

## Is the outpatient management of acute diverticulitis safe and effective? A systematic review and meta-analysis

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### Abstract

**Background** In Western countries, the incidence of acute diverticulitis (AD) is increasing. Patients with uncomplicated diverticulitis can undergo a standard antibiotic treatment in an outpatient setting. The aim of this systematic review was to assess the safety and efficacy of the management of acute diverticulitis in an outpatient setting.

**Methods** A literature search was performed on PubMed, Scopus, Embase, Central and Web of Science up to September 2018. Studies including patients who had outpatient management of uncomplicated acute diverticulitis were considered. We manually checked the reference lists of all included studies to identify any additional studies. Primary outcome was the overall failure rates in the outpatient setting. The failure of outpatient setting was defined as any emergency hospital admission in patients who had outpatient treatment for AD in the previous 60 days. A subgroup analysis of failure was performed in patients with AD of the left colon, with or without comorbidities, with previous episodes of AD, in patients with diabetes, with different severity of AD (pericolic air and abdominal abscess), with or without antibiotic treatment, with ambulatory versus home care unit follow-up, with or without protocol and where outpatient management is a common practice. The secondary outcome was the rate of emergency surgical treatment or percutaneous drainage in patients who failed outpatient treatment.

**Results** This systematic review included 21 studies including 1781 patients who had outpatient management of AD including 11 prospective, 9 retrospective and only 1 randomized trial. The meta-analysis showed that outpatient management is safe, and the overall failure rate in an outpatient setting was 4.3% (95% CI 2.6%–6.3%). Localization of diverticulitis is not a selection criterion for an outpatient strategy ( $p=0.512$ ). The other subgroup analyses did not report any factors that influence the rate of failure: previous episodes of acute diverticulitis ( $p=0.163$ ), comorbidities ( $p=0.187$ ), pericolic air ( $p=0.653$ ), intra-abdominal abscess ( $p=0.326$ ), treatment according to a registered protocol ( $p=0.078$ ), type of follow-up ( $p=0.700$ ), type of antibiotic treatment ( $p=0.647$ ) or diabetes ( $p=0.610$ ). In patients who failed outpatient treatment, the majority had prolonged antibiotic therapy and only few had percutaneous drainage for an abscess (0.13%) or surgical intervention for perforation (0.06%). These results should be interpreted with some caution because of the low quality of available data.

**Conclusions** The outpatient management of AD can reduce the rate of emergency hospitalizations. This setting is already part of the common clinical practice of many emergency departments, in which a standardized protocol is followed. The data reported suggest that this management is safe if associated with an accurate selection of patients (40%); but no subgroup analysis demonstrated significant differences between groups (such as comorbidities, previous episode, diabetes). The main limitations of the findings of the present review concern their applicability in common clinical practice as it was impossible to identify strict criteria of failure.

**Keywords** Acute diverticulitis · Outpatient · Uncomplicated diverticulitis · Outpatient management

### Introduction

In Western countries the incidence of diverticulosis is constantly increasing and is reported approximately in 30% of people at the age of 60 years and 60% of people older

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than 80 years [1]. Only 15% of patients with diverticulosis develop acute diverticulitis (AD) [2]. The severity of presentation of acute diverticulitis (AD) may range from mild to life threatening, depending on the extent of inflammation and peritoneal contamination [3]. In the last years, some studies based on administrative databases showed an increase of hospitalization for AD. Often patients with mild diverticulitis are admitted to hospital and kept nil by mouth, while intravenous fluids and antibiotic therapy are administered [4]. The median length of stay for AD is 4 days [5]. This increases healthcare costs significantly [6, 7]. For these reasons patients with mild diverticulitis receive antibiotic treatment in an outpatient setting [8].

Several scientific societies have reported either a consensus or an expert opinion paper about the outpatient management of patients with AD. The characteristics of patients are different in these statements:

- The ASCRS (American Society of Colon and Rectal Surgeons) includes only patients who tolerate oral hydration, without relevant comorbidities, or who do have adequate support at home [9].
- The WES (World Emergency Society) includes patients with no comorbidities [10].
- The SICCR (Italian Society of Colon and Rectal Surgery) reported that an ambulatory treatment protocol is safe and effective for a majority of patients [11].

Currently there is a gap in evidence supporting this approach. These recommendations are supported from low (1C) or moderate (1B) quality evidence based respectively on observational studies or randomized controlled trials (RCTs) with important limitations.

Despite these limits, the aim of this systematic review was to assess the safety and efficacy of the management of AD in an outpatient setting.

## Materials and methods

A systematic literature search was performed on PubMed, Scopus, Embase, Central and Web of Science up to 13 September 2018. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12] was followed. The following search strategies were used in PubMed: (“outpatients” [MeSH Terms] OR “outpatients” [All Fields] OR “outpatient” [All Fields]) AND (“diverticulitis” [MeSH Terms] OR “diverticulitis” [All Fields]).

All titles and abstracts were assessed to select those focusing on outpatient management of patients with uncomplicated colonic diverticulitis. Successively, the full-text of these studies were evaluated by two authors (RC and SG). In PubMed, the function “related articles” and in Scopus

“related documents” were used to research other articles. The references of the included studies were evaluated for other potential trials. Two other authors (RM and PR) evaluated the eligibility of each study.

### Inclusion criteria

All control and observational studies, irrespectively of their size, publication status and language, which included patients who had outpatient management for uncomplicated colonic diverticulitis. Randomized and not-randomized comparative studies were included if they focused on emergency hospitalization versus no hospitalization in patients with acute colonic diverticulitis.

### Exclusion criteria

Studies in which the clinical evaluation after hospital discharge was not reported.

### Primary outcome

Overall failure of outpatient treatment. The failure was defined as any emergency hospital admission in patients treated in an outpatient setting. The time to event was reported from 11 studies: the readmission in hospital was reported during the first 30 days from discharge in 7 studies [13–19] and during the first 60 days from discharge in 4 studies [20–23]. We considered 60 days the time limit. A subgroup analysis was performed:

- Failure of outpatient setting in patients with AD of the left colon.
- Failure of outpatient setting in patients with or without comorbidities.
- Failure of outpatient setting in patients with previous episodes of AD.
- Failure of outpatient setting in patients with diabetes.
- Failure of outpatient setting in patients with different severity of AD (pericolic air and abdominal abscess).
- Failure of outpatient setting in patients with or without antibiotic treatment.
- Failure of outpatient setting in patients where outpatient management is a common practice.
- Failure of outpatient setting in patients with ambulatory versus home care unit follow-up.
- Failure of outpatient setting in patients with or without protocol.

### Secondary outcome

Rate of emergency surgical treatment or percutaneous drainage in patients with failure of outpatient setting.

## Statistical analyses

Outpatient failure rates were pooled under a random effects model (REML) using the MetaFor package in R (3.4.2). Prior to synthesis proportions were transformed using the Freeman–Tukey double arcsine transformed proportion; all data in the results section have been backtransformed. No correction factor was added to each proportion. Default values in Metafor's escalc and rma functions were used otherwise. Cochrane's  $Q$  and its  $p$  value,  $I^2$ , and  $\tau^2$  are included as statistical measures of heterogeneity. A subgroups moderator analysis was performed with the MetaFor package. Cochrane's  $Q$ , degrees of freedom, and the  $p$  value of  $Q$  are reported for each moderator variable as measures of heterogeneity. The QM statistic was used a measure of statistical significance for differences between sub-groups.

To explore bias, a funnel plot was visually examined, and a leave-one-out sensitivity analysis was conducted for each outcome using MetaXL. Note that studies were not excluded based on the results of the sensitivity analyses unless otherwise noted; visual analyses of funnel plots have been shown to be inaccurate for the reliable identification of publication bias [24]. We only used funnel plots to identify studies for exclusion in an exploratory sensitivity analysis. Publication bias tests were not used unless they met the criteria specified in Ionnidas and Trikalinos [25].

## Risk of bias in included studies

The assessment of methodological quality was performed independently by two authors (RC and MA), who assessed methodological quality of included studies using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions for randomized controlled trials (RCTs) [26]. The methodological index for nonrandomized studies (MINORS) [27] was used to evaluate the methodological quality of the included comparative and noncomparative studies.

The protocol of this systematic review and meta-analysis was registered on PROSPERO CRD42018096781 (<http://www.crd.york.ac.uk/prospero>). In single-arm meta-analysis, GRADE [28] is not used to evaluate the quality of outcomes included; recently, Zafer et al. modified GRADE to evaluate evidence quality for meta-analysis of single arm studies [29]; we used the GRADE' modifications reported by Zafer.

## Results

The PRISMA flow diagram is presented in Fig. 1. The search strategy identified 3301 studies and 4 additional records identified through other sources. After de-duplication, 2302 citations were screened of which 2275 were excluded based

on title and abstract. For the remaining 27 studies, the full texts were obtained and reviewed. Six studies were excluded on the basis of reasons listed in the section of characteristics of excluded studies [20, 21, 30–33]. In total, 21 studies fulfilled the inclusion criteria [13–19, 22, 23, 34–45], (Table 1). No ongoing study was found.

## Studies excluded

Six studies reported early discharge from hospital and described the possibility of outpatient management in patients with AD [20, 21, 30–33] but the outpatient treatment was not performed [20, 21, 30–32]. One study performed only an analysis on risk factors for severe outcomes in uncomplicated AD [33].

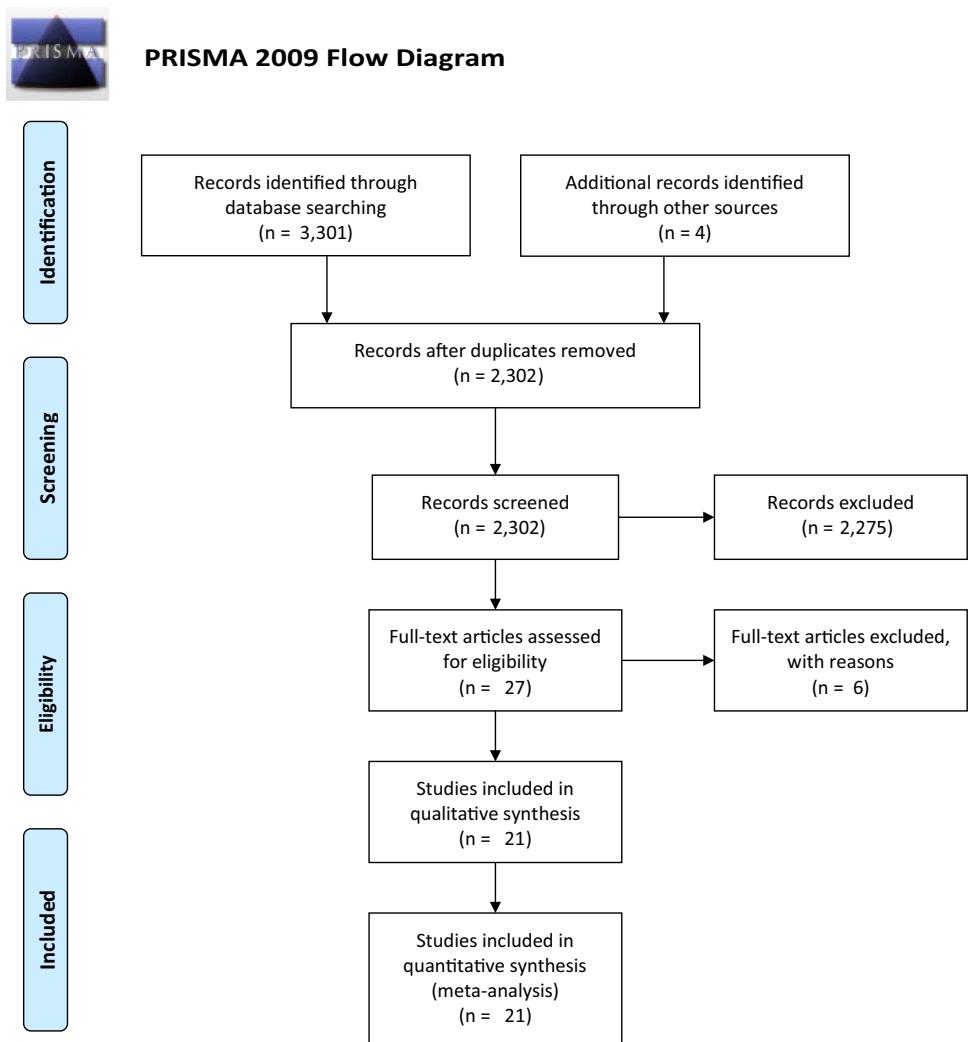
## Characteristics of included studies

Twenty-one studies that met the inclusion criteria were included in this review in which 1781 patients were treated for AD in an outpatient setting (Table 1). The enrollment of patients was performed between 1997 and 2015. The study design was prospective (13 studies) and retrospective cohort study (7 studies), only 1 study was a randomized control trial (RCT). Only 12 studies reported the site of the diverticulitis: 100% in the left colon (6 studies), between 94–96% (4 studies), 84% (1 study). A study reported only patients with AD localized in right colonic side. Patient's age and sex were very heterogeneous (Table 2). Fourteen studies reported the service that performed the follow-up.

## Risk of bias of included studies

The summary of the quality assessment of the included RCT [23] is shown in SDC 1. The principal limit of this trial is that there was a lack of blinding to surgeons and patients, in effect, it is impossible to blind surgeon teams or patients to surgery. The risk for blinding of outcome assessment (detection bias) was unclear, in effect Biondo et al. [23] does not describe that the personnel for data collection and analysis were independent from the study. The methodological evaluation of included studies with the MINORS scale showed that, among noncomparative studies, 7 scored 13 points, 3 had 12 points, and 3 a total of 11 points out of 16 points. In the included comparative study, 1 scored 22 points, 1 scored 20 points, 1 scored 19 points, 2 scored 18 points, 1 scored 17 points and 1 scored 14 points over a total of 24 (SDC 2). The modified Zafer' GRADE reported "very low-quality evidence" of included studies, in effect, there is a downgrade for the lack of internal comparators (SDC 3).

**Fig. 1** PRISMA flow chart of the literature search



### Strategy of the studies

Sixteen studies (76.1%) included a protocol (1399 patients, 78.5%), but only 9 studies reported protocol approval and/or registration (954 patients, 53.56%). Nine studies were performed in hospitals in which outpatient management was already used as common clinical practice (778 patients, 43.68%). The follow-up reported ranged between 0 and 74 months. Only 9 studies reported the follow-up (349 patients, 19.6%). Five studies reported an ambulatory follow-up (400 patients), while in 5 studies therapy at home and follow-up of the outpatients (204 patients) were provided by the home care units (Table 3). These provided admitted care to public hospital patients in the comfort of their home. Skilled nurses administer the daily dose of intravenous antibiotic and take blood samples, if need. A specialist doctor performed a home visit two or three times during the week.

### Patients with diverticulitis evaluated in the emergency department

Nine studies reported data about the overall number of patients with AD evaluated in the Emergency Department (2198 patients). In these studies, only 879 patients (40.0%) were enrolled to outpatient management. Seventeen studies (77.3%) reported data about the overall number of patients with uncomplicated AD evaluated (2394). In these studies, only 1498 patients (62.6%) were enrolled in outpatient management.

### Confirmation of diagnosis and evaluation of inflammatory process

In the majority of the studies (90.5%) the diagnosis and the evaluation of inflammatory process was performed with

**Table 1** Characteristics of included studies

References	Nation	Study design	Time of enrollment	Patients with diverticulitis	Patients with uncomplicated diverticulitis	Managed as outpatients
Mizuki et al. [13]	Japan	Prospective cohort	1997–2002	137	83	70
Peláez et al. [34]	Spain	Prospective cohort	2003–2005	NR	53	40
Martín Gil et al. [35]	Spain	Prospective cohort	2000–2006	NR	NR	74
Rodríguez-Cerrillo et al. [36]	Spain	Prospective cohort	2007–2009	NR	NR	24 <sup>a</sup>
Alonso et al. [14]	Spain	Prospective cohort	2003–2008	NR	96	70
Park et al. [37]	Korea	Prospective cohort	2007–2009	NR	103	40
Latuwak [38]	USA	Retrospective cohort	2010–2011	NR	50	21
Rueda et al. [39]	Spain	Retrospective cohort	2008–2010	NR	56	38
Moya et al. [40]	Spain	Prospective clinical control trial	2007–2009	111	34 <sup>b</sup>	32 <sup>b</sup>
Rodríguez-Cerrillo et al. [41]	Spain	Prospective clinical control trial	2011–2012	NR	72	34 <sup>c</sup>
Ünlü et al. [22]	The Netherlands	Retrospective cohort	2004–2012	627	214	118
Lorente et al. [42]	Spain	Retrospective cohort–clinical control trial	2005–2011	NR	136	90
Mora Lopez et al. [43]	Spain	Prospective clinical control trial	2010–2013	205	149	68
Biondo et al. [23]	Spain	Randomized control trial	2009–2011	258	63	63
Isacson et al. [15]	Sweden	Prospective cohort	2012–2013	NR	NR	155
Estrada Ferrer et al. [44]	Spain	Prospective cohort	2013–2014	110	99	68
Mali et al. [16]	Finland	Prospective cohort	2014–2015	248	161	140
Moya et al. [45]	Spain	Retrospective cohort	2010–2014	262	235	224
Joliat et al. [17]	Switzerland	Retrospective cohort	2006–2012	NR	540	171
Sirany et al. [18]	USA	Retrospective cohort	2010–2015	240	NR	96
Jasacson et al. [19]	Sweden	Prospective clinical control trial	2011–2014	NR	254	51 (20%)
					240	145 (60%)

<sup>a</sup> 2008–2009<sup>b</sup> Only patients with co-morbidities<sup>c</sup> Only elderly patients

the use of abdominal computed tomography (CT) scan with contrast media. Only Isacson [15, 19] and Mizuki [13] reported the use of ultrasonography. Few studies reported the time of radiological evaluation, which was in all cases 24 h after admission. Similarly, few studies reported the time at discharge from the Emergency Department ranging between 12 and 48 h. Inclusion criteria were CT findings of inflammation limited to the diverticulum (focal diverticulitis), colonic wall thickening ( $> 4$  mm), soft tissue stranding of the pericolic fat and small collection of pericolic free peritoneal air and fluid. Nine studies (746 patients, 41.9%) did not include patients with intra-abdominal abscess, while 6 studies included any intra-abdominal abscess  $\leq 2$  cm in diameter (753 patients, 42.3%) and 3 studies any intra-abdominal abscess  $\geq 2$  cm in diameter (142, 8.0%) (Table 3).

### Presence of comorbidities

In some studies, only selected patients were included in the outpatient's settings, while in other studies patients were included without restriction for comorbidities [18, 19, 36, 39–41, 45]. The most common comorbidities reported were diabetes (50%) and heart failure (43.7%).

### Previous episodes of diverticulitis

Seventeen studies reported the previous episodes of diverticulitis; of these, 14 studies (82.35%) considered these episodes as an exclusion criteria for the outpatient setting. Another exclusion criterion in all studies was the lack of family support.

**Table 2** Characteristics of patients reported in the included studies

References	Age, years, mean $\pm$ SD	Sex, male %	Left side	Follow-up (months) mean $\pm$ SD
Mizuki et al. [13]	NR	NR	NR	30.8 (0.9–58) <sup>a</sup>
Peláez et al. [34]	56.9 (31–87) <sup>a</sup>	50%	100%	18 $\pm$ 6
Martín Gil et al. [35]	55 (31–90) <sup>a</sup>	59.5%	NR	NR
Rodríguez-Cerrillo et al. [36]	73.4 (67–84) <sup>a</sup>	NR	NR	NR
Alonso et al. [14]	57	54.3%	100%	39 $\pm$ 23
Park et al. [37]	36.8 $\pm$ 10.4	20	0 <sup>++</sup>	19
Latuwak [38]	62 (28–89) <sup>a</sup>	100%	NR	NR
Rueda [39]	63.97	NR	NR	NR
Moya et al. [40]	56.06 (32–83) <sup>a</sup>	50%	84%	7 $\pm$ 9
Rodríguez-Cerrillo et al. [41]	77 (71–90) <sup>a</sup>	82.4%	NR	NR
Ünlü et al. [22]	54.5 $\pm$ 11.1	42.4%	100%	48 $\pm$ 26.4
Lorente et al. [42]	58.75 $\pm$ 15	44.4%	NR	17 $\pm$ 5
Mora Lopez et al. [43]	59 (25–90) <sup>a</sup>	NR	NR	NR
Biondo et al. [23]	55.9 (13.4)	48.5%	100%	2
Isacson et al. [15]	57 $\pm$ 12	34.8%	100%	3
Estrada Ferrer et al. [44]	NR	NR	100%	6 (3–12) <sup>a</sup>
Mali et al. [16]	57 (25–86) <sup>a</sup>	36%	94%	1
Moya et al. [45]	57.7 (19–89) <sup>a</sup>	47.7%	95%	15 $\pm$ 5
Joliat et al. [17]	53 (44–64)	63.7%	96%	46.5 (29–74) <sup>a</sup>
Sirany et al. [18]	NR	50%	96%	36.5 (25–43) <sup>a</sup>
Jasacson et al. [19]	61	37%	NR	1
	60	33%		

SD standard deviation

<sup>a</sup>Median, range<sup>++</sup> Only right colonic side

## Antibiotic treatment after the discharge from emergency department

Eighteen studies reported data about the use of antibiotics during the home stay. Three studies did not report the use of antibiotics after discharge from the emergency department [15, 16, 19]. The type of home antibiotic treatment was heterogeneous. The highest number of authors used co-amoxiclav 1.2 g TDS IV or ciprofloxacin 400 mg BD IV and metronidazole [14, 18, 23, 34, 35, 37, 40, 45]. Others administrated ertapenem every day [36, 39, 41] or intravenous ceftriaxone 2 g/24 h [43, 44]. Estrada Ferrer et al. [44] performed a tailored antibiotic therapy based on AD severity.

## Endoscopic evaluation during the follow-up

In ten studies, a colonoscopy or a CT colonography was performed during the follow-up to exclude a synchronous cancer, between 1 and 3 months after the acute episode.

## Results

### Overall outpatient failure rate

Out of 1781 patients across 21 studies, the overall pooled outpatient failure rate was 4.3% (95% CI 2.64, 6.28). There was a statistically significant amount of heterogeneity,  $I^2=64.84\%$ ,  $Q(20)=53.3$ ,  $p<0.001$  (Table 3) (Fig. 2). Similar results were reported in the RCT by Biondo et al., with a raw failure rate of 4.5% (3/66) [23].

We conducted several sensitivity analyses. First, a visual analysis of Fig. 2 indicated that the studies performed by Rueda et al. [39], Estrada Ferrer et al. [44], and Sirany et al. [18] appeared to be outlying studies. Without those two studies, the outpatient failure rate was 3.3% (95% CI 2.08, 4.82), but a statistically significant amount of heterogeneity remained,  $I^2=42.6\%$ ,  $Q(17)=29.4$ ,  $p<0.031$ . A leave-one-out-analysis indicated that no single study's exclusion changed the pooled failure rate more than 1%. Visual analyses of funnel plots indicated that the three outlying studies [39, 44] and one other article [35] fell slightly outside

**Table 3** Outpatient failure rate

Subgroup	Studies	N	FailureRate	95% CIs	$I^2$	$T^2$	Q	P of Q
All studies	21	1781	4.3	2.64	6.28	64.84	0.01	53.23
Abscess: $QM(2)=2.24, p=0.326$								<0.001
Abscess < 2 cm	6	753	5.57	2.3	10.01	79.44	0.01	19.82
No Abscess	9	746	3.43	1.86	5.35	24.94	0.00	11.15
Abscess > 2 cm	3	142	1.3	0	6.45	54.55	0.01	4.46
Presence of comorbidities: $QM(1)=1.74, p=0.187$								
No comorbidity	12	1094	3.95	2.31	5.92	44.75	<0.00	20.38
Comorbidity	5	335	6.93	1.46	15.25	79.11	0.02	18.73
Diabetic: $QM(df=1)=2.59, p=0.610$								
No diabetic patients	6	451	3.59	1.93	5.66	0	0	1.83
Diabetic patients	5	319	4.82	0.11	13.78	83.72	0.02	21.32
Antibiotic: $QM(df=2)=0.87, p=0.647$								
Oral	10	799	4.17	1.91	7.11	63.36	0.01	24.41
Endovenous	4	164	4.35	0	15.48	80.93	0.03	14.51
No antibiotics	3	440	2.73	1.33	4.54	<0.01	0.00	0.02
Common practice: $QM(df=1)=0.712, p=0.399$								
Not common practice?	12	1003	3.72	2	5.84	51.51	<0.00	22.04
Common practice	9	778	5.06	1.86	9.43	77.86	0.01	27.84
Type of follow-up: $QM(df=1)=0.18, p=0.700$								
Home care	5	204	4.53	0.14	12.68	74.38	0.02	14.51
Ambulatory	5	400	3.73	1.94	5.98	0	<0.00	2.08
Protocol: $QM(df=2)=5.09, p=0.078$								
Registered protocol	9	954	4.26	2.48	6.43	46.07	<0.00	15.08
Unregistered protocol	7	445	2.15	0.33	5.01	47.54	<0.00	11.49
None protocol	5	382	7.9	2.43	15.75	81	0.01	15.97
Left colon diverticulitis: $QM(df=1)=0.43, p=0.512$								
Not left colon diverticulitis?	15	1267	3.79	1.76	6.41	71.8	0.01	43.52
Left colon diverticulitis	6	514	5.38	2.78	8.66	47.38	<0.00	9.43
Previous diverticulitis: $QM(df=1)=1.94, p=0.163$								
No previous diverticulitis	14	1253	4.43	2.46	6.84	62.43	<0.00	32.85
Previous diverticulitis	3	254	8.51	5.28	12.37	0	<0.00	1.4
Pericolic air: $QM(1)=0.20, p=0.653$								
Without pericolic air	11	861	4.71	2.44	7.54	57.86	<0.01	23.19
With pericolic air	7	738	3.95	1.08	8.22	81.3	0.01	27.01

The QM statistic indicates the degree of statistical significance for between group effects. The Q statistic is a measure of statistical heterogeneity between studies within a group

of the funnel area (Fig. 3). Removing those 4 studies, the pooled failure rate decreased to 3.8% (95% CI 2.6%, 5.2%) and heterogeneity was also reduced significantly ( $I^2=28.5\%$ ,  $Q(16)=22.0, p<0.145$ ).

### Subgroup analysis

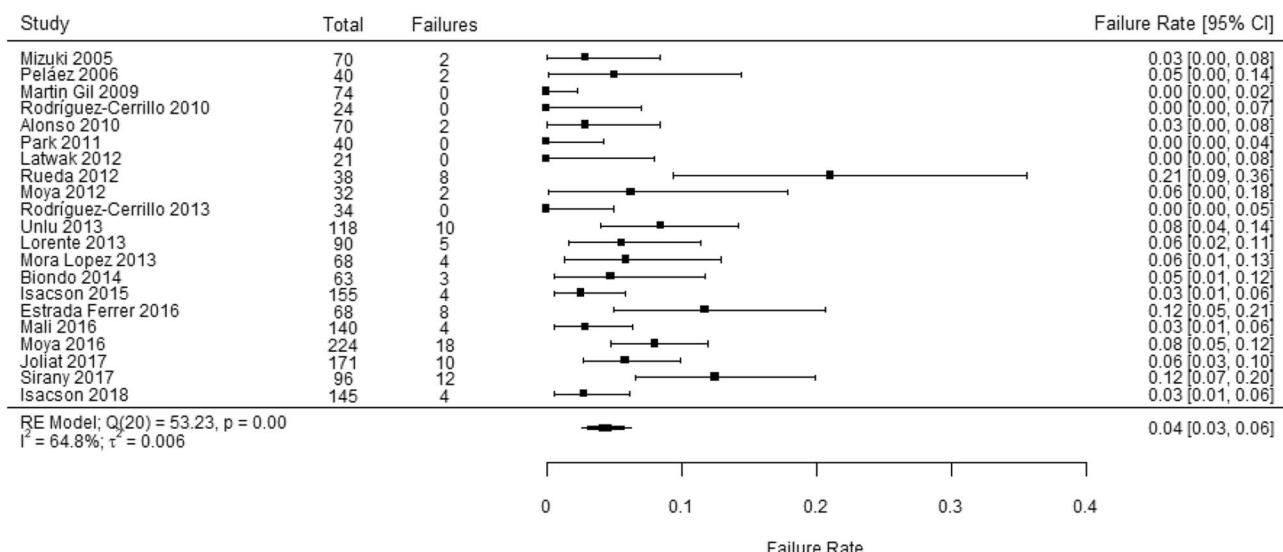
#### Outpatient failure rates for patients with diverticulitis of the left colon

In the 6 studies that reported on 514 patients with diverticulitis only of the left colon, the pooled outpatient failure rate

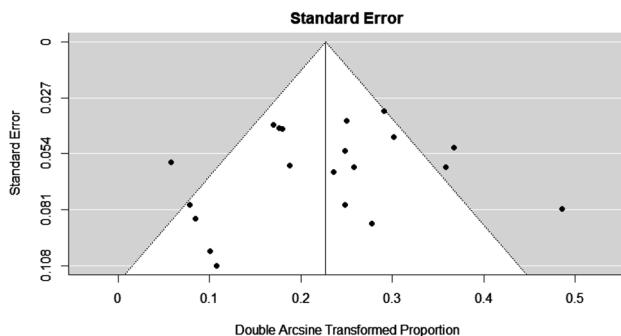
was 5.4% (95% CI 2.8%, 8.7%) compared to a 3.8% pooled failure rate (95% CI 1.76, 6.41) in 15 studies that reported on patients without diverticulitis of the left colon. The difference between groups was not statistically significant:  $QM(1)=0.43, p=0.512$  (Table 3; Fig. 4).

#### Outpatient failure rates for patients with or without comorbidities

The overall outpatient pooled failure rate for patients without comorbidities was 4.0% (95% CI 2.3%, 5.9%, 12 studies, 1094 patients) compared to 6.9% for patients with



**Fig. 2** Overall pooled outpatient failure rate



**Fig. 3** Funnel plot for all studies

comorbidities (95% CI 1.5%, 15.6%, 6 studies, 335 patients). The difference between groups was not statistically significant:  $QM(1) = 1.74, p = 0.187$  (Table 3; Fig. 4).

#### Outpatient failure rates for patients with or without previous episodes of diverticulitis

The pooled failure rate for patients with previous episodes of diverticulitis was 8.5% (95% CI 5.28, 12.37, 3 studies, 254 patients) compared to 4.4% (95% CI 2.5%, 6.8%, 14 studies, 1253 patients) for patients without previous episodes. The difference was not statistically significant however:  $QM(1) = 1.94, p = 0.163$  (Table 3).

#### Outpatient failures rates for patients with diabetes

There was no statistically significant difference in the outpatient failure rates between diabetic and nondiabetic patients,  $QM(1) = 2.59, p = 0.610$ . Diabetic patients' failure rate

(4.8%, 95% CI 0.11% 13.8%, 5 studies, 319 patients) was 4.8% compared to 3.6% (95% CI 1.9%, 5.7%, 6 studies, 451 patients) for patients without diabetes. (Table 3).

#### Outpatient failure rates for patients with or without pericolic air

Patients with pericolic air had an outpatient failure rate of 4.0% (95% CI 1.1%, 8.2%, 7 studies, 738 patients) compared to an outpatient failure rate of 4.7% for patients without pericolic air (95% CI 2.4, 7.5, 11 studies, 861 patients). The difference in outpatient failure rates between groups was not statistically significant:  $QM(1) = 0.20, p = 0.653$ .

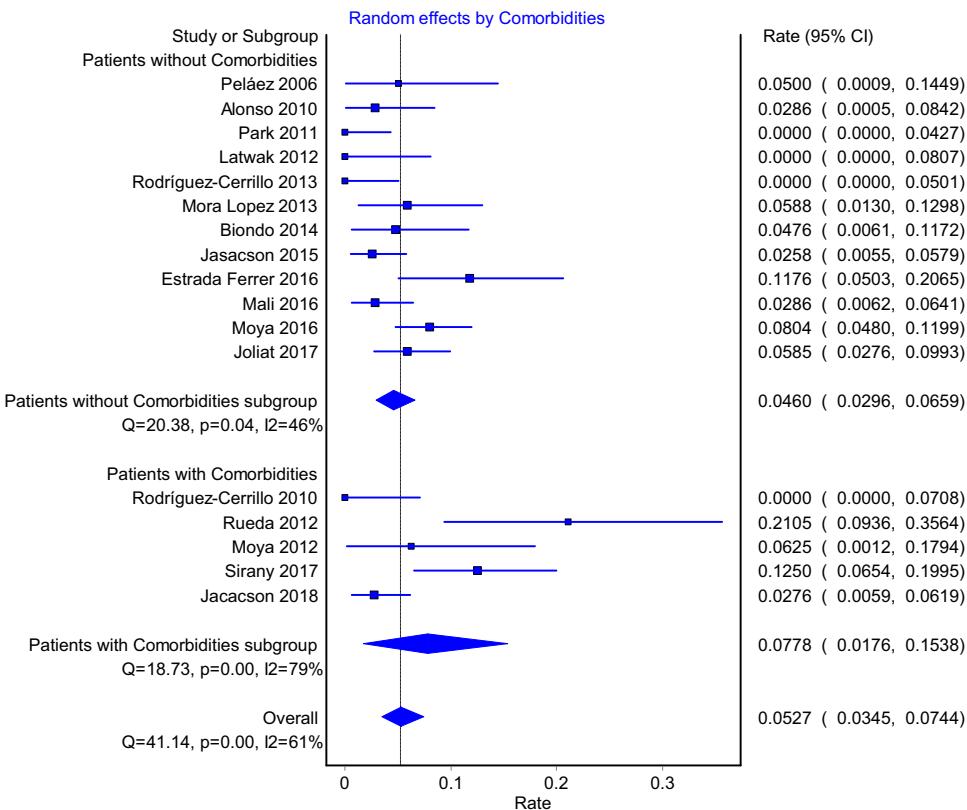
#### Outpatient failure rates for patients with or without abdominal abscess

There was no statistically significant difference in outpatient failure rates between patients without an abscess (3.4%, 95% CI 1.9%, 5.4%, 9 studies, 746 patients); patients with an abscess, but less than 2 cm (5.6%, 95% CI 2.3%, 10.1, 6 studies, 753 patients) and patients with an abscess greater than 2 cm (1.3%, 95% CI 0.0, 6.45%, 3, studies, 142 patients). The difference between groups was not statistically significant:  $QM(2) = 2.24, p = 0.326$ .

#### Outpatient failure rates for patients by type of antibiotic treatment

There was no statistically significant difference in outpatient failure rates between types of antibiotic treatment,  $QM(2) = 0.87, p = 0.647$ . Patients without antibiotic treatment at home had an outpatient failure rate of 2.7% (95%

**Fig. 4** Pooled rates for patients with and without comorbidities



CI 1.3%, 4.5%, 3 studies, 440 patients), compared to 4.2% (95% CI 1.9%, 7.1%, 10 studies, 799 patients) for patients treated with oral antibiotics, and 4.4% (95% CI 0.0, 15.5%, 4 studies, 164 patients) for patients treated with endovenous antibiotics. The difference between groups was not statistically significant:  $QM(df=2)=0.87, p=0.647$ .

#### Failure of outpatient setting in patients where outpatient management is a common practice

The rate of failure in the outpatient setting was 1.3% lower in hospitals where outpatient management was a common clinical practice (5.1%, 95% CI 1.9%, 9.4%, 9 studies, 778 patients) compared to hospitals where it was not a common practice (3.7%, 95% CI 2.05, 5.8%, 12 studies, 1003 patients). The difference was not statistically significant:  $QM(1)=0.71, p=0.399$  (Table 3).

#### Failure of outpatient setting in patients with ambulatory versus home care unit follow-up

The overall failure rate was lower in patients who underwent ambulatory follow-up (3.7%, 95% CI 1.9%, 6.0%, 5 studies, 400 patients) than patients who were in a home care unit (4.5%, 95% CI 0.1%, 12.7%, 5 studies, 204 patients); the

difference was not statistically significant between groups however:  $QM(1)=0.18, p=0.700$  (Table 3).

#### Outpatient failure rate in patients with or without protocol

The outpatient failure rate was 7.9% (95% CI 2.4%, 15.8%, 382 patients) in the 5 studies with no protocol, 2.2% (95% CI 0.3%, 5.0%, 7 studies, 445 patients) in the 7 studies with an unregistered protocol, and 4.3% (95% CI 2.5%, 6.4%, 954 patients) in the 9 studies with a registered protocol. Type of protocol registration was not a statistically significant moderator of outpatient failure rates:  $QM(2)=5.09, p=0.078$  (Table 3).

#### Results of analysis: secondary outcome

##### Rate of emergency surgical treatment or percutaneous drainage in patients with failure of outpatient setting

All studies, except Rueda et al. [39] and Joliat et al. [17], reported on the treatment of patients with outpatient failure (1572). The majority of patients were treated by further antibiotic therapy (1569); only few patients with failure of outpatient management underwent percutaneous drainage for an abscess (0.13%, 2/1572) or emergency surgical treatment for perforation (0.06%, 1/1572).

## Discussion

This systematic review included 21 studies and enrolled 1781 selected patients with AD had outpatient management. The meta-analysis showed that outpatient management is safe, but the subgroup analysis did not report any factors (previous episodes of AD, intra-abdominal abscess, strategy of the studies, types of follow-up, antibiotic treatment after discharge from the emergency department) that influence the rate of failure.

The first outcome of this systematic review is the failure of outpatient management, although the rate of severe adverse events in uncomplicated diverticulitis is very low [46, 47]. This review showed that the localization of diverticulitis in the sigmoid colon is not a selection criterion for outpatient management; there is no difference in failure rate between overall (3.79%) versus a selected group with left colon diverticulitis (5.38%). This result disagrees with the results of Yoo et al. [32], in which the hospital stay was significantly lower in right diverticulitis ( $p = < 0.001$ ).

Outpatient treatment can be performed in patients with uncomplicated diverticulitis (Hinchey 1); the failure of an outpatient strategy is higher in patients with complicated diverticulitis. This setting is suggested in all guidelines, but the level of evidence to support this management is very low and the selection of patients is not homogeneous. Differentiating between uncomplicated and complicated AD is possible only with clinical evaluation and/or laboratory evaluation; many studies reported CT scan as the standard needed for adequate selection. An international, expert-based, consensus statement regarding the management of AD and all guidelines also support CT scan of the abdomen and pelvis as the most suitable modality with which to gauge the severity of AD [48]. In effect during the past decade, CT scan has dramatically changed the way diverticulitis is diagnosed. CT clearly depicts diverticulitis in its early stage, demonstrates complications with high sensitivity (79–99%), and is of use in noninvasive therapeutic approaches such as percutaneous drainage [49, 50]. The American Society of Colon and Rectal Surgeons reported “CT scan of the abdomen and pelvis is the most appropriate initial imaging modality in the assessment of suspected diverticulitis”. Although CT scan is the standard imaging evaluation for the diagnosis and staging of diverticulitis, a step-up approach with CT scan performed after an inconclusive or negative ultrasound (US), has been suggested for patients with suspected AD [10]. Differently, the ASCRS suggested that ultrasound and magnetic resonance imaging (MRI) “can be useful alternatives in the initial evaluation of a patient with suspected AD” [9]. In the common clinical practice, these protocols may be not feasible [51]; in effect, the CT scan might be difficult to

perform in every Emergency Department during the first 24 h after admission [49]. For this reason, multidisciplinary hospital teams should develop local protocols based on the available hospital resources.

The CT scan selection criteria are very different between the studies; a lower failure rate is reported only in the patients without abscesses. The presence of a small amount of pericolic air is not associated with a higher incidence of failure. It is not possible to determine if some laboratory markers can be an index for the severity of diverticulitis; no study has reported the evaluation of white blood cell (WBC) or C-reactive protein (CRP) levels. Yoo et al. [32] evaluated WBCs and CRP as severity markers, but this analysis does not show any significant prediction of outcome. However, Joung et al. reported that a level of  $\text{CRP} \geq 200 \text{ mg/L}$  is associated with a severe clinical course. The patients who have outpatient management were followed up in the outpatient clinic, with the exception of studies from Spain, where a home care service is active so that therapy administration and follow-up take place in a patient's home. The results of the home care service are not significantly better than the standard ambulatory service. The intravenous antibiotic therapy does not cause significant improvement compared to oral antibiotic treatment [52–55]. These results are in line with those of the literature. In effect, some RCTs reported that oral antibiotics are not inferior to intravenous antibiotics in achieving resolution of clinically diagnosed diverticulitis [56]. The antibiotic therapy is not superior to no-antibiotic therapy. Our results agree with the Cochrane systematic review and meta-analysis published from Shabanzadeh and Wille-Jørgensen [57] and with the statement of some societies:

- The Italian Society of Colorectal Surgery (SICCR) suggests avoiding antibiotic therapy in acute uncomplicated diverticulitis since it may not improve short- or long-term outcomes. Use on a case-by-case basis should possibly be considered.
- The World Society of Emergency Surgery (WSES) reported “antimicrobial therapy can be avoided in immunocompetent patients with uncomplicated diverticulitis without systemic manifestations of infection”.

Our results are similar to those of other systematic reviews concerning the ambulatory management of AD in selected patients. In our systematic review the number of studies ( $n=21$ ) is the largest in effect the study reporting a greater number is that published by van Dijk et al. [58] reported only 19 studies. In other two systematic reviews, Balasubramanian et al. [59] reported ten studies and Jakson et al. [60] reported nine studies. Balasubramanian et al. do not report differences in failure rates of medical treatment (6.5 versus 4.6%) or in recurrence rates (13.0 versus 12.1%) between outpatients and

inpatients. Ambulatory treatment is associated with a lower hospital cost (savings of between 600 versus 1900 euros). Four studies [23, 35, 40, 41] reported a cost-saving ranging from 42 to 82%. Our review does not compare the results of inpatient versus outpatient management and analyses, like Jakson and van Dijk. Differently from Van Dijk et al. we performed a subgroup analysis for the failure of the outpatient setting. The major limitation is the high risk of bias of the reported papers.

Malpractice claims are increasingly important aspects of medical practice and frequently of emergency medicine. The Institute of Medicine (IOM) report estimated the total cost of medical error as USD 17–29 billion per annum [61]. In medical malpractice cases, the defendant's behavior is compared to the standard of care for that specific situation [62]. The standard of care is most commonly defined as, “that reasonable and ordinary care, skill, and diligence as physicians and surgeons in good standing in the same neighborhood, the same general line of practice, ordinarily have been exercising in like cases”.

With regard to outpatient management in patients with AD, management should be standardized to reduce medical malpractice and to increase patient safety. Accurate selection of patients (uncomplicated versus complicated AD) is mandatory [63]. Medical records should be accurately and clearly compiled. Any medical prescriptions should be listed in detail. The patient should be given correct and clear information and should be advised to return to the emergency room as soon as symptoms worsen.

In this meta-analysis there is a high statistical heterogeneity (“larger differences in the outcome of the individual studies than could be expected to result from chance alone”) [64], which may result from clinical (“differences in patient populations and treatment protocol”) [64] or methodological heterogeneity (“differences in study design and risk of bias”) [64].

It was impossible to avoid the clinical heterogeneity using strict criteria of study selection, based on design, populations, severity of AD, type of antibiotic treatment and outcomes. Information such as comorbidities, CT staging, antibiotic treatment and clinical follow-up was often not available. Other limitations were the differences in measurement of exposure time and types of clinical evaluation (ambulatory or home care) and incomplete follow-up.

Furthermore, this heterogeneity may be due to the small sample size of the studies and overlooked unpublished data, especially regarding the failure of outpatient management.

## Conclusions

The outpatient management of acute diverticulitis, performed in selected patients, can reduce the rate of emergency hospitalisation and the related costs. This is already

part of the common clinical practice of many emergency departments, in which a standardized protocol is followed. The data reported suggests that outpatient management is safe if patients are properly selected (40%) with an overall pooled outpatient failure rate of only 4.3% (95% CI 2.64%, 6.28%); fewer of whom required percutaneous drainage for an abscess (0.13%) or emergency surgical treatment for perforation (0.06%).

No subgroup analysis demonstrated significant differences between groups (comorbidities, previous episode, diabetes, use of antibiotics).

The degree of heterogeneity between studies limits the strength of conclusions drawn but highlights the need for further work in this area with well-conducted studies and further randomized studies.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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