitis or another infectious focus dictated starting antibiotics - start criteria were: Temperature above 39°C, positive blood cultures and sepsis.. Indirectness: No indirectness
Funding	Academic or government funding (Netherlands Organisation for Health Research and Development and the Digestive Disease Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANTIBIOTICS versus NO INTERVENTION

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Sigmoid resection at 24 months; Group 1: 12/241, Group 2: 20/221
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46, Reason: Lost to follow-up (24), deaths (1), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 62, Reason: Lost to follow-up (32), deaths (3), wrongly included (20), withdrew informed consent (1), enrolled in DIRECT trial (6)

Protocol outcome 2: Hospitalisation at Define
- Actual outcome: Readmission within 6 months at 6 months; Group 1: 32/266, Group 2: 46/262
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: Lost to follow-up (10), discontinued participation (13); Group 2 Number missing: 28, Reason: Lost to follow-up (6), discontinued participation (22)

Protocol outcome 3: Mortality at Define
- Actual outcome: Mortality at 24 months; Group 1: 1/242, Group 2: 3/230
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 45, Reason: Lost to follow-up (24), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 53, Reason: Lost to follow-up (32), wrongly included (20), withdrew informed consent (1)

Protocol outcome 4: Complications (abscesses) at Define
- Actual outcome: Complication: abscess (>5cm) at 24 months; Group 1: 3/241, Group 2: 2/227
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46, Reason: Lost to follow-up (24), deaths (1), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 56, Reason: Lost to follow-up (32), deaths (3), wrongly included (20), withdrew informed consent (1)
- Actual outcome: Complication: fistula at 24 months; Group 1: 1/241, Group 2: 1/227
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46, Reason: Lost to follow-up (24), deaths (1), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 56, Reason: Lost to follow-up (32), deaths (3), wrongly included (20), withdrew informed consent (1) Protocol outcome 5: Complications (perforation) at Define - Actual outcome: Complication: perforation at 24 months; Group 1: 2/241, Group 2: 5/227 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46, Reason: Lost to follow-up (24), deaths (1), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 56, Reason: Lost to follow-up (32), deaths (3), wrongly included (20), withdrew informed consent (1) Protocol outcome 6: Recurrence rates of acute diverticulitis at Define - Actual outcome: One or more episodes of recurrent acute diverticulitis (with or without imaging confirmation) at 24 months; Group 1: 36/241, Group 2: 35/227 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46, Reason: Lost to follow-up (24), deaths (1), wrongly included (19), withdrew informed consent (2); Group 2 Number missing: 56, Reason: Lost to follow-up (32), deaths (3), wrongly included (20), withdrew informed consent (1)	
Protocol outcomes not reported by the study	Quality of life at Define; Symptom control (pain relief) at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	**Ribas 2010[55]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Spain; Setting: Two hospitals
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a clinical diagnosis of uncomplicated acute diverticulitis, which was confirmed by a computed tomography (CT) scan within 24–48 hr of admission.
Exclusion criteria	Exclusion criteria before randomization were (1) immunocompromised patients (treatment with immunosuppressive agents, chronic treatment with corticosteroids, or chronic renal failure in haemodialysis), (2) patients under 18 years of age, (3) pregnant women, (4) clinical suspicion or CT confirmation of complicated acute diverticulitis (abscess, peritonitis, bowel obstruction, stricture disease, or fistula formation), (5) Karnofsky performance score less than 50%, or (6) allergy to penicillin. Exclusion criteria after randomization were (1) withdrawal of the trial at any time without stating a reason, (2) confirmation of complicated acute diverticulitis (abscess, peritonitis, bowel obstruction, or fistula) in the CT, (3) the CT not conforming to acute diverticulitis, (4) CT performed 72 h after the admission of the patient, (5) adverse reaction to the antibiotic, and (6) in cases of bacteremia (positive blood culture), the patient would follow intravenous antibiotic.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 53.5. Gender (M:F): 26/24. Ethnicity:
Further population details	

Extra comments	The presence of fever, change in bowel habits, dysuria, urinary frequency and urgency, as well as leukocytosis was also taken into account to reach the diagnosis of diverticulitis.
Indirectness of population	No indirectness: CT confirmed diagnosis
Interventions	(n=25) Intervention 1: Antibiotics - IV antibiotics. Upon symptomatic improvements at 24-48 hours, continued IV administered amoxicillin plus clavulanic acid 1 g every 8 h for 7 days. At the point of discharge, the patient had to take oral antibiotic for five more days and was controlled as an outpatient in a week.. Duration 14 days. Concurrent medication/care: Began oral diet 24–48 h after admission when their symptoms improved. If the clinical evolution was right, a regular diet was initiated.. Indirectness: Serious indirectness; Indirectness comment: Took oral antibiotic for 5 days after discharge Comments: All patients were admitted to hospital and treated with intravenously administered amoxicillin plus clavulanic acid 1 g every 8 h, bowel rest, intravenous fluid therapy, and analgesia with paracetamol alternating with dypirone every 4 h. (n=25) Intervention 2: Antibiotics - Oral antibiotics. Upon symptomatic improvements at 24-48 hours, initiated orally administered amoxicillin plus clavulanic acid 1 g every 8 h in place of IV antibiotics. Advised to continue treatment for 10 days.. Duration 10 days. Concurrent medication/care: Began a liquid diet 24–48 h after admission when their symptoms improved. If the clinical evolution was right, a regular diet was initiated, and the patient was discharged the following day.. Indirectness: Serious indirectness; Indirectness comment: Initial IV treatment, before oral antibiotic treatment. Comments: All patients were admitted to hospital and treated with intravenously administered amoxicillin plus clavulanic acid 1 g every 8 h, bowel rest, intravenous fluid therapy, and analgesia with paracetamol alternating with dypirone every 4 h.
Funding	Academic or government funding (Fundació Joan Costa Roma of the Consorci Sanitari de Terrassa.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ANTIBIOTICS versus ORAL ANTIBIOTICS

Protocol outcome 1: Hospitalisation at Define
- Actual outcome: Hospital re-admission at 30 days; Group 1: 0/22, Group 2: 0/22

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3 Protocol outcome 2: Symptom control (pain relief) at Define - Actual outcome: Patients reporting abdominal pain at 2 months; Group 1: 1/22, Group 2: 1/22 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Recurrence rates of acute diverticulitis at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Ridgway 2009[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=71)
Countries and setting	Conducted in Canada; Setting: Community hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Symptomatic of diverticulitis. CT diagnosis was not available for participants.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who presented with a clinical syndrome of left iliac fossa pain and local tenderness. Pyrexia and/or leucocytosis were desirable to support but not essential to confirm diagnosis of diverticulitis
Exclusion criteria	Patients with generalised tenderness or perforation.
Recruitment/selection of patients	Recruited at the diagnosis of acute diverticulitis was made.
Age, gender and ethnicity	Age - Median (range): 67(31-86). Gender (M:F): 33/46. Ethnicity:
Further population details	
Indirectness of population	Serious indirectness: Inclusion of all left iliac fossa pain syndromes, the majority of whom would be expected to have diverticulitis.
Interventions	(n=38) Intervention 1: Antibiotics - IV antibiotics. Ciprofloxacin 400mg BD / Metronidazole 500mg TDS. Duration Until discharge. Concurrent medication/care: Fasted on entry for 24 hours, IV fluids only. Progressed onto oral intake/ oral antibiotics according to attending physician's daily examination. Indirectness: Serious indirectness; Indirectness comment: IV fluids for 24 hours; progressed onto oral antibiotics thereafter as per attending physician's decision (n=41) Intervention 2: Antibiotics - Oral antibiotics. Ciprofloxacin 400mg BD / Metronidazole 500mg TDS.

	Duration Until discharge. Concurrent medication/care: Fluids and diet were allowed as tolerated from admission.. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ANTIBIOTICS versus ORAL ANTIBIOTICS Protocol outcome 1: Symptom control (pain relief) at Define - Actual outcome: Left illiac fossa tenderness (Wexford scale) at 3 days; MD; 0.06 (p: 0.79) Wexford Scale 0-4 Top=High is poor outcome, Comments: Oral: 1.20 IV: 1.26; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Hospitalisation at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Recurrence rates of acute diverticulitis at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Schug-pass 2010[62]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=123)
Countries and setting	Conducted in Germany; Setting: Hospitals
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Computed tomography (CT) was performed for 97.2% (103/106) of patients and ultrasonography in 49.1% (52/106) of cases.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between the age of 18 and 75 years admitted to hospital because of a diagnostically confirmed acute episode of sigmoid diverticulitis and the necessity of an inpatient treatment with parenteral nutrition.
Exclusion criteria	Study medication or other betalactam antibiotics are contraindicated, e.g., patients with advanced renal insufficiency or patients requiring hemodialysis. Patients with hypersensitivity to betalactam antibiotics Use of antibiotic treatment within the previous 2 weeks before enrolment in the trial. Patients with incurable haematological/oncological diseases. Patients taking immunosuppressants. Existing complications of sigmoid diverticulitis requiring emergency surgery. Women who are pregnant, breastfeeding, or who could become pregnant during the study Participation in another clinical trial or use of another study medication during the previous 4 weeks before enrolment in the study or during the trial.
Recruitment/selection of patients	Patients from 11 hospitals recruited
Age, gender and ethnicity	Age - Mean (SD): 59.4 (12.1). Gender (M:F): 58/48. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Antibiotics - IV antibiotics. Ertapenem (a 1-ß-carbapenem, available as an intravenous

	broad-spectrum antibiotic) 1g/d. Duration 7 days. Concurrent medication/care: NA. Indirectness: No indirectness Comments: If treatment had proved successful, randomization was conducted on day4, via the study centre, with antibiotic therapy being then either terminated or continued for a further 3 days. (n=50) Intervention 2: Antibiotics - IV antibiotics. Ertapenem (a 1-ß-carbapenem, available as an intravenous broad-spectrum antibiotic) 1g/d. Duration 4 days. Concurrent medication/care: NA. Indirectness: No indirectness Comments: If treatment had proved successful, randomization was conducted on day4, via the study centre, with antibiotic therapy being then either terminated or continued for a further 3 days.
Funding	Study funded by industry (MSD Sharp & Dome)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ANTIBIOTICS (LONG COURSE) versus IV ANTIBIOTICS (SHORT COURSE)

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Surgery performed elective at 1 year; Group 1: 21/48, Group 2: 16/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 7

Protocol outcome 2: Complications (abscesses) at Define
- Actual outcome: Abscess at 1 year; Group 1: 0/48, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 7

Protocol outcome 3: Complications (perforation) at Define
- Actual outcome: Fistula at 1 year; Group 1: 0/48, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 7

Protocol outcome 4: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrence of diverticulitis at 1 year; Group 1: 5/48, Group 2: 3/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 10	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Symptom control (pain relief) at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Stollman 2013[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=117)
Countries and setting	Conducted in USA; Setting: Across 34 medical sites in America.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of acute diverticulitis confirmed by CT scan
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 35-85 with a clinical diagnosis of acute diverticulitis confirmed by CT scan. Global symptom score of ≥12 at baseline, abdominal pain score of ≥2
Exclusion criteria	Patients with complications of their diverticulitis (abscess, perforation), IBS, with peptic ulcer, chronic abdominal pain, consumption within 4 weeks of study of product containing mesalamine or probiotic, recent treatment of narcotics, antibiotics or antispasmodics were excluded.
Recruitment/selection of patients	Recruited from medical centres
Age, gender and ethnicity	Age - Mean (range): 58 (35-83). Gender (M:F): 56/61. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Aminosalicylates. Mesalamine (Asacol) 400mg 6 times daily + probiotic (Align) B. infantis 35624, 1billion units, once daily.. Duration 12 weeks. Concurrent medication/care: During the first 10-14 days patients received standard of care plus mesalamine. Dietary supplementation of probiotic added thereafter. Indirectness: No indirectness (n=40) Intervention 2: Aminosalicylates. Mesalamine (Asacol) 400mg 6 times daily. Duration 12 weeks.

	Concurrent medication/care: During the first 10-14 days patients received standard of care plus mesalamine. Dietary supplementation of placebo added thereafter. Indirectness: No indirectness (n=41) Intervention 3: No intervention/placebo - Placebo. Placebo 6 times daily.. Duration 12 weeks. Concurrent medication/care: During the first 10-14 days patients received standard of care plus placebo. Dietary supplementation of additional placebo added thereafter.. Indirectness: No indirectness
Funding	Study funded by industry (Warner Chilcott)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES + PROBIOTIC versus AMINOSALICYLATES

Protocol outcome 1: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrence of diverticulitis at 1 year; Group 1: 10/27, Group 2: 9/32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 8

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES + PROBIOTIC versus PLACEBO

Protocol outcome 1: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrence of diverticulitis at 1 year; Group 1: 10/27, Group 2: 9/29
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 12

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES versus PLACEBO

Protocol outcome 1: Symptom control (pain relief) at Define
- Actual outcome: Global symptom score at 12 weeks and 1 year; The difference between groups did not reach statistical significance at the end of the 12 week intervention period, or at any of the 9 month follow up visits. ;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrence of diverticulitis at 1 year; Group 1: 9/32, Group 2: 9/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 12	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Hospitalisation at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Appendix E: Forest plots

E.1 Antibiotics compared to control for acute diverticulitis

Figure 2: Complication: perforation

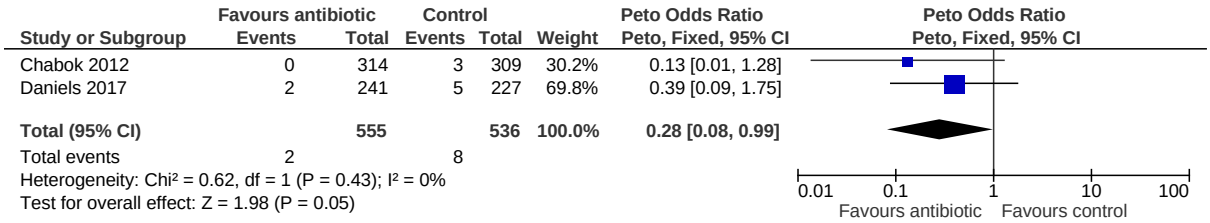


Figure 3: Complication: abscess

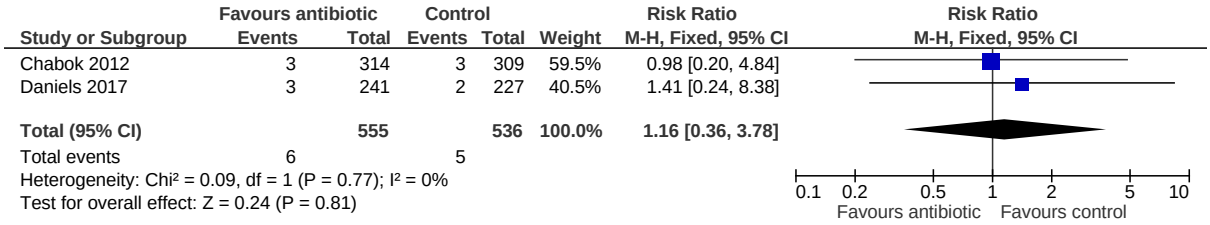


Figure 4: Complication: fistula

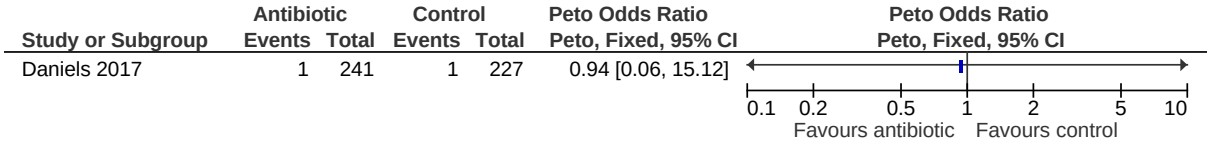


Figure 5: Surgery: sigmoid resection

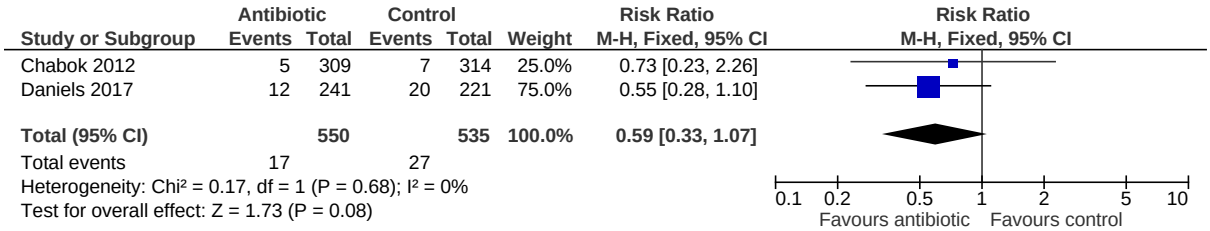


Figure 6: Recurrent diverticulitis

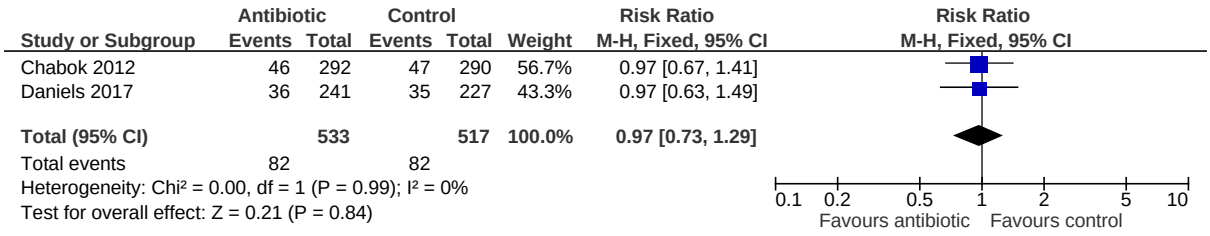


Figure 7: Hospitalisation

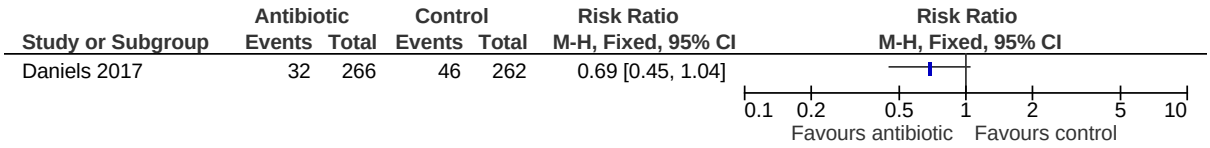
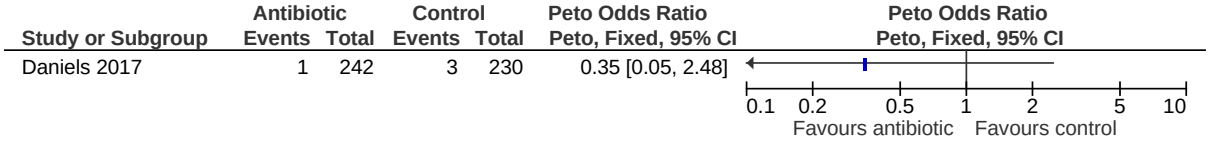


Figure 8: Mortality



E.2 Antibiotics (IV) compared to antibiotics (oral) for acute diverticulitis

Figure 9: Hospitalisation

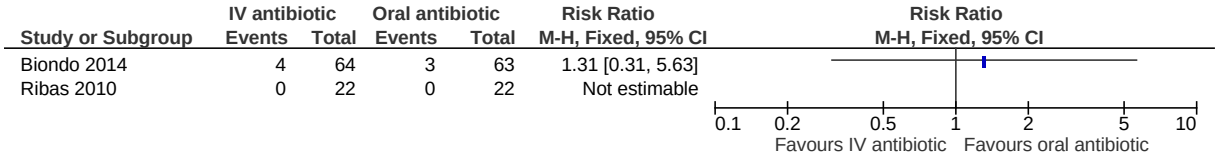


Figure 10: Quality of life (physical)

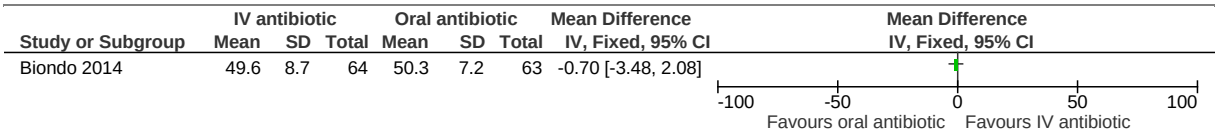


Figure 11: Quality of life (mental)

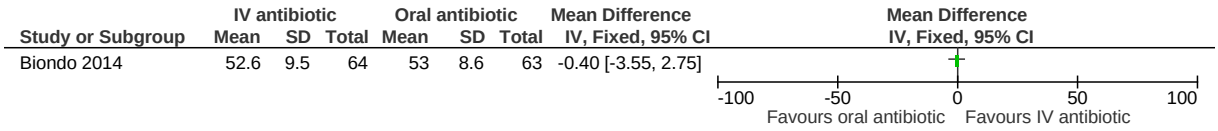


Figure 12: Symptom: abdominal pain

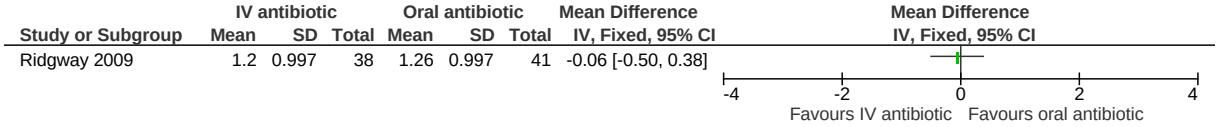
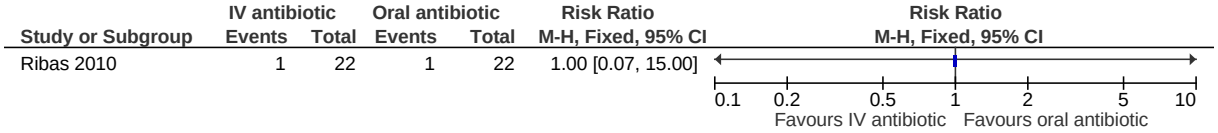


Figure 13: Symptom: people experiencing abdominal pain



E.3 Antibiotics (7 days/long course) compared to antibiotics (4 days/long course) for acute diverticulitis

Figure 14: Complication: abscess

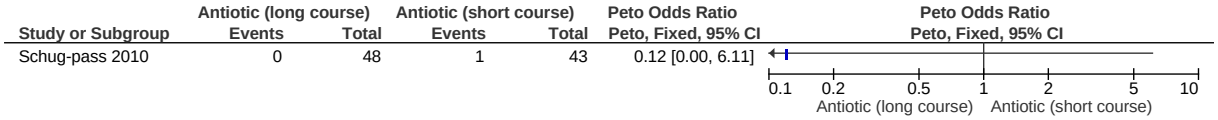


Figure 15: Complication: fistula

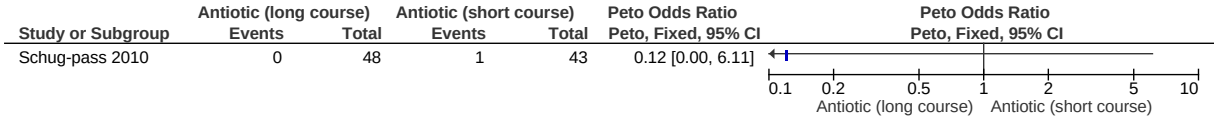


Figure 16: Recurrent diverticulitis

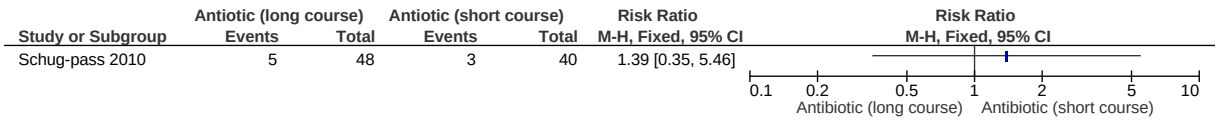
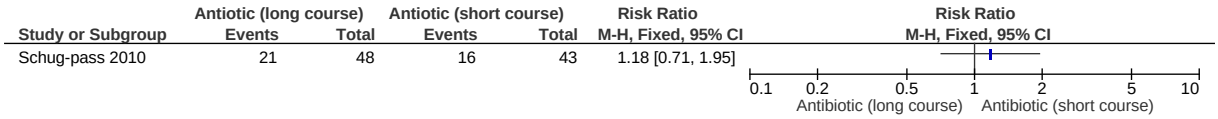
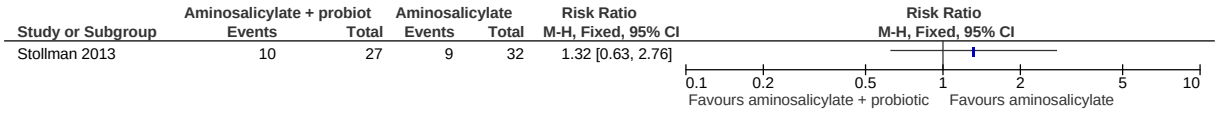


Figure 17: Surgery



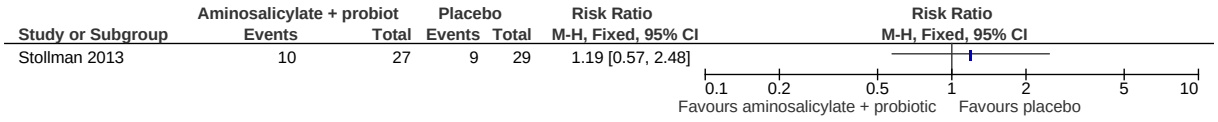
E.4 Aminosalicylate + probiotic vs aminosalicylate for acute diverticulitis

Figure 18: Recurrent diverticulitis



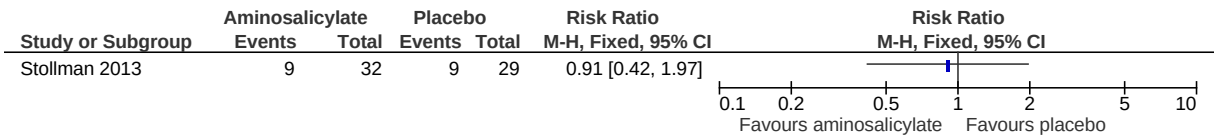
E.5 Aminosalicylate + probiotic vs placebo for acute diverticulitis

Figure 19: Recurrent diverticulitis



E.6 Aminosalicylate vs placebo for acute diverticulitis

Figure 20: Recurrent diverticulitis



Appendix F: GRADE tables

Table 25: Clinical evidence profile: Antibiotic compared to control for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Control	Relative (95% CI)	Absolute		
Complication: perforation (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/555 (0.36%)	1.6%	OR 0.28 (0.08 to 0.99)	10 fewer per 1000 (from 20 fewer to 0 more)[3]	⊕⊕OO LOW	CRITICAL
Complication: abscess (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/555 (1.1%)	0.9%	RR 1.16 (0.36 to 3.78)	1 more per 1000 (from 6 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Complication: fistula (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/241 (0.41%)	0.4%	OR 0.94 (0.06 to 15.12)	0 fewer per 1000 (from 4 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Sigmoid resection (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/550 (3.1%)	5.6%	RR 0.59 (0.33 to 1.07)	23 fewer per 1000 (from 38 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Recurrent diverticulitis (follow-up 12-24 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	82/533 (15.4%)	15.8%	RR 0.97 (0.73 to 1.29)	5 fewer per 1000 (from 43 fewer to 46 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation (follow-up mean 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32/266 (12%)	17.6%	RR 0.69 (0.45 to 1.04)	55 fewer per 1000 (from 97 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/242 (0.41%)	1.3%	OR 0.35 (0.05 to 2.48)	8 fewer per 1000 (from 12 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect value calculated manually using risk difference as event rate <1% and zero events in one arm of at least one study

Table 26: Clinical evidence profile: Antibiotic (IV) compared to antibiotic (oral) for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic (IV)**	**Antibiotic (oral)**	**Relative (95% CI)**	**Absolute**		
Hospitalisation (follow-up 30-60 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/86 (4.7%)	2.4%	RR 1.31 (0.31 to 5.63)	7 more per 1000 (from 17 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-12 (physical) (follow-up mean 60 days; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	63	-	MD 0.7 lower (3.48 lower to 2.08 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: SF-12 (mental) (follow-up mean 60 days; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	63	-	MD 0.4 lower (3.55 lower to 2.75 higher)	⊕⊕⊕O MODERATE	CRITICAL
Symptom: abdominal pain (follow-up mean 3 days; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	38	41	-	MD 0.06 lower (0.5 lower to 0.38 higher)	⊕OOO VERY LOW	CRITICAL

Symptom: abdominal pain (follow-up mean 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/22 (4.5%)	4.6%	RR 1 (0.07 to 15)	0 fewer per 1000 (from 43 fewer to 644 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 27: Clinical evidence profile: Antibiotic (long course) compared to antibiotic (short course) for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic (long course)**	**Antibiotic (short course)**	**Relative (95% CI)**	**Absolute**		
Complication: abscess (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/48 (0%)	1/43 (2.3%)	OR 0.12 (0 to 6.11)	20 fewer per 1000 (from 23 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
								2.3%		20 fewer per 1000 (from 23 fewer to 103 more)		
Complication: fistula (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/48 (0%)	2.3%	OR 0.12 (0 to 6.11)	20 fewer per 1000 (from 23 fewer to 103 more)	⊕OOO VERY LOW	CRITICAL
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/48 (10.4%)	7.5%	RR 1.39 (0.35 to 5.46)	29 more per 1000 (from 49 fewer to 335 more)	⊕OOO VERY LOW	CRITICAL
Surgery (follow-up mean 1 years)												
1	randomised	serious[1]	no serious	no serious	very	none	21/48	37.2%	RR 1.18	67 more per 1000	⊕OOO	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(43.8%)		(0.71 to 1.95)	(from 108 fewer to 353 more)	VERY LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 28: Clinical evidence profile: Aminosalicylate + probiotic compared to Aminosalicylate for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate + probiotic**	**Aminosalicylate**	**Relative (95% CI)**	**Absolute**		
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/27 (37%)	28.1%	RR 1.32 (0.63 to 2.76)	90 more per 1000 (from 104 fewer to 495 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 29: Clinical evidence profile: Aminosalicylate + probiotic compared to Placebo for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate + probiotic**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/27 (37%)	31%	RR 1.19 (0.57 to 2.48)	59 more per 1000 (from 133 fewer to 459 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

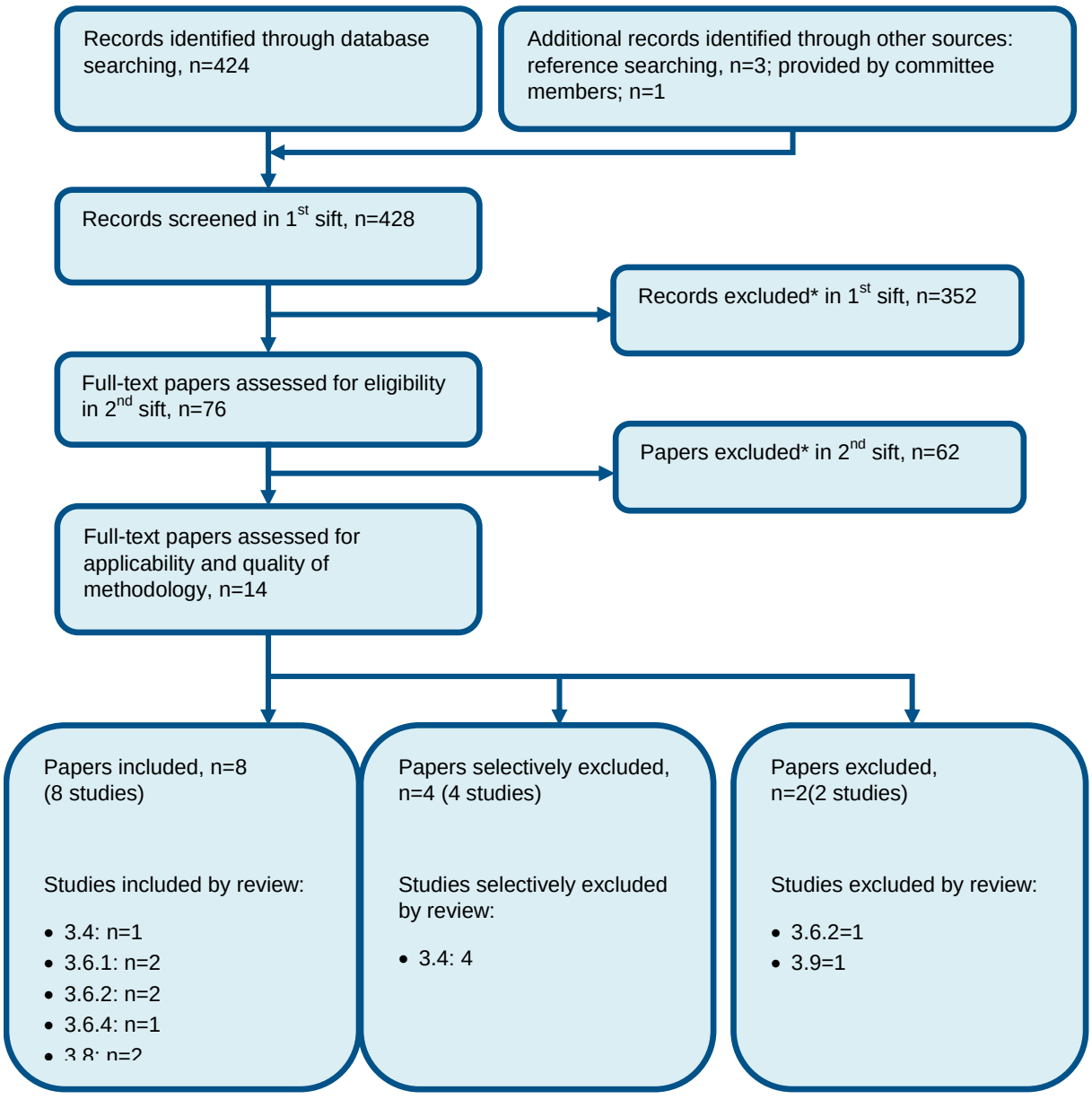
Table 30: Clinical evidence profile: Aminosalicylate compared to Placebo for acute diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate	Placebo	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	9/32 (28.1%)	31%	RR 0.91 (0.42 to 1.97)	28 fewer per 1000 (from 180 fewer to 301 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 21: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3.4 Non-surgical treatment of acute diverticulitis (Evidence review H)

3.6.1 Timing of surgery (Evidence review J)

3.6.2 Laparoscopic versus open resection (Evidence review K)

3.6.4 Primary versus secondary anastomosis (Evidence review M)

3.8 Laparoscopic lavage versus resection for perforated diverticulitis (Evidence review O)

3.9 Management of recurrent diverticulitis (Evidence review P)

1

Appendix H: Health economic evidence tables

Table 31: Health economic evidence tables

Study	Biondo 2014 [5]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: quality of life (SF-12)) **Study design:** Within-trial analysis of multicentre RCT **Approach to analysis:** Cost analysis performed for one hospital, using accounting system of the financial department of the hospital. Costs were attributed to each intervention based on resource use. Quality of life assessment using SF-12 obtained from all patients. Linear mixed-effects model performed on SF-12 data. **Perspective:** Spanish hospital **Follow-up:** 60 days **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Adults (aged 18+) with uncomplicated acute diverticulitis (defined as modified Hinchey classification grade 1a), able to tolerate oral intake and responding to first treatment of pain and fever in emergency department. **Patient characteristics:** Mean age (SD): 56.3 (13.0) Male: 54.5% **Intervention 1:** Hospitalisation: intravenous antibiotics (amoxicillin and clavulanic acid (1g per 125mg)) and fluids for 36-48 hours, then oral feeding. Diet recommendations via information sheets and during ward rounds **Intervention 2:** Outpatient: Oral antibiotics (amoxicillin and clavulanic acid (875mg per 125mg)). Liquid diet with electrolyte-balanced drinks for two days, increased to a low-fibre diet. Diet recommendations via information sheets and by phone call. 1g paracetamol every 8 hours for 10 days, if required.	**Total costs (mean per episode/patient):** Intervention 1: £1,653 Intervention 2: £541 Incremental (2−1): saves £1,112 (95% CI: NR; p=NR) **Currency & cost year:** 2009-2011 euros (presented here as 2011 UK pounds)[(a)] **Cost components incorporated:** Diagnostics, treatments, follow-up, hospital beds based on length-of-stay	**Quality of life (physical) 60 days (SF-12) (mean per patient):** Intervention 1 was 0.7 lower (3.48 lower to 2.08 higher) **Quality of life (mental) (SF-12) 60 days (mean per patient):** Intervention 1 was 0.4 lower (3.55 lower to 2.75 higher)	Intervention 2 dominates Intervention 1 **Analysis of uncertainty:** n/a

Data sources				
Health outcomes: DIVER trial [5] **Quality-of-life weights:** SF-12 questionnaire administered to all patients with linear fixed effects model performed on SF-12 data. **Cost sources:** Financial department of Bellvitge University Hospital, 2009-2011				
Comments				
Source of funding: NR **Limitations:** Population limited to people with uncomplicated acute diverticulitis who responded to first treatment with antibiotics and analgesia. 126 of 258 (49%) patients assessed for eligibility were not suitable for randomisation as they did not meet the exclusion criteria or refused to be included in the trial (n=49). 3 patients in the hospitalisation group and 1 in the outpatient group refused to comply with their allocated protocol (analysis was conducted according to intention-to-treat). Treatment effect from DIVER trial only. Follow-up of only 60 days may omit important costs and outcomes. Costs reported interchangeably as per patient and per episode. Cost year not reported. Costs were calculated in one centre (Bellvitge University Hospital) whereas quality of life assessment was conducted in colorectal units of 5 tertiary hospitals. No conflicts of interest reported. **Other:**				
Overall applicability: Partially applicable(b)		**Overall quality:** Potentially serious limitations(c)		

Abbreviations: CCA: cost–consequences analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years; RCT: randomised clinical trial; SF-12: 12 item short-form health survey
(a) Converted using 2011 purchasing power parities [49]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 32: Studies excluded from the clinical review

Study	Exclusion reason
Alonso 2010[2]	Incorrect study design
Al-sahaf 2008[1]	Incorrect study design
Amin 1984[3]	Incorrect study design
Banasiewicz 2017[4]	Not review population
Biondo 2012[6]	Systematic review: studies already included in review
Brar 2013[7]	Incorrect study design
Brochmann 2016[8]	Confounders not adjusted for
Byrnes 2009[9]	Literature review
Carter 2017[10]	Systematic review: studies already included in review
Chabok 2013[12]	Not in English
Chang 2015[13]	Incorrect interventions
Chautems 2002[14]	Incorrect study design
Chiu 2001[15]	Incorrect interventions
Colas 2017[16]	Incorrect study design
Dahl 2018[17]	Systematic review: methods are not adequate/unclear
Dharmarajan 2011[19]	Incorrect study design
Dughera 2004[20]	Incorrect interventions
Eglinton 2012[21]	Incorrect study design
Estrada ferrer 2016[22]	Incorrect study design
Ha 2017[23]	Incorrect study design
Hjern 2007[24]	Evidence from RCTs already included.
Isacson 2014[25]	Confounders not adjusted for
Issa 2012[26]	Incorrect study design
Jackson 2014[27]	Systematic review: studies already included in review
Kaushik 2016[28]	Literature review
Kellum 1992[29]	Confounders not adjusted for
Khan 2016[30]	Systematic review: studies already included in review
Kruis 2017[31]	Not review population
Lanas 2013[33]	Not review population
Leahy 1985[34]	Not review population
Macias 2004[36]	Incorrect study design
Mali 2016[37]	Incorrect study design
Markun 2014[38]	Not in English
Mayl 2017[39]	Literature review
Mizuki 2005[40]	Incorrect study design

Study	Exclusion reason
Moon 2007[41]	Incorrect interventions
Mora lopez 2017[42]	Protocol only
Moya 2016[44]	Incorrect study design
Mueller 2005[45]	Incorrect interventions
Neumann 1991[47]	Not in English
Ogawa 2013[48]	Incorrect interventions
Parente 2013[50]	Not review population
Park 2010[51]	Incorrect study design
Park 2011[52]	Confounders not adjusted for
Picchio 2016[53]	Not review population
Raskin 2014[54]	Not review population
Rodriguez-cerrillo 2010[57]	Incorrect study design
Rueda 2012[58]	Incorrect interventions
Sallinen 2014[59]	Incorrect study design
Sanchez-velazquez 2016[60]	Systematic review: studies already included in review
Scarpa 2015[61]	Evidence already attained through RCTs
Shabanzadeh 2012[63]	Systematic review: studies already included in review
Shaikh 2007[64]	Incorrect study design
Stam 2017[65]	Incorrect study design
Tan 2013[67]	Incorrect interventions
Thomas 2013[68]	Protocol only
Titos-garcia 2017[69]	Incorrect study design
Trespi 1997[71]	Not in English
Trespi 1999[70]	Not in English
Tursi 2002[73]	Confounders not adjusted for
Tursi 2007[74]	Not review population
Tursi 2008[72]	Incorrect study design
Tursi 2016[75]	Not review population
Unlü 2010[77]	Protocol only
Unlu 2012[76]	Not review population
Urushidani 2017[78]	Systematic review: studies already included in review
Van dijk 2018[79]	Systematic review: methods are not adequate/unclear
Van ooteghem 2013[81]	Incorrect study design
Vetter 2016[82]	Incorrect study design
Weisberger 2009[83]	Incorrect study design

I.2 Excluded health economic studies

Table 33: Excluded health economic studies

Reference	Reason for exclusion
Lorente 2013 [35] (Spain)	This study was selectively excluded in favour of the Biondo 2014[5] within-trial analysis. This study was considered inferior because it

Excluded studies

Reference	Reason for exclusion
	was based on an observational study without adequate controlling for confounders.
Mizuki 2005 [40] (Japan)	This study was assessed as not applicable because the costs were from 1997-2002 and were considered too old to be informative.
Moya 2012 [43] (Spain)	This study was selectively excluded in favour of the Biondo 2014[5] within-trial analysis. This study was considered inferior because it was based on an observational study without adequate controlling for confounders. Also costs were presented per episode instead of per patient.
Park 2011 [52] (Korea)	This study was selectively excluded in favour of the Biondo 2014[5] within-trial analysis. This study was considered inferior because it was based on an observational study without adequate controlling for confounders.

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Appendix J: Research recommendations

What is the clinical and cost effectiveness of antibiotics for the management of acute complicated diverticulitis in primary care?

There is a need for high quality research to establish the effectiveness of prescribing antibiotics to people displaying symptoms of suspected acute uncomplicated diverticulitis in primary care. Since diagnostic tests such as CT scans are not available in primary care and results for blood tests take longer to arrive than in secondary care, primary care physicians are more likely to use antibiotics as a precaution in situations where acute diverticulitis is suspected. Thus, to avoid complications of antibiotics resistance and to ensure consistency in practice, this is an area which needs research to inform evidence based guidance.

PICO question	Population: Adults 18 years and over with a diagnosis of first episode suspected acute diverticulitis **Intervention/comparison:** Antibiotics No intervention/placebo **Outcomes:** Critical: • Progression of disease • Hospitalisation • Need for surgery • Complications (infections, abscesses, perforation, stricture, fistula) • Recurrence rates of acute diverticulitis (minimum 1year) • Quality of life Important: • Mortality • Symptom control (pain relief) • Side effects of o Antibiotics: nausea and vomiting, diarrhoea, infections related to antibiotics o Analgesics: nausea and vomiting, constipation Study design: RCTs
Importance to patients or the	High quality research in this area would identify whether antibiotics should be prescribed for acute diverticulitis in primary care.

population	
Relevance to NICE guidance	Currently there is uncertainty about whether antibiotics should be prescribed in primary care for people with symptoms of acute diverticulitis. To avoid unnecessary antibiotic exposure, research in this area is needed.
Relevance to the NHS	A research recommendation could inform the requirement of antibiotics in primary care and avoid further complication i.e. antibiotic resistance, in people with suspected first episode acute diverticulitis.
Current evidence base	There are no RCTs in this area.
Equality	Patients of Asian origin may develop right sided diverticula and so present differently with right sided abdominal pain. These people should be identified, and sub-group analysis performed.
Study design	Randomised controlled trial
Feasibility	There is a potentially large population of patients with this condition who could be recruited to a trial in primary care.
Other comments	
Importance	High-The committee consider this an important area for further research although they are aware of current research ongoing in the area

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