Scandinavian Diverticulitis Trial SCANDIV II

Treatment of acute complicated diverticulitis: a prospective observational study

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1. Introduction

All surgical clinics in Sweden and Norway that treat patients with complicated diverticulitis may participate in the study after approval from the protocol committee.

1.1 Protocol committee

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1.2 Writing committee

The results of this study are planned to be published in an international “peer review” medical journal and may be part of a doctoral thesis. The members of the protocol committee, a PhD student Johanna Sigurdardottir together with some participating researchers in the SCANIDIV II study group handling the enrolment and follow-up of patients locally and fulfilling the “Vancouver criteria” will be part of the writing committee. The final decision on participation in the writing committee will be left to the PI and the deputy PI based on the researchers contribution to the study. All other study group members will be mentioned in the acknowledgements paragraph.

1.3 Principal Investigator

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1.4 Deputy Principal Investigator

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2. Background

Diverticular disease is among the five most common gastrointestinal disorders (1, 2). Among individuals with diverticulosis the lifetime risk of suffering from diverticulitis is between 10 and 25% (3-5). The most common complications of diverticulitis are perforation, abscess formation, fistula and obstruction. Emergency surgery is necessary in up to 25% of diverticulitis patients (6).

The American Society of Colon and Rectal Surgeon (ASCRS, 2014) recommends abscess drainage and antibiotic treatment and later elective surgery as treatment for complicated diverticulitis, Hinchey I and II (table 1) for abscesses larger or equal to 5 cm (7, 8, 9) while others recommend resection surgery for only Hinchey II (8). The recommendations for surgery are motivated by the belief that surgical treatment will reduce the risk for relapsing disease with intra-abdominal/pelvic sepsis by more than 40% (9, 10). However, these recommendations are based on small and out-dated retrospective studies.

Perforated diverticulitis with radiologically confirmed free intraperitoneal air is a life threatening disease with significant mortality and morbidity therefore several guidelines recommend acute surgical intervention (7). However, a conservative non-surgical approach for the treatment of perforated diverticulitis has been shown to be effective for hemodynamically stable patients with radiologically confirmed free air (11,12). A Swedish study recently showed the incidence of complicated diverticulitis to be 9/100.000 inhabitants/year of which about one third required acute surgical intervention (Thorisson et al Abstract ESCP Milano 2016). The most common operation in perforated diverticulitis is Hartman's procedure, which involves removal of the involved sigmoid segment, a terminal colostomy and blind closure of the rectal stump. Also primary resection of the sigmoid colon with anastomosis is frequently used, sometimes combined with a loop-ileostomy. Laparoscopic lavage without resection has emerged as an alternative operation method (7, 13-15). However, the SCANDIV trial showed limitations of laparoscopic lavage with a higher frequency of re-operation in the lavage group compared to primary resection after 90 days. However several meta-analysis based on three randomized studies showed comparable rates regarding overall mortality and morbidity in laparoscopic lavage versus resection in perforated diverticulitis(11-14).

For patients with diverticulitis complicated with fistula (colovesical, colovaginal or colo cutaneous) surgery is the recommended treatment (15, 16). This condition, however, rarely presents in an acute setting.

In Scandinavia a conservative approach restricted to antibiotics and percutaneous drainage is widely accepted as solitary treatment for patients with diverticular abscesses (Hinchey I and II). Also hemodynamically stable and non-immunocompromised patients with perforated diverticulitis (Hinchey III) are often managed conservatively with antibiotics and, if required, percutaneous drainage. Acute surgical intervention is performed if the condition of the patient deteriorates during hospital stay or if the CT shows signs of faecal peritonitis (Hinchey IV). Elective surgery for patients after an episode of acute complicated diverticulitis (Hinchey I-III) is usually reserved for patients with frequent relapses or with a persisting diverticular abscess.
However, some patients have frequent relapses with abscesses which are difficult to treat and suffer for a long time until the problem is solved. This clinical experience raises the question whether the Scandinavian treatment policy might be too conservative sometimes. Although elective surgery itself can lead to new complications and eventual deterioration in quality of life, early resection might be a better option for some patients. Also the quality of life for patients after conservative management of complicated diverticulitis has not been examined in detail previously.

The aim of this prospective observational study is to evaluate the type of treatment and the success rate in acute complicated diverticulitis (ACD) at participating hospitals in Sweden and Norway. Furthermore, the effects on quality of life for this patient group will be evaluated.

Tabel 1. Hinchey classification for complicated perforated diverticulitis (8)

I	Pericolic abscess
II	Distant/pelvic abscess
III	Generalized purulent peritonitis
IV	Faecal peritonitis

3. Aims

3.1 Primary aim

To explore the current treatment strategies in patients with acute complicated diverticulitis according to the Hinchey classification in Swedish and Norwegian hospitals and to assess failure rates during a one year period.

3.2 Secondary aim

To evaluate the course of disease for patients with complicated diverticulitis who do not undergo resection surgery. To study the quality of life for all patients with complicated diverticulitis.

4. Definitions

Acute complicated diverticulitis (ACD): Diverticulitis with signs of abscess or perforation (on CT or peroperativly).
Persistent disease: Persistent diverticulitis necessitating in-patient treatment (surgical/radiological/pharmacological) for more than 30 days.
Recurrent complicated disease: Complicated diverticulitis in the same bowel segment 30 days after the initial episode.

5. Hypothesis

This is an exploratory study including several hypotheses:

- Conservative non-surgical treatment for diverticulitis abscess (Hinchey I) is suitable for majority of patients.
- Conservative non-surgical treatment in Hinchey II patients leads to persistent/recurrent disease for a large proportion of patients.
- Conservative treatment for perforated diverticulitis is suitable for haemodynamically stable patients.
- Routine elective surgery after successful conservative treatment of complicated diverticulitis is not required.

- Complicated diverticulitis affects QoL in patients beyond the episode of acute diverticulitis, but quality of life improves over time. Recurrent complications and persistent disease have a negative impact on quality of life.

6. Patient Selection

All patients from participating centres, whom fulfil the inclusion criteria listed below, shall be evaluated for eventual participation in the study. In order to evaluate the representativeness of the study population, also all potentially eligible patients with acute complicated diverticulitis will be registered continuously along with information as to why they were not included. After completion of the study inclusion a retrospective journal search will be performed at each participating centre to identify all not included potentially eligible patients.

All patients treated for complicated diverticulitis will be informed about the study and asked orally and in writing to participate if eligible.

6.1 Inclusion criteria

- Age ≥18 years
- Clinical symptoms and laboratory results suspicious for diverticulitis
- CT findings of complicated diverticulitis with extraluminal air, presence of abscess with or without fistula or operative findings of complicated diverticulitis in an emergency setting
- Informed consent

6.2 Exclusion criteria

- Uncomplicated diverticulitis
- Language barrier or other reasons why informed consent is not possible.

6.3 Exclusion criteria for quality of life study

- Cognitive disability that causes incapacity to fill in questionnaires
- Participants not able to fill in questionnaires.

7. Study design

SCANDIV II is and exploratory, prospective, longitudinal, non-interventional, multicentre study for the evaluation of treatment of patients with ACD. Complications, proportion of patients requiring surgery, type of operation, complications of treatment and proportion of permanent colostomy will be registered. Quality of life will be studied for all included patients.

Patients will be identified at participating emergency rooms or hospital wards. For patients with suspected diverticulitis a routine medical history will be taken and the patient will undergo a clinical examination. Routine laboratory tests such as (haemoglobin, white blood cell count, S-Creatinine, C-reactive protein and S-albumin level) as well as a urinary test (including u-HCG test for all fertile women) will be obtained. CT abdomen is ordered by the on-call physician at the emergency department. If findings are consistent with complicated diverticulitis the patient will be asked if he/she is willing to participate in the study. Oral and written information will be given to participants and signed informed consent is required from all participants. The participants will receive hospitalization and treatment according to routines at the participating hospitals. The on-call physician will fill out the **CRF** which includes findings from the CT examination.

In a case of urgent surgery preventing that informed consent can be obtained preoperatively the patient may be informed and consent obtained later during the same hospitalization.

In all cases of either urgent or elective surgery the **operation-form** should be filled in.

At discharge from the surgical ward the patient should be planned for a follow up at the surgical clinic one month later where all complications/interventions/readmissions will be noted in the **one month follow-up-form**.

During the interview at one month follow-up participants will receive the quality of life protocols after additional oral information.

Further follow-up is done with patients receiving a quality of life questionnaire by mail and a further follow-up by telephone call.

The **telephone follow-up** contacts are at **one and three years**. In preparation for follow-up phone calls the patient medical journal is reviewed and presence of relapsing disease, hospitalization, operations, type of operation and whether the patient has a stoma is registered at each centre. The results from follow-up colon investigation will be registered in the follow-up form at three months.

Patients will be asked to fill in **quality of life questionnaires** at 1, 12 and 36 months. The questionnaires for 12 and 36 months will be send to the patients by two centres, Västerås in Sweden and Ahus in Norway.

To clarify patient selection, all patient with discharge diagnosis complicated diverticulitis will be identified according to the hospital discharge register (ICD-10 K57.2, K57.4 och K57.8) during the study period. The medical records for these patients will be reviewed.

7.1 CRF

CRF will be filled out during patients primary hospital stay.

Operation-form will be filled out during operation. New form for each new operation.

One month follow-up-form -form will be filled one month discharge from hospital or month after operation.

Telephone Follow-up-form (12m, 36m) will be filled out during follow-up contacts at 12 months and 36 months.

Quality of Life questionnaires at 1, 12 and 36 months.

7.2 Variables

The following variables will be studied:

- Age, gender.
- Comorbidity, ECOG performance status, medication (NSAID, corticosteroids, immunomodulatory).
- Previous hospitalization for diverticulitis and eventual complications.
- Status at admission *(CRP at admission and max CRP prior to intervention, signs of haemodynamic instability, clinical localized or diffuse peritonitis).*
- Type of complication to the diverticulitis (Hinchey I-IV).
- Surgical/radiological intervention.
- Indications for surgery along with time from admission to surgery.
- Complications after surgical/radiological intervention according to Clavien Dindo ≥ 3 (table 2).
- Overall mortality. Mortality during observational period due to diverticulitis or complications from diverticulitis.

- Quality of life according to Short Health Scale Likert-scale, GIQLI and EQ5D (evaluated at follow up after 1, 12 and 36 months).
- Total hospitalization time (primary hospitalization plus re-hospitalization due to complications or relapsing disease).
- Permanent stoma at the end of follow up period.
- Total cost for hospitalization.

Table 2. Clavien-Dindo Classification of Surgical Complications

Grade I: Any deviation from the normal course without the need for pharmacological treatment or surgical, endoscopic and radiologic interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I Complications. Blood transfusions and total parenteral nutrition are also included
Grade III: Requiring surgical, endoscopic or radiological intervention **III a** Intervention not under general anesthesia **III b** Intervention under general anesthesia
Grade IV: Life-threatening complication (including CNS complications)* requiring IC/ICU management **IV a** Single organ dysfunction (including dialysis) **IV b** Multiorgan dysfunction
Grade V: Death of a patient the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

8. Registration of complications

All complications secondary to diverticulitis or the treatment for diverticulitis will be registered in the *One month follow up form*.

9. Time Schedule

The study will start in 2018. The follow-up period is up to three years. There will be two publications, one after one year to evaluate the primary aim and a second after three years to evaluate the quality of life.

10. Ethical considerations

The study must first be approved by the ethics committee in participating countries. In Sweden Abbas Chabok will apply for all Swedish participating centres and in Norway Tom Øresland and Johannes Kurt Schultz will apply for all participating Norwegian centres. All eligible patients will be informed by a medical doctor and informed consent is obtained.

Patients with impaired cognitive function may be included in the observational part of the study but will not be included in the quality of life section. An approval may be obtained from relatives or a trustee who receives information in the form entitled "Consultation" that ensures which information has been given. This information does not need to be signed, a verbal consent is enough but will be documented in the patient's record in concordance with the recommendations from the ethical review board.

11. Statistics

This is a population-based observational study which will include all patients with ACD. We plan to describe the disease course for the large group of patients whom do not undergo surgical intervention. Power calculations are not suitable for this study. Under the

inclusion period of one year we plan to include a total of 500 patients. Data will be presented with descriptive statistics. Changes in quality of life and complications will be analysed in patients with different Hinchey classifications and different given treatments.

12. Administration

A secretariat will be prepared at the Department of Surgery Vastmanlands Hospital Vasteras, and the principal research nurse is Malin Engdahl.
For every participating hospital a principal physician will be responsible for the study. Relevant information about the study as well as participating hospitals and principal physicians for each hospital will be available on the studies web page. The protocol committee is responsible for study start and eventual problems that may come up during the time of the study.

13. Appendices

1) CRF
2) Operation form
3) One month follow-up form
4) Telephone follow-up form 12, 36 months
5) Patient information (Swedish)
6) Patient information “Consultation”
7) Quality of life questionnaires (Short Health Scale Likert-scale, EQ5D, GI-QLI)
8) Flowchart (Swedish)

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