Risk of colectomy after conservative treatment of diverticulitis of the left hemicolon complicated by abdominal or pelvic abscess: protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Acute diverticulitis of the sigmoid colon is increasingly treated by a non-operative approach. The need for colectomy after recovery from a flare of acute diverticulitis of the left colon, complicated diverticular abscess is still controversial. The primary aim of this study is to assess the risk of interval emergency surgery by systematic review and meta-analysis.

Methods and analysis The systematic review and meta-analysis will be conducted in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement. PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and EMBASE will be screened for the predefined searching term: (Diverticulitis OR Diverticulum) AND (Abscess OR pelvic abscess OR pericolic abscess OR intraabdominal abscess) AND (surgery OR operation OR sigmoidectomy OR drainage OR percutaneous drainage OR conservative therapy OR watchful waiting). All studies published in an English or German-speaking peer-reviewed journal will be suitable for this analysis. Case reports, case series of less than five patients, studies without follow-up information, systematic and non-systematic reviews and meta-analyses will be excluded. Primary endpoint is the rate of interval emergency surgery. Using the Review Manager Software (Review Manager/RevMan, V.5.3, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) meta-analysis will be pooled using the Mantel-Haenszel method for random effects. The Risk of Bias in Non-randomized Studies of interventions tool will be used to assess methodological quality of non-randomised studies. Risk of bias in randomised studies will be assessed using the Cochrane developed RoB 2-tool.

Ethics and dissemination As no new data are being collected, ethical approval is exempt for this study. This systematic review is to provide a new insight on the need for surgical treatment after a first attack of acute diverticulitis, complicated by intra-abdominal or pelvic abscesses. The results of this study will be presented at national and international meetings and published in a peer-reviewed journal.

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Strengths and limitations of this study

- By systematic review, the study intends to provide a comprehensive and structured analysis of natural disease history after conservative treatment of patients with diverticulitis complicated by an abscess to be used for further guideline development and evidence-based clinical treatment.
- Included data will be transparently and rigorously analysed concerning its impact on the primary and secondary endpoints of the review using the Cochrane developed Risk of Bias in Non-randomized Studies of Interventions tool.
- Since data inclusion of the latest systematic review on this subject was terminated in February 2015, new publications from the last 5 years will be added.
- Limitation of this analysis will be the fewness of randomised controlled trials on the specific subject.

INTRODUCTION

Rationale

Acute diverticulitis of the left colon is one of the most frequent abdominal disorders in the industrialised world. A population-based study from the USA showed an increasing incidence of acute diverticulitis within the last decades from 115/100,000 patient-years between 1980 and 1989 to 188/100,000 between 2000 and 2007.1 In Germany, 125,417 patients were treated for diverticular disease in 2014. Of these, 24,067 had a complicated stage of the disease with a total of 40,902 surgical procedures (Data: Federal Statistical Office, information 12/2015). Although the majority of patients remain asymptomatic, 10%-25% develop diverticulitis during their lifetime.15%-20% thereof suffer from a complicated course.2,3 In this context, the overall risk of recurrence varies up to 48%.4,7 However, a differentiated analysis of
Table 1  Inclusion and exclusion parameters

| Inclusion parameters | Exclusion parameters |
|----------------------|----------------------|
| Journal type         |                      |
| Peer-reviewed        | Non-peer reviewed    |
| Study type           |                      |
| Randomised           | Congress articles    |
| Non-randomised       | Case reports         |
| Prospective          | Case series          |
| Retrospective        | Studies without follow-up information |
|                      | Non-systematic reviews |
|                      | Systematic reviews with or without meta-analysis |
| Language             | Other                |
| English              |                      |
| German               |                      |
| Diagnosis            |                      |
| CT-proven pericolic, intra-abdominal or pelvic abscess | No results on a CT-scan available |
| Initial therapy      |                      |
| Conservative treatment | Emergency or urgent operation |
| Follow-up            |                      |
| Follow-up information on the outcome of initial conservative therapy available | No follow-up available |

recurrences shows that the risk of a complicated relapse of the disease is significantly lower with a probability of 3%–5%. Consequently, the first disease episode bears the highest risk for a complicated course while the frequency of recurrences does not correlate with complication rates. The risk of perforation decreases over time, as does the rate of emergency surgeries. Based on these findings, it is not surprising that the treatment of diverticular disease has fundamentally changed in recent years towards a less invasive and more frequently conservative approach with increasing individualisation of therapy. However, the optimal treatment of patients having suffered from pericolic, intra-abdominal or pelvic abscess after recovery from the acute inflammation is still not ultimately defined. In their meta-analysis, Gregersen et al could demonstrate that abscesses with a diameter up to 3 cm can be successfully treated by antibiotics whereas the best strategy for larger abscesses could not be precisely identified. As disease recurrence was 25% after an initial non-operative treatment in this study, the authors conclude that additional research is necessary to characterise the best treatment. An earlier systematic review by Lamb et al from 2014 could not draw a final conclusion due to heterogeneity, low sample size of studies as well as selection and treatment biases of current studies. Data included into the systematic review with meta-analysis suggest that patients with an acute diverticulitis have a high probability of sigmoidectomy while non-operative therapy may lead to chronic or recurrent disease. The aim of this analysis is to provide an up-to-date systematic review with meta-analysis which focuses on the need for surgical treatment in patients suffering from acute diverticulitis.

Hypothesis and objectives
Hypothesis of the planned systematic review and meta-analysis is that elective colectomy in the inflammation-free interval is not necessary in patients after a first flare of acute diverticulitis of the left colon complicated by abdominal or pelvic abscess, if patients are free of symptoms. It is supposed that the renouncement of surgery neither leads to an increased number of emergency operations and unplanned stoma formations, nor to an increase of morbidity and mortality compared with patients undergoing elective colectomy.

The aim of this work is to identify all reports including a follow-up of patients who suffered from diverticulitis of the left colon, complicated by abdominal or pelvic abscess. Primary endpoint is the risk of interval emergency surgery. Secondary endpoints comprise the rate of interval non-planned elective surgery, the rate of stoma formation, the number of recurrence flares, the number of recurrent abscess, disease associated morbidity and mortality.

METHODS AND ANALYSIS
The review protocol is constructed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement as well as to the suggestions of the Cochrane Handbook for systematic reviews.

Amendments
If protocol amendments become necessary during the course of the review, each amendment will be endowed by the date of the change and a specific description of the change and the underlying reason.

Eligibility criteria
Study design and inclusion criteria
Randomised and non-randomised studies published in English-speaking and German-speaking, peer-reviewed journals focusing on acute diverticulitis of the left hemicolectomy (descending and sigmoid colon), complicated by pericolic, abdominal or pelvic abscess are eligible for the systematic review. No restrictions are planned in regard to the date of publication. Congress articles, articles in other languages than English and German, case reports, case series, studies without follow-up information, and previous systematic reviews with or without meta-analysis...
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Open access will be excluded but will be consulted for additional sources. Only one study per institution will be selected to reduce the risk for doubled inclusion of data. Studies are required to report on the outcome after initial conservative therapy for a pericolic, intra-abdominal or pelvic abscess due to diverticulitis of the left colon. These analyses can include either a study group (WW) and a control group (descending colon: left hemicolectomy/sigmoid colon: sigmoidectomy), or a follow-up of patients merely conservatively treated without surgical control or of patients who undergo elective sigmoidectomy. Studies in which the diagnosis was not made or verified by a CT-scan will not be included into the analysis.

Table 2 Definitions

Abscesses

| Size   |   |
|--------|---|
| A1: 0–1 cm |   |
| A2: 1–2.9 cm |   |
| A3: 3.0–5.9 cm |   |
| A4: >6 cm |   |

Localisation

- Pericolic: immediate contact to the bowel wall
- Intra-abdominal: distant from the bowel wall, above the pelvic level
- Pelvic: distant from the bowel, in the pelvis

Initial treatment

- Conservative treatment: Non-operative care
- Non-antibiotic non-interventional treatment
- Antibiotic (p.o. vs intravenous) treatment
- Percutaneous drainage placement (±antibiotics)

Surgical setting

- Emergent operation: Surgery within 24 hours after admission
- Urgent operation: Surgery within the hospital stay
- Elective operation: Surgery within a scheduled later hospital stay

its accuracy by comparing respective results with those of relevant systematic reviews. To extend potential hits, the ‘related articles’ function of PubMed will be used. Additionally, all references of selected articles are planned to be screened by hand-search for additional publications matching inclusion criteria. As additional sources, the Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov will be screened for studies, which are recently ongoing or completed. To avoid unnecessary double-publication, the PROSPERO-Database and the WHO-Trials Database were checked for similar systematic reviews, which are currently underway or finalised. The search strategy is depicted in figure 1.

Study records

Data management

All abstracts identified by the primary search will be stored with title and respective uniform resource locator to the original source in a Microsoft Excel database. Therein, reasons for potential exclusion will be given. After the primary exclusion process, duplicates from different databases will be deleted. Then, full-texts of all included abstracts will be analysed. In case of exclusion after full-text screening, reasons will be attributed. After completed selection of all full-text articles, data will be extracted as indicated in table 3 and by the use of standardised data extraction forms and then transferred to the RevMan Software V.5.3 (see earlier: statistical analysis) by AT. Data inclusion in the review software will be rechecked by a second author (SS).

Data selection process

All reports will be independently screened for predefined data items by two authors (SM, SS) through each phase

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Figure 1 Search strategy. CENTRAL, Central Register of Controlled Trials.

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Data source and search strategy

PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and EMBASE will be systematically screened for the predefined searching algorithm (Diverticulitis OR Diverticulum) AND (Abscess OR pelvic abscess OR pericolic abscess OR intra-abdominal abscess) AND (surgery OR operation OR sigmoidectomy OR drainage OR percutaneous drainage OR conservative therapy OR watchful waiting). The term was tested on its accuracy by comparing respective results with those of relevant systematic reviews. To extend potential hits, the ‘related articles’ function of PubMed will be used. Additionally, all references of selected articles are planned to be screened by hand-search for additional publications matching inclusion criteria. As additional sources, the Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov will be screened for studies, which are recently ongoing or completed. To avoid unnecessary double-publication, the PROSPERO-Database and the WHO-Trials Database were checked for similar systematic reviews, which are currently underway or finalised. The search strategy is depicted in figure 1.

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of the review. If any inconsistency occurs concerning in- or exclusion of a study, data will be presented to a third independent researcher (DW) to draw a final decision. If data are incomplete, the study author will be contacted to provide lacking information.

**Data items**

Data items to be extracted from identified reports are depicted in table 2. Inclusion criteria of this systematic review were set according to the patient, intervention, comparison, outcome, study type question (table 4).

| Event/intervention of interest | Extracted parameters |
|--------------------------------|----------------------|
| **Index hospital stay**        | ▶ First author       |
|                                | ▶ Year of publication|
|                                | ▶ Study type         |
|                                | ▶ Patient age        |
|                                | ▶ Patient gender     |
|                                | ▶ Body mass index (BMI)|
|                                | ▶ Immunosuppression  |
|                                | ▶ Steroid intake     |
|                                | ▶ Abscess localisation (pericolic, abdominal, pelvic) |
|                                | ▶ Abscess size (mm)  |
|                                | ▶ Antibiotic treatment|
|                                | ▶ Placement of a percutaneous drainage |
|                                | ▶ Scheduling for watchful waiting or elective resection |
|                                | ▶ Recommendation for further treatment: no surgery, mandatory elective surgery, optional elective surgery on case-by-case base |

**Watchful waiting**

Baseline information on recurrence

▶ Interval recurrence
▶ Length until recurrence (months)
▶ Length of follow-up (months)
▶ Number of recurrent flares
▶ Severity of recurrence (uncomplicated/complicated)
▶ Abscess within recurrence
▶ Abscess localisation (abdominal/ pelvic)
▶ Abscess size (mm)
▶ Interval perforation with generalised peritonitis
▶ Treatment of recurrence (conservative, interventional, emergency operation, elective operation)
▶ Morbidity for recurrence (Clavien-Dindo)
▶ Mortality for recurrence

Additional items in case of emergency interval colectomy

▶ Surgical approach for emergency surgery (open colectomy (left hemicolectomy or sigmoid resection) with colorectal anastomosis with/without loop ileostomy; laparoscopic colectomy (left hemicolectomy or sigmoid resection) with colorectal anastomosis with/without loop ileostomy, open Hartmann’s procedure, laparoscopic Hartmann’s procedure)
▶ Postoperative 30 days morbidity (Clavien-Dindo)
▶ Stoma formation
▶ Stoma closure
▶ Timing of stoma closure

**Elective colectomy**

Baseline information on recurrence

See above

Additional items in case of emergent interval sigmoid resection

See above

Items on elective interval sigmoid resection

▶ Timing of elective colectomy (weeks after initial flare)
▶ Surgical approach for elective surgery (open colectomy with colorectal anastomosis with/without loop ileostomy; laparoscopic colectomy with colorectal anastomosis with/without loop ileostomy, open Hartmann’s procedure, laparoscopic Hartmann’s procedure)
▶ Postoperative 30 days morbidity (Clavien-Dindo)
▶ Stoma formation
▶ Stoma closure
▶ Timing of stoma closure

| Event/intervention of interest | Extracted parameters |
|--------------------------------|----------------------|
| **Elective colectomy**         | ▶ Stoma formation    |
|                                | ▶ Stoma closure       |
|                                | ▶ Timing of stoma closure |
|                                | Additional items if the procedure was changed to elective interval sigmoid resection |
|                                | ▶ Surgical approach for emergency surgery (open colectomy (left hemicolectomy or sigmoid resection) with colorectal anastomosis with/without loop ileostomy; laparoscopic colectomy (left hemicolectomy or sigmoid resection) with colorectal anastomosis with/without loop ileostomy, open Hartmann’s procedure, laparoscopic Hartmann’s procedure)
|                                | ▶ Postoperative 30 days morbidity (Clavien-Dindo)
|                                | ▶ Stoma formation    |
|                                | ▶ Stoma closure       |
|                                | ▶ Timing of stoma closure |

**Items on elective interval sigmoid resection**

▶ Timing of elective colectomy (weeks after initial flare)
▶ Surgical approach for elective surgery (open colectomy with colorectal anastomosis with/without loop ileostomy; laparoscopic colectomy with colorectal anastomosis with/without loop ileostomy, open Hartmann’s procedure, laparoscopic Hartmann’s procedure)
▶ Postoperative 30 days morbidity (Clavien-Dindo)
▶ Stoma formation
▶ Stoma closure
▶ Timing of stoma closure

Continued
Table 4 PICOS-question

| P Patient, Population, Problem | Patients with diverticulitis complicated by pericolic/abdominal or pelvic abscess. No restrictions on comorbidities, age groups or sex |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| I Intervention, prognostic factor or exposure | Patients receiving antibiotic, interventional (percutaneous drainage placement, PD) or antibiotic and PD within initial treatment and who undergo ‘watchful-waiting’ without planned elective colectomy in the further course |
| C Comparison or intervention (if appropriate) | Patients who undergo elective sigmoidectomy after initial non-operative treatment of the acute flare |
| O Outcome you would like to measure or achieve | Rate of interval emergency surgery, rate of interval non-planned elective surgery, rate of interval stoma formation, severity of recurrent diverticulitis (uncomplicated/complicated), number of recurrence flares, recurrent abscess, morbidity, mortality |
| S Study types | Randomised, non-randomised, prospective, retrospective |

Outcomes and prioritisation

Primary and secondary outcome parameters are depicted in table 5.

Subgroup analysis

Subgroup analysis will be performed for the following groups:

- Patients initially treated with and without percutaneous drainage, if sufficient information on the preinterventional abscess size enables the formation of balanced groups.
- Abscess localisation: pericolic versus intra-abdominal versus pelvic abscess.

Quality assessment and risk of publication bias

According to the recommendations of the Cochrane network, the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I)\(^\text{17}\) will be used to assess methodological quality of included non-randomised studies. Thereby, studies are screened and judged for a low, moderate, serious or critical risk of confounding bias, selection bias or bias occurring due to different definition or explanation of interventions, missing data, measurement of outcome or reporting results and an overall estimated risk of bias is estimated.\(^\text{17}\) In this context, quality assessment reflects how well the identified study is associated with the primary endpoint of this systematic review regardless of the primal objective of the included study itself. Risk of bias in randomised studies will be assessed using the Cochrane developed RoB 2-tool.\(^\text{18}\) This tool constitutes signalling questions, which need to be answered for different predefined domains of each randomised trial. Algorithm based evaluation of theses answers leads to the final judgement. Thereby, the selected trial can be estimated to be at low or high risk of bias or is tainted with ‘some concerns’.

Data synthesis and statistical methods

In case of sufficient homogenous data, a meta-analysis will be conducted. Statistical analyses will be performed using the Review Manager Software (Review Manager/RevMan, V.5.3, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Numbers of patients, continuous variables, OR and HRs with their corresponding descriptive data (95% CI; p value, etc) with the primary and secondary endpoints will be extracted and meta-analysis will be constructed using the Mantel-Haenszel method for random effects. Heterogeneity is planned to be estimated using the inconsistency statistic (I\(^2\)) and defined as absent or as low level of heterogeneity if I\(^2\) is zero or less than 50%. All results will be expressed as OR with their corresponding 95% CI and a two-sided p value will be calculated of each meta-analysis with a level of significance of α=0.05.

Confidence in cumulative evidence

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.\(^\text{19}\)

DISCUSSION

This systematic review will focus on the rate of interval emergency surgery as well as the rate of interval non-planned elective surgery, the rate of stoma formation, the number of recurrence flares, the number of recurrent
abscess, and disease associated morbidity and mortality in patients who passed an acute flare of diverticulitis of the left colon, complicated by abdominal or pelvic abscess. Thereby, the safety and feasibility of a non-operative approach might be assessed.

ETHICS AND DISSEMINATION
This systematic review will provide data on the need for surgery after a first attack of acute diverticulitis, complicated by intra-abdominal or pelvic abscess. Since diverticulitis counts among the most common abdominal disorders in the industrialised world even in complicated stages and the need for elective surgery is still matter of debate, the analysis will help physicians offer reasonable and evidence-based recommendations to affected patients. The findings of this study will be submitted to a peer-reviewed journal (BMJ Open, Annals of Surgery, British Journal of Surgery, Colorectal Diseases, Diseases of the Colon and the Rectum). Abstracts will be submitted to relevant national and international conferences. Moreover, a randomised-controlled trial will be conducted to transfer these results into clinical practice.

Patient and public involvement
A verbal survey prior to the study design showed that a renouncement of surgery is preferred by the majority of patients if the implementation is safe and feasible. Therefore, the need for emergency surgery was chosen as primary outcome. Patients were not directly involved in the design and recruitment of the study.

Contributors MS is the guarantor of the manuscript. MS and SS designed the review and developed the search strategy. MS drafted the manuscript. SS provided statistical expertise. HF and AA supervised and reviewed the development of the review and developed the search strategy. MS drafted the manuscript. SS provided the primary outcome. Patients were not directly involved in

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