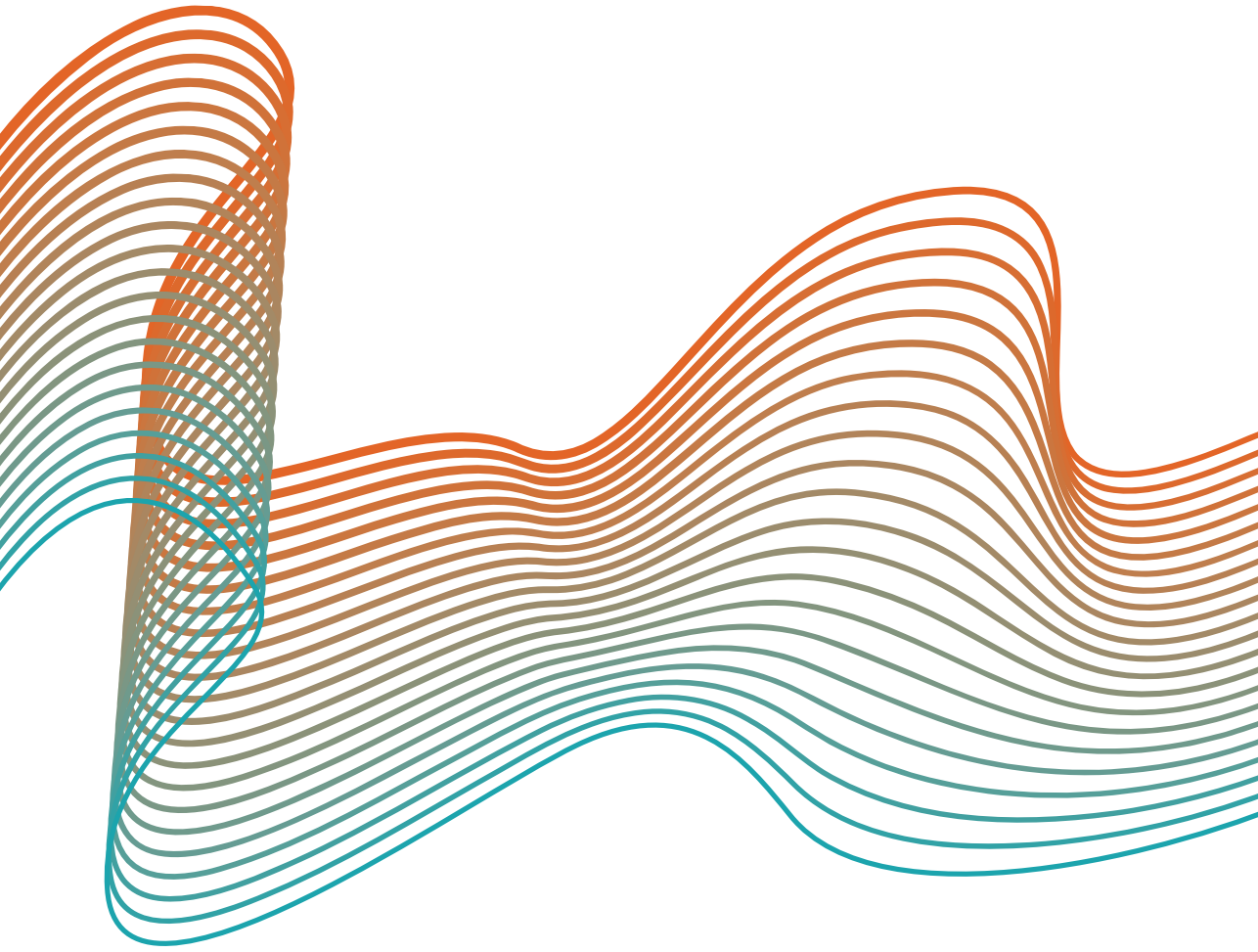
IMPROVING EFFICIENCY IN THE SURGICAL TREATMENT OF ACUTE APPENDICITIS

E.M.L. (Elisabeth) de Wijkerslooth



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IMPROVING EFFICIENCY IN THE SURGICAL TREATMENT OF ACUTE APPENDICITIS

Het optimaliseren van de chirurgische behandeling van appendicitis acuta

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Promotor
Prof. dr. B.P.L. Wijnhoven

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Copromotor
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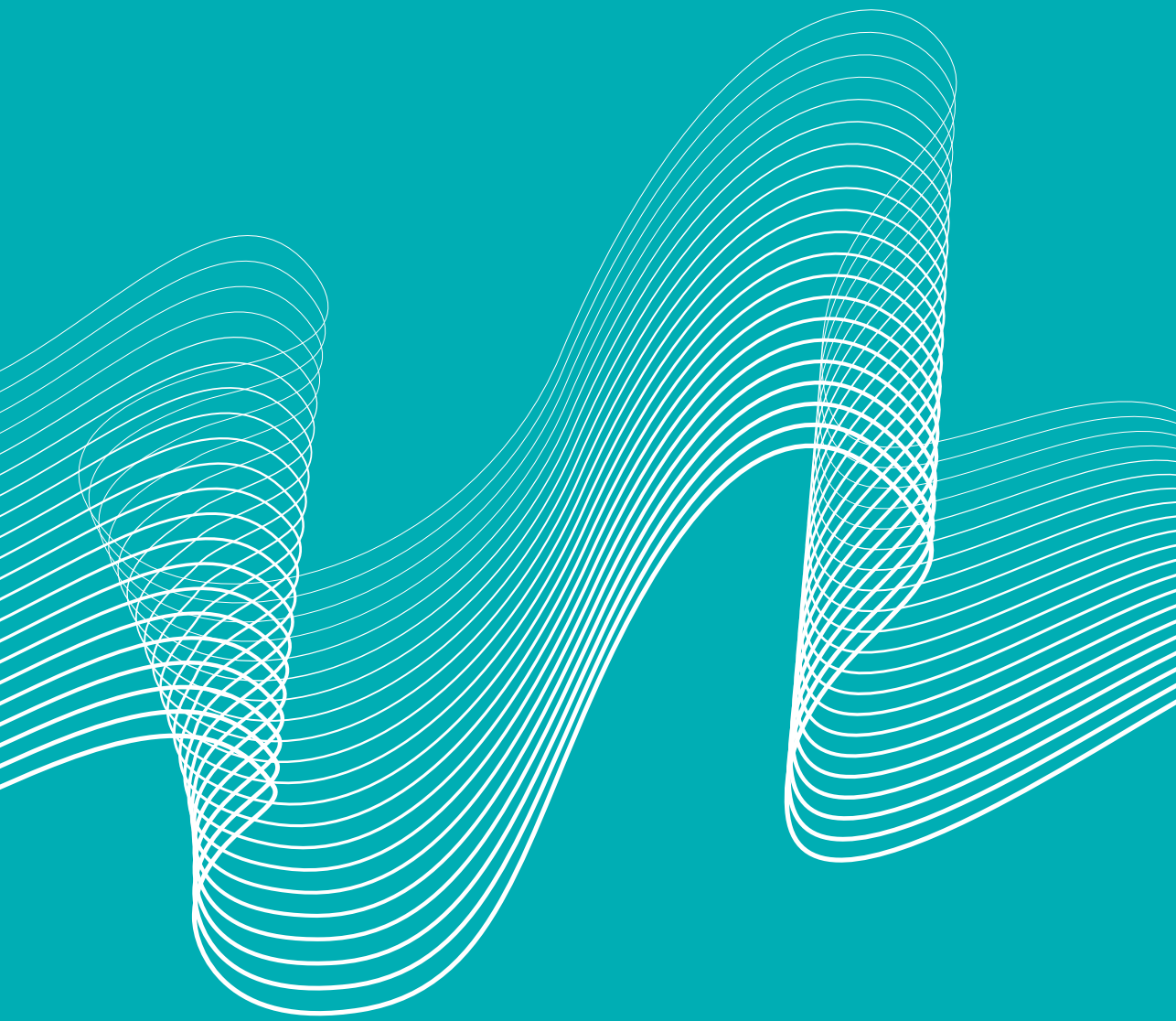

1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Acute appendicitis is the most common surgical emergency worldwide in children and adults.[1, 2] As such, most medical professionals have repeatedly encountered patients presenting with appendicitis. The diagnosis is made through medical history, physical examination, laboratory and imaging tests. Surgical removal of the inflamed appendix (appendectomy) has been the treatment of choice since its introduction in the 1880s.[3, 4] Conservative management with antibiotics is a valid option for non-complex, simple appendicitis.

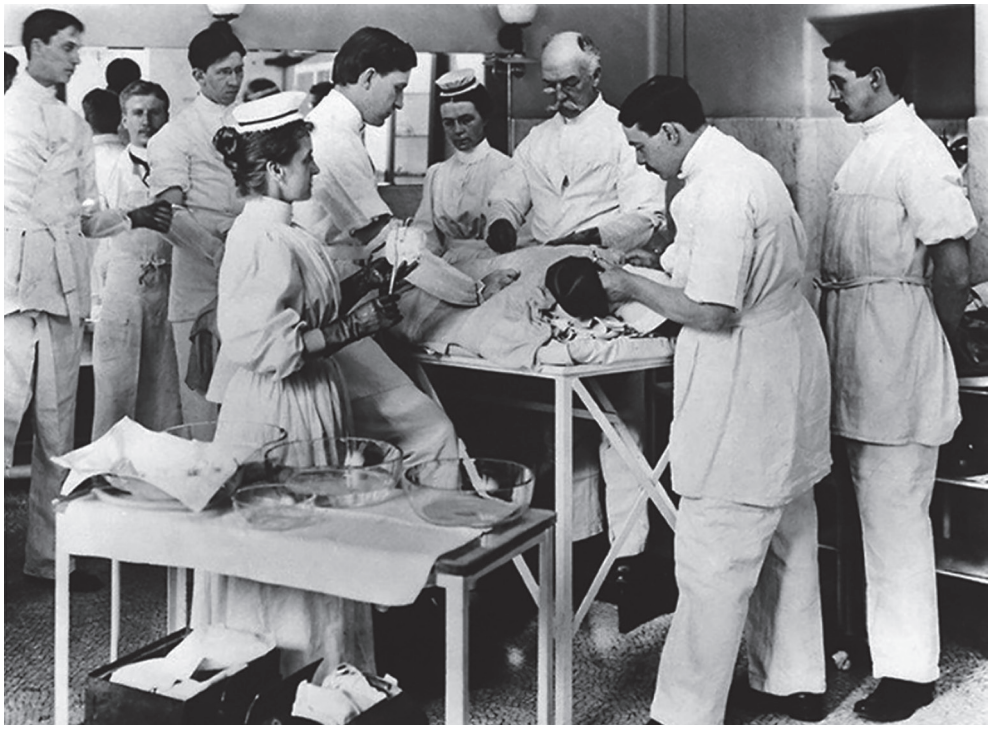

Photo: Charles McBurney operating at Roosevelt Hospital in 1901. McBurney described the clinical presentation of acute appendicitis, including tenderness at "almost exactly two inches from the anterior iliac spine, on a line drawn from the process through the umbilicus." (now commonly known as McBurney's tender point).[3, 4]

One might expect that for such a highly prevalent disease, questions with regards to its optimum treatment have long been answered. The first publications regarding acute appendicitis date from the 1840s,[3, 4] and a spectacular amount of research has been published since. Nevertheless, many research questions concerning its etiology, diagnosis and treatment remain insufficiently answered today. Some of these questions are addressed in this thesis, with a special focus on complex appendicitis.

This chapter briefly outlines the background that gave rise to the studies presented in this thesis.

Appendicitis acuta

The clinical presentation of patients with acute appendicitis varies from nearly asymptomatic to severe sepsis. Proper management of intra-abdominal infections requires in succession: 1) in case of sepsis: resuscitation, 2) adequate antimicrobial therapy, 3) appropriate source control intervention, and 4) in case of a complex type infection: maintained or adjusted antimicrobial agents to eradicate residual pathogens.[5, 6] Originating in the 1880s, the appendectomy has become the source control intervention of first-choice for acute appendicitis. Alternatively, non-operative treatment may include antibiotics and/or percutaneous drainage of abscesses. The non-operative approach has recently attracted a lot of attention and is increasingly being investigated in patients with (suspected) simple appendicitis.[7, 8] Due to advances in perioperative anesthetics, the introduction of laparoscopy and enhanced recovery after surgery (ERAS) protocols, most patients recover quickly. Intraoperatively, the type of appendicitis can be classified as simple or complex (i.e. uncomplicated or complicated).[9] Postoperative management is stratified according to this classification, the complex type requiring postoperative continuation of antibiotic prophylaxis. Severe postoperative complications are rare. Then again, postoperative development of an intra-abdominal abscess (which sometimes requires percutaneous or surgical drainage) still occurs in up to 20% of patients with complex appendicitis.[10-13] In contrast, the rate for simple appendicitis is 1 to 3%.[8, 14-16]

Ever since imaging studies were incorporated in standard diagnostic work-up per the Dutch guideline, the negative appendectomy (i.e. appendix sana) rate has dropped from 16% to 3%.[17] A considerable number of studies has assessed different surgical techniques for appendectomy. In general, laparoscopy offers advantages over open surgery.[18, 19] A similarly conclusive amount of evidence has demonstrated that a perioperative dose of antibiotic prophylaxis is effective in prevention of surgical site infection and intra-abdominal abscess.[20] Strikingly, several components of the standard treatment pathway for (simple and complex) acute appendicitis remain underexposed in literature. For instance, patient selection in the vast majority of appendicitis research relies heavily on the intraoperative classification of the type of appendicitis. Yet, definitions used vary greatly and the reproducibility of intraoperative findings has hardly been evaluated. Based on this (questionable) classification, approximately one third of patients are eligible for prolongation of antibiotic prophylaxis after surgery. Yet, no literature exists that irrefutably demonstrates a benefit of this therapy. To some extent, the current treatment strategy for acute appendicitis is based on clinical customs more than it is evidence-based. Contemporary (global) challenges such as the growing antimicrobial resistance, rising

healthcare costs and increasing pressure on hospital bed capacity, drive us to critically review *standard* surgical strategy.

Contemporary challenges

Restraints on hospital bed capacity is a recurring issue in most Dutch hospitals. This problem has further manifested itself during the COVID-19 pandemic. Ultimately, constant overload of hospital bed capacity leads to inferior care. Since acute appendicitis is such a highly prevalent disease requiring surgery and admission, it is particularly of interest to find ways to reduce hospital stay for these patients. Associated with length of hospital stay, are direct healthcare costs. Zorginstituut Nederland estimated that one day of hospital admission at a surgical department costs €405 on average, excluding diagnostics and medication.[18] Healthcare costs have risen over the past decades, in the developed and developing countries alike. In February 2019, the World Health Organization (WHO) reported that 'spending on health is growing faster than the rest of the global economy, accounting for 10% of global gross domestic product (GDP).' Again, since the annual number of patients treated for acute appendicitis is so high, a reduction in direct- or indirect costs can have a large effect.

Antimicrobial resistance (AMR) is another increasingly urgent global health issue. Very recently, Naghavi *et al.* estimated 541,000 deaths (95% CI 370,000 – 763,000) associated with AMR and 133,000 deaths (95% CI 90,100 to 188,000) attributable to AMR in Europe in 2019.[21] Resistance is a natural biological outcome of antibiotic use. Antibiotic *overuse* accelerates this process unnecessarily. Hence, tackling antibiotic overtreatment is key in slowing down the emergence of antimicrobial resistance. The bacteriology of appendicitis includes both aerobic and anaerobic enteric flora and 40 to 60% of all patients has mixed aerobic cultures.[22, 23] The most common bacteria associated with acute appendicitis are E. Coli, Bacteroides Fragilis, Klebsiella, Proteus and Pseudomonas Aeruginosa.[15] In the Netherlands, cefuroxime is one of the most often prescribed antibiotic in hospitals and most widely used after appendectomy in combination with metronidazole. Metronidazole resistance among anaerobes is rare. Resistance to cefuroxime is common among E. Coli (13%) and Klebsiella (15%) pneumonia isolates in inpatients, as reported in the latest national report on antimicrobial agents and resistance published in 2021.[24] A substantial 25 to 30% of patients undergoing surgery for appendicitis is classified as having a complex type appendicitis and, as such, is treated with antibiotics postoperatively. To reduce antibiotic use, it is paramount to establish which patients benefit from prolonged antibiotic prophylaxis, and what the optimum effective and necessary duration of therapy is.

To address the issues listed above, the main focus of this thesis was on the intraoperative classification of acute appendicitis, duration of postoperative hospital stay and duration of postoperative antibiotic use.

Aims and thesis outline

The overall aim of this thesis was to optimize treatment strategy for acute appendicitis. In order to do so, we performed retrospective, prospective and literature studies on patients treated for acute appendicitis, as well as cross-sectional studies among surgeons. All studies were conducted in a multicenter setting.

An abundance of literature reports the incidence of acute appendicitis. Few studies have also evaluated the clinical and economic burden of disease in a large-scale setting. In **chapter 2**, we present an overview of the burden of disease of acute appendicitis in the Netherlands. Key outcomes of interest were the incidence of surgically treated appendicitis, length of hospital stay and reimbursed hospital costs. This chapter sheds light on the impact that improved treatment efficiency could have on a population level.

Part II of this thesis focusses on the surgical classification of acute appendicitis, associated treatment preferences and outcomes. In **chapter 3** we analyzed the reliability of the intraoperative classification of appendicitis by Dutch surgeons, through a cross-sectional study using laparoscopy video material. Preferences in postoperative treatment for varying types of appendicitis are described as well. Thereafter **chapter 4** describes preferences in classification and postoperative treatment among an international pool of surgeons. Then, in **chapter 5**, we present a prospective snapshot study that demonstrates differences in postoperative outcomes for patients with non-perforated gangrenous appendicitis as compared to other types of appendicitis.

Part III deals with the perioperative pathway for patients presenting with *simple* appendicitis. Various low-risk surgical procedures have become outpatient procedures over time, e.g. inguinal hernia repair and cholecystectomy. Clearly, appendicitis presents as an acute disease and, as such, its surgical treatment cannot be pre-scheduled in a similar manner. Nevertheless, we hypothesize that the appendectomy could become an outpatient procedure for a selection of the total population. In **chapter 6** we present a systematic literature review on the safety of same-day discharge after appendectomy for acute simple appendicitis.

Part IV addresses the treatment of *complex* appendicitis, particularly its postoperative management. Traditionally, postoperative management of complex appendicitis includes

a course of intravenous antibiotics. This may be a course of fixed duration or a course discontinued based on clinical signs. At discharge, patients may or may not be prescribed additional oral antibiotics. High-level studies that have evaluated the efficacy of this treatment are scarce. The available data indicates that there is no added value of this extended prophylaxis. Two small-scale randomized trials[25, 26] and various observational studies[13, 27] suggest that a three- or four-day regimen delivers similar results to five days or more. This was further supported by a larger randomized trial on complicated intraabdominal infections (incl. 73 complex appendicitis patients) published by Sawyer *et al.* in 2015.[28] Patients with an adequate source control procedure (surgical or radiological) for various complicated intraabdominal infection were recruited. A median duration of 4 days was shown to be non-inferior to 8 days in terms of infectious complications and mortality in the postoperative course. Level I evidence specific for patients with complex appendicitis had yet to be obtained at this point. We hypothesized that restricting the postoperative prophylaxis to only two days would be non-inferior to five days (most common at the time). **Chapter 7** summarizes our protocol for the APPIC trial, a randomized trial aimed at establishing non-inferiority of two versus five days of intravenous antibiotics after appendectomy for complex appendicitis. Onwards, in **chapter 8**, we reveal the primary outcome of this trial. Lastly, the associated analyses of costs and cost-effectiveness of the APPIC trial are presented in **chapter 9**.

Finally, in the last chapters (**chapters 10 and 11**) we present a general discussion, conclusions and summary. Furthermore, we discuss some future perspectives on the continued optimization of treatment for acute appendicitis.

Chapter	Research question(s)
2	What is the burden of appendicitis in the Netherlands, in terms of incidence, length of hospital stay and hospital costs?
3	What is the extent of interobserver variability in the intraoperative classification of appendicitis during laparoscopy?
4	To what extent is there variation in the classification and postoperative management of complex appendicitis on an international level?
5	What is the risk of postoperative infectious complications for patients with unperforated gangrenous appendicitis?
6	Is it safe to discharge patients within the same calendar day after an appendectomy for simple acute appendicitis?
7	Is 2 days of antibiotics after appendectomy for complex appendicitis non-inferior to 5 days?
8	Is 2 days of antibiotics after appendectomy for complex appendicitis non-inferior to 5 days?
9	Is it cost-effective to reduce duration of antibiotic treatment to 2 days after appendectomy for complex acute appendicitis?

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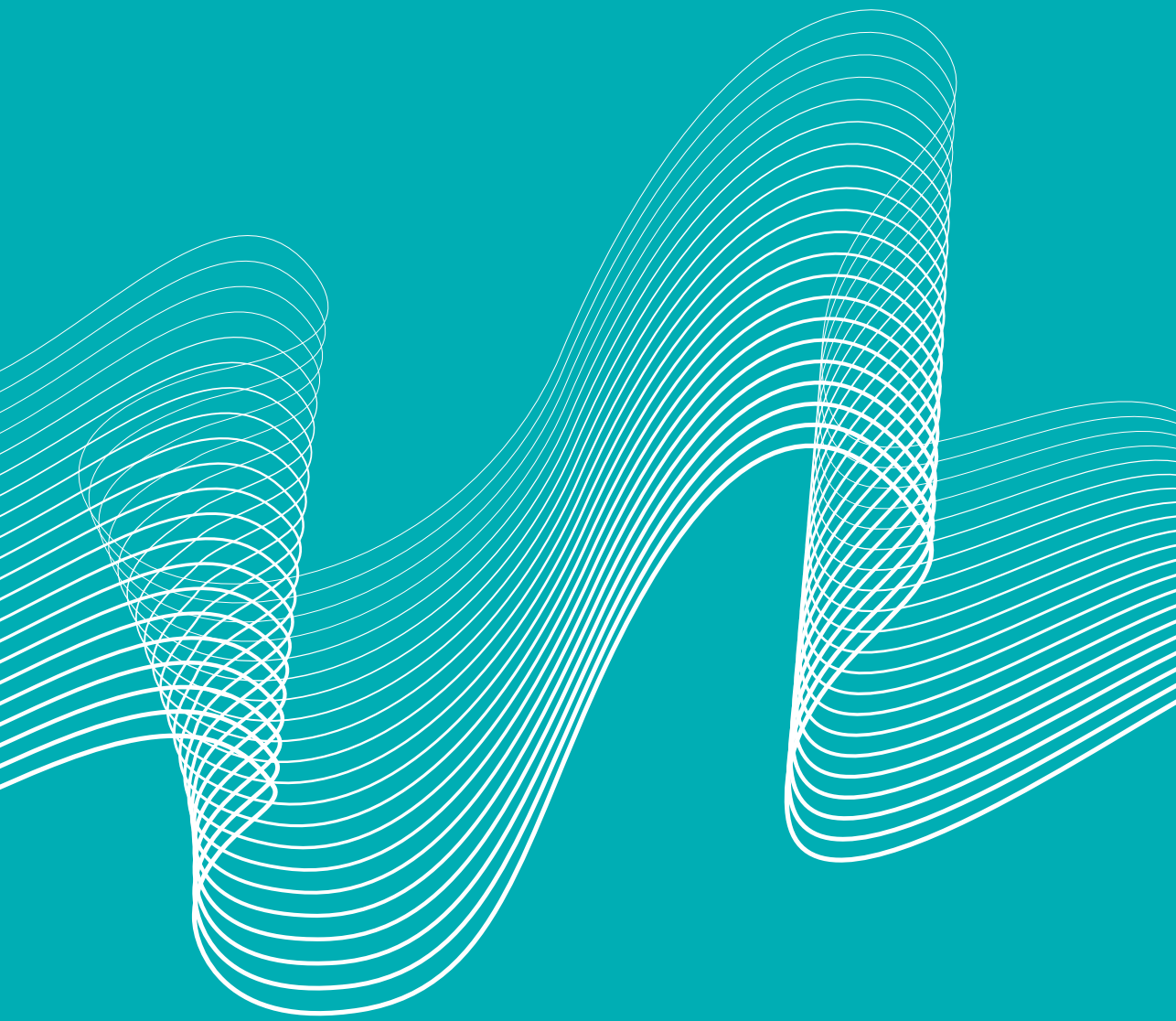

Elisabeth M.L. de Wijkerslooth, Anne Loes van den Boom, Bas P.L. Wijnhoven

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2

DISEASE BURDEN OF APPENDECTOMY FOR APPENDICITIS: A POPULATION-BASED COHORT STUDY

ABSTRACT

Background:

Few large-scale epidemiologic studies evaluate the clinical and economic burden of appendicitis. These data may impact future research and treatment strategies. In this study the objective was to determine the burden of appendectomy for appendicitis in terms of incidence rates, length of hospital stay (LOS) and hospital costs on a national level. In addition outcomes were compared for subgroups based on surgical treatment, age and hospital setting.

Methods:

Observational retrospective population-based cohort study using the national Dutch healthcare reimbursement registry, which covers hospital registration and reimbursement for 17 million inhabitants. Patients with a diagnosis of appendicitis who underwent appendectomy between 2006 and 2016 were included. Primary outcomes were incidence rates, LOS and hospital costs.

Results:

A total of 135,025 patients were included. Some 53% of patients was male and 64% was treated in a general hospital. The overall incidence rate of appendectomy was 81 per 100,000 inhabitants and showed a significant decreasing trend across time and age. Mean ±sd LOS per patient was 3.66 ±3.5 days. LOS showed a significant increase with age and was significantly longer for open vs. minimally invasive appendectomy. Mean ±sd hospital costs per patient were €3700 ±1284. Costs were initially lower for open compared to minimally invasive appendectomy, but were similar from 2012 onwards. Compared to non-university hospitals, patients treated in university hospitals had a significantly longer LOS and higher costs.

Conclusions:

Appendectomy for appendicitis represents a substantial clinical and economic burden in the Netherlands. A preference for minimally invasive technique seems justified.

INTRODUCTION

Although acute appendicitis is highly prevalent among adults and children worldwide, literature on the clinical and economic burden of the disease is scarce. Emergent appendectomy remains the cornerstone of treatment and is nowadays mostly performed via the minimally invasive approach in Western countries.[1-3] It is known as a low-risk surgical procedure, with reported mortality rates between 0.03% and 0.24%.[4-6] Depending on the intraoperative classification, patients may be discharged within 24 – 48 hours, or after a few days of prolonged antibiotic prophylaxis.[7,8] Infectious complications occur in some 9% to 20% of patients, accompanied by a hospital readmission rate of 6%.[5,9] Whereas morbidity and mortality are estimators of the burden of disease in a population, the economic burden should also be taken into account. Data on the hospital costs related to appendicitis may impact future treatment and research strategies. This is especially relevant in light of the increasing interest in the non-operative treatment approach.[10-14] Apart from avoiding surgery and its potential complications, non-operative treatment might also be beneficial in terms of healthcare cost savings. However, the available evidence is ambiguous.[15-18] Regarding the choice of operative approach, most studies have demonstrated comparable or better clinical outcomes for minimally invasive compared to open appendectomy, however at higher medical care costs.[19-22]

Several population-based studies on the incidence of appendicitis have been published, as recently summarized in a systematic review on the global incidence of appendicitis.[23] Fewer large-scale studies have taken the economic burden of appendicitis into account.[24-27] No study to our knowledge has yet simultaneously evaluated both the clinical and financial burden of appendicitis and appendectomy on a population-level.

The primary aim of this study was to evaluate the burden of appendectomy for appendicitis in the Netherlands in terms of hospital costs, length of hospital stay and incidence. Secondary aims were to evaluate outcomes according to surgical approach, registration year, age and hospital setting, and explore trends.

MATERIALS AND METHODS

Study design and setting

The present study was a population-based retrospective observational cohort study based on the national healthcare reimbursement system, which contains data from all hospitals and medical facilities in the Netherlands. The study protocol was reviewed and approved by the Erasmus MC Ethics Committee. Requirement for informed consent was waived, owing to the observational and anonymous nature of this study.

Database

Hospital reimbursement by means of Diagnosis Related Groups (DRGs) has become common worldwide. Since 2005, medical care registration and reimbursement in the Netherlands is performed through a DRG-like case-mix system based on Diagnosis Treatment Combinations (DBCs). A DBC contains the complete set of care activities required to establish a particular diagnosis and treatment, from first presentation to the hospital up to the last check-up.[28] DBC registration is collected in a national healthcare database: the so-called DBC Information System (DIS). All data relevant for reimbursement is registered (diagnoses, treatment activities, hospital setting, length of stay) as well as a limited number of patient characteristics. Detailed data such as type of appendicitis, complications and readmission cannot be retrieved from the DIS. The database is managed by the Dutch Healthcare Authority (NZa), an autonomous administrative authority that is part of the Dutch Ministry of Health, Welfare and Sport. For the current study, data was extracted and aggregated by the NZa, as available per March 1st 2018. Subsequent analyses were performed by the authors.

Case selection

The DIS database was queried for all patients registered with a diagnosis of appendicitis that underwent appendectomy between 2005 and 2016, as from 2016 onwards the registration was not complete yet. Appendicitis was identified using specialist-diagnosis codes for appendicitis belonging to medical specializations Surgery (0303; 113) and Pediatrics (0316; 3302). Appendectomy was identified via specific care activity codes for open appendectomy (034910) and minimally invasive appendectomy (034911). Patients that had other surgical procedures of the appendix (i.e. periappendiceal abscess surgery or synchronous cholecystectomy and appendectomy) were excluded from the present analysis. The data for 2005 reflected less dependable registration during the starting year of the DIS database. Hence, a choice was made to limit the final case selection to January 2006 – December 2015 for the most valid analysis.

Collected data

Data were collected on year of presentation, gender, age, hospital setting (university hospital, top-clinical hospital, general hospital), surgical procedure (open or minimally invasive appendectomy), length of hospital stay (LOS) and hospital costs. LOS concerns the duration of the admission from first presentation to the hospital until discharge after surgery. Admission days related to readmission(s) are not included in the same DBC. Hospital costs were calculated based on reimbursements per DBC by the hospitals in the DIS-system. Each specific DBC has a fixed price – either nationally standardized or negotiated upon between health insurers and hospitals – which covers both direct medical costs and specialists' fees. Cases representing the lowest and highest 10% of reimbursed costs were excluded from cost analysis, as per standard NZa-policy.

Outcome measures

The outcome measures in this study are: incidence (per 100,000 inhabitants), LOS (in days) and direct hospital costs (in euros). Outcomes were stratified by year of DBC registration, age and hospital-setting. Dutch population statistics were retrieved from the electronic databank Statline, managed by Statistics Netherlands (CBS).

Statistical analysis

Outcomes are reported using descriptive statistics. Incidence rates are presented as number per 100,000 inhabitants. Categorical outcomes are presented as no. of cases (%) and continuous outcomes as means ± standard deviations (sd) as well as medians and interquartile ranges (IQR). The Student t test and Chi Square test were used to compare means and proportions, as appropriate. Furthermore, the Cochrane-Armitage test was used to evaluate trends in incidence and proportion of minimally invasive surgery over time (per registration year) and age group (per decade). A value of $p < 0.05$ was considered significant. The Holm method was used to correct for multiple testing.[29] Adjusted p-values are reported. Data analysis was performed using Excel 2010 (Microsoft, Redmond, Washington, USA), SPSS version 21 (IBM, Armonk, New York, USA) and R version 3.5.1 (Feather Spray package; https://cran.r-project.org/).

This manuscript was written using the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement checklist.[30]

RESULTS

Study Population

A total of 135,025 patients met the inclusion criteria (fig. 1). Basic patient characteristics and outcomes are shown in table 1. The proportion of minimally invasive appendectomy was lower for men compared to women (42% vs. 60%, $p < 0.0001$). Over time the proportion of patients operated minimally invasive increased (table 2). This trend was statistically significant ($p < 0.0001$) for the total study population as well as for male and female patients separately.

Incidence

The overall incidence was 81 per 100,000 inhabitants (range 75 – 90). Incidence was higher for men compared to women (table 1) and showed a decreasing trend over time ($p < 0.0001$) for the total study population (table 2) and for men and women separately as well. Incidence was highest at 182 per 100 000 inhabitants aged 10 to 19 years. A decreasing trend across age groups ($p < 0.0001$) was observed towards 23 per 100 000 inhabitants aged ≥80 years (table 2).

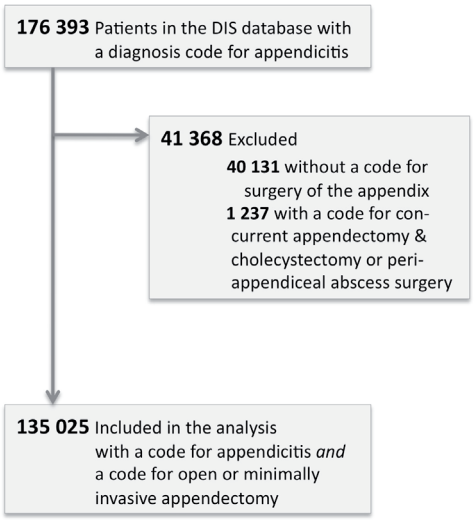

Figure 1. Study flowchart
Another 20,442 patients had a registered surgical procedure of the appendix but no registered diagnosis of appendicitis (13% of all patients 156,704 patients with a surgical procedure of the appendix within the study timeframe).

Table 1. Characteristics and outcomes of patients with appendicitis and appendectomy 2006 – 2015.

			Length of stay in days			Hospital costs in euros		
Variable	**No. (%)**	**Incidence[a]**	**Mean ±sd**	***p* Value**	**Median (IQR)**	**Mean ±sd**	***p* Value**	**Median (IQR)**
Total	135 025	81	3.66 ±3.52		3 (2 – 4)	3700 ±1284		3645 (3350 – 4095)
Sex								
Male	71 054 (53)	86	3.71 ±3.63	< 0.0001	3 (2 – 4)	3680 ±1313	< 0.0001	3580 (3350 – 4075)
Female	63 971 (47)	76	3.60 ±3.40		3 (2 – 4)	3723 ±1250		3720 (3390 – 4125)
Surgical approach								
Open	67 444 (50)	41	3.83 ±3.82	< 0.0001	3 (2 – 5)	3584 ±1320	< 0.0001	3455 (3280 – 3905)
Minimally invasive	68 067 (50)	41	3.49 ±3.21		2 (2 – 4)	3817 ±1242		3850 (3555 – 4125)
Hospital setting[b]								
UMC	6 933 (5)		4.49 ±4.83	< 0.0001	3 (2 – 6)	4244 ±2141	< 0.0001	4030 (3555 – 4925)
Top-clinicalc	41 955 (31)		3.66 ±3.55		2 (2 – 4)	3820 ±1232		3850 (3450 – 4130)
General	86 104 (64)		3.59 ±3.37	< 0.01	3 (2 – 4)	3598 ±1198	< 0.0001	3555 (3315 – 4030)

Abbreviations: *SD*, standard deviation; *IQR*, interquartile range; *UMC*, university medical center.
[a] Incidence rates are presented per 100,000 inhabitants.
[b] 33 remaining patients were treated in a hospital setting other than UMC, top-clinical or general hospital (i.e. privat clinic)
[c] Top-clinical centers are non-academic hospitals that provide more complex care than general hospitals and usually have an important role in training doctors and in conducting scientific research.

Table 2. Outcomes according to surgical approach, year of registration and age group.

					Length of stay in days		Hospital costs in euros	
Subgroup			**No. (%)[a]**	**Incidence[b]**	**Mean ±sd**	**Median (IQR)**	**Mean ±sd**	**Median (IQR)**
By year of registration and surgical approach	All cases	2006	14 651 (11)	90	4.08 ±4.45	3 (2 – 5)	4517 ±1951	4950 (4325 – 5510)
		2007	14 161 (11)	87	3.75 ±3.77	3 (2 – 5)	3061 ±1054	3085 (2720 – 3640)
		2008	13 851 (10)	84	3.91 ±3.57	3 (2 – 5)	3636 ±476	3455 (3450 – 4030)
		2009	14 015 (10)	85	3.75 ±3.40	3 (2 – 4)	3835 ±503	3725 (3555 – 4125)
		2010	13 179 (10)	80	3.69 ±3.47	3 (2 – 4)	3436 ±453	3430 (3280 – 3555)
		2011	12 516 (9)	75	3.46 ±3.25	2 (2 – 4)	3534 ±776	3850 (3350 – 3850)
		2012	12 615 (9)	75	3.37 ±3.36	2 (2 – 4)	3708 ±1433	3525 (3030 – 3980)
		2013	12 754 (10)	76	3.53 ±3.26	2 (2 – 4)	3886 ±1261	3710 (3475 – 4070)
		2014	14 137 (11)	84	3.46 ±3.08	2 (2 – 4)	3776 ±1399	3850 (3510 – 4155)
		2015	13 146 (10)	78	3.50 ±3.23	2 (2 – 4)	3556 ±1796	3860 (3565 – 4115)
	Open procedures	2006	11 016 (75)		4.17 ±4.67**	3 (2 – 5)	4423 ±1945***	4865 (4275 – 5410)
		2007	10 007 (71)		3.80 ±3.87	3 (2 – 5)	2853 ±964***	2905 (2645 – 3215)
		2008	9 044 (65)		4.06 ±3.79***	3 (2 – 5)	3438 ±424***	3455 (3440 – 3455)
		2009	8 178 (58)		3.85 ±3.57**	3 (2 – 4)	3590 ±437***	3555 (3555 – 3555)
		2010	6 778 (51)		3.77 ±3.56*	3 (2 – 4)	3275 ±408***	3280 (3260 – 3280)
		2011	5 672 (45)		3.54 ±3.38	2 (2 – 4)	3260 ±685***	3350 (3350 – 3370)
		2012	5 104 (41)		3.52 ±3.64**	2 (2 – 4)	3733 ±1495	3530 (3105 – 3980)
		2013	4 381 (34)		3.70 ±3.53**	2 (2 – 5)	3906 ±1407	3705 (3460 – 4040)
		2014	4 133 (29)		3.58 ±3.27*	2 (2 – 4)	3833 ±1560*	3835 (3530 – 4115)
		2015	3 131 (24)		3.80 ±3.52***	2 (2 – 5)	3613 ±2119	3905 (3570 – 4115)
	Minimally invasive	2006	3 693 (25)		3.85 ±3.76**	3 (2 – 5)	4794 ±1939***	5105 (4520 – 5835)
		2007	4 239 (30)		3.63 ±3.53	3 (2 – 4)	3563 ±1088***	3680 (3245 – 4075)
		2008	4 886 (35)		3.65 ±3.14***	3 (2 – 4)	4007 ±319***	4030 (4030 – 4030)
		2009	5 942 (42)		3.61 ±3.16**	3 (2 – 4)	4176 ±372***	4125 (4125 – 4125)
		2010	6 455 (49)		3.61 ±3.36*	2 (2 – 4)	3606 ±433***	3555 (3510 – 3630)
		2011	6 881 (55)		3.41 ±3.14	2 (2 – 4)	3760 ±774***	3850 (3850 – 3850)
		2012	7 532 (60)		3.27 ±3.15**	2 (2 – 4)	3692 ±1390	3510 (3030 – 3980)
		2013	8 395 (66)		3.45 ±3.11**	2 (2 – 4)	3875 ±1176	3715 (3495 – 4095)
		2014	10 013 (71)		3.41 ±3.00*	2 (2 – 4)	3753 ±1326*	3870 (3490 – 4160)
		2015	10 031 (76)		3.42 ±3.16***	2 (2 – 4)	3542 ±1719	3830 (3550 – 4120)
By age group and surgical approach	All cases	0 – 9	10 237 (8)	54	3.79 ±3.57	3 (2 – 5)	3652 ±1401	3555 (3300 – 4085)
		10 – 19	36 466 (27)	182	3.40 ±3.13	2 (2 – 4)	3698 ±1299	3620 (3350 – 4085)
		20 – 29	25 595 (19)	126	3.08 ±2.65	2 (2 – 3)	3709 ±1170	3715 (3390 – 4125)
		30 – 39	19 652 (15)	90	3.28 ±2.99	2 (2 – 4)	3710 ±1270	3690 (3370 – 4125)
		40 – 49	16 444 (12)	64	3.66 ±3.21	3 (2 – 5)	3710 ±1218	3675 (3360 – 4115)
		50 – 59	12 703 (9)	55	4.20 ±4.04	3 (2 – 5)	3709 ±1303	3650 (3350 – 4085)
		60 – 69	8 363 (6)	45	4.72 ±4.72	4 (2 – 6)	3700 ±1379	3620 (3350 – 4075)
		70 – 79	4 038 (3)	36	5.77 ±5.61	4 (2 – 7)	3707 ±1529	3615 (3350 – 4080)
		≥ 80	1 527 (1)	23	7.53 ±6.99	6 (3 – 9)	3627 ±1373	3555 (3280 – 4030)
	Open procedures	0 – 9	7 654 (75)		3.76 ±3.52	3 (2 – 5)	3573 ±1387	3485 (3485 – 3910)
		10 – 19	19 324 (53)		3.45 ±3.18	3 (2 – 4)	3575 ±1287	3455 (3280 – 3870)
		20 – 29	10 511 (41)		3.16 ±2.70	2 (2 – 4)	3566 ±1216	3455 (3280 – 3900)
		30 – 39	8 749 (45)		3.41 ±3.11	3 (2 – 4)	3557 ±1318	3455 (3280 – 3925)
		40 – 49	7 560 (46)		3.86 ±3.49	3 (2 – 5)	3597 ±1291	3460 (3280 – 3980)
		50 – 59	6 142 (48)		4.49 ±4.58	3 (2 – 6)	3619 ±1381	3485 (3280 – 3950)
		60 – 69	4 268 (51)		5.01 ±5.36	4 (2 – 6)	3646 ±1446	3485 (3280 – 3915)
		70 – 79	2 252 (56)		6.21 ±6.07	5 (3 – 8)	3640 ±1454	3490 (3280 – 3970)
		≥ 80	984 (64)		8.13 ±7.59	6 (4 – 10)	3591 ±1436	3455 (3245 – 3970)
	Minimally invasive	0 – 9	2 597 (25)		3.89 ±3.69	3 (2 – 5)	3891 ±1419	3960 (3555 – 4185)
		10 – 19	17 255 (47)		3.34 ±3.08	2 (2 – 4)	3838 ±1322	3850 (3555 – 4125)
		20 – 29	15 169 (59)		3.03 ±2.63	2 (2 – 3)	3809 ±1126	3850 (3555 – 4125)
		30 – 39	10 978 (56)		3.20 ±2.93	2 (2 – 4)	3834 ±1215	3850 (3555 – 4125)
		40 – 49	8 977 (55)		3.50 ±2.94	2 (2 – 4)	3804 ±1144	3850 (3550 – 4125)
		50 – 59	6 614 (52)		3.94 ±3.47	3 (2 – 5)	3792 ±1218	3850 (3535 – 4125)
		60 – 69	4 130 (49)		4.44 ±3.92	3 (2 – 6)	3758 ±1301	3850 (3510 – 4125)
		70 – 79	1 799 (45)		5.24 ±4.91	4 (2 – 6)	3796 ±1614	3840 (3515 – 4125)
		≥ 80	548 (36)		6.47 ±5.64	5 (3 – 8)	3687 ±1250	3850 (3510 – 4125)

Abbreviations: *SD*, standard deviation; *IQR*, interquartile range.

[a] Numbers of open and minimally invasive procedures may not add up to the total numbers in this column owing to 486 double procedure registries. Percentages have been rounded and may not total 100.

[b] Incidence rates are presented per 100,000 inhabitants.

* P < 0.05, **P < 0.001 and ***P < 0.0001 for the difference in outcome between open vs. minimally invasive appendectomy.

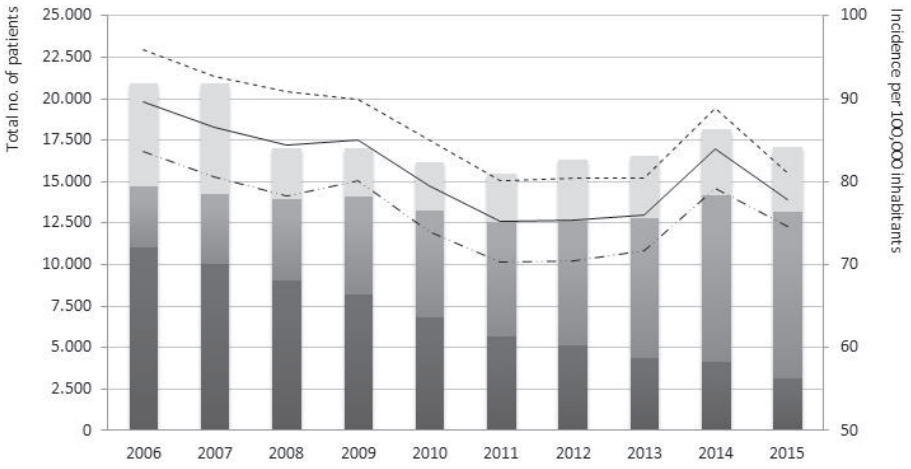

Figure 2. Absolute number and incidence rate of patients with appendicitis and appendectomy

Legend:
- Open appendectomy
- Minimally invasive appendectomy
- No surgery
- Incidence (all)
- Incidence men
- Incidence women

Length of hospital stay

Some 127,942 patients (95%) had at least one registered day of hospital stay. Mean LOS ±sd per patient was 3.66 ±3.52 days. The mean total number of admission days registered per year for patients undergoing appendectomy for appendicitis was 49,419. Mean ±sd LOS was shorter for minimally invasive compared to open surgery (3.49 ±3.21 vs. 3.83 ±3.82, $p < 0.0001$) as well as for general vs top-clinical hospitals ($p < 0.01$) and for top-clinical vs. university hospitals ($p < 0.0001$): 3.6 ±3.2 vs 3.7 ±3.6 vs 4.5 ±4.8 days, respectively (table 1). Overall mean LOS decreased over time, and from age group 30 - 39 years onwards mean LOS gradually increased with age (table 2; figure 3a and 3b).

Hospital costs

Overall mean ±sd hospital costs were €3700 ±1284 per patient, which corresponds to national annual mean of €49,959,250 during the study period. Costs were higher for patients who underwent minimally invasive vs. open appendectomy (€3817 ±1242 vs €3584 ±1320, $p < 0.0001$). Analysis per registration year demonstrated that the difference was significant from 2006 to 2011, but costs were in the same range or significantly lower for minimally invasive appendectomy from 2012 onwards (table 2). Mean costs per patient in university hospitals compared to top-clinical and general hospitals were €4244 vs €3820 vs €3598, respectively ($p < 0.0001$).

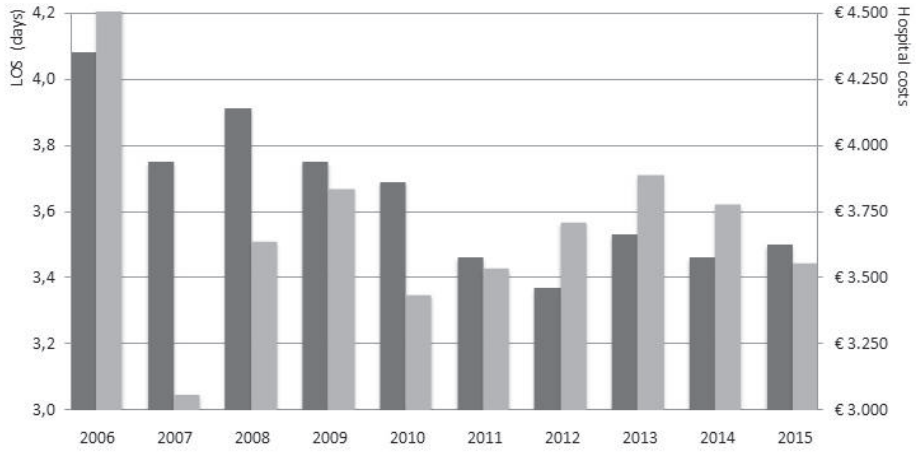

Figure 3a. Mean LOS and hospital costs per patient according to year of registration

Legend:

Mean LOS per patient

Mean hospital costs per patient

LOS, length of hospital stay.

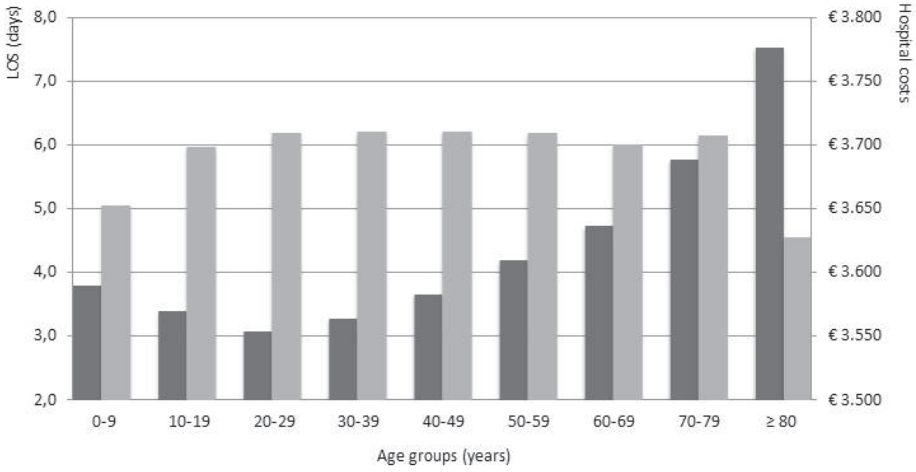

Figure 3b. Mean LOS and hospital costs per patient according to age group

Legend:

Mean LOS per patient

Mean hospital costs per patient

LOS, length of hospital stay.

DISCUSSION

The present study demonstrates that the burden of appendectomy for appendicitis is substantial and implicates that treatment by means of minimally invasive appendectomy at a general hospital is most favorable. Between 2006 and 2016 the incidence was 81 per 100,000 inhabitants, associated with an average 3.7 admission days and €3700 hospital costs per patient. This translates into approximately 13,500 patients annually that are responsible for nearly 50,000 admission days and close to 50 million euro of hospital costs. Minimally invasive appendectomy was consistently associated with shorter LOS compared to open surgery and with comparable hospital costs from 2012 onwards. And treatment in university hospitals resulted in significantly longer LOS and higher costs, compared to other hospital settings. However, it is important to point out that we were unable to correct for potential confounders in this analysis, which may have influenced the results (i.e. university hospitals have likely treated patients with more comorbidities, which may have affected their recovery and length of stay).

The number of patients in this cohort is an underestimation of the total population with appendicitis, who underwent surgical *and* non-surgical treatment. Non-operative treatment for appendicitis and incidental appendectomies were excluded as it was impossible to identify these patients from the database. Twenty-three per cent of patients with a diagnosis of appendicitis did not have a surgical procedure linked and were excluded. Clearly, this cannot entirely be interpreted as non-operative treatment of appendicitis, since a much lower proportion would be expected given the time period that was selected. Non-operative treatment has just recently been advocated as an alternative to surgery, at least in the Netherlands. More likely, for some patients the (initial) diagnosis of appendicitis may have been wrong, given that no surgical treatment was registered. At the same time a considerable number of patients with a surgical procedure of the appendix were excluded since a diagnosis of appendicitis was missing. It is doubtful that those patients all underwent incidental appendectomies. We consider it more likely that some of them underwent a diagnostic laparoscopy under suspicion of different pathology and turned out to have appendicitis, but afterwards the DBC diagnosis was not adjusted. Taken together, the actual number of patients annually treated for appendicitis in the Netherlands may be higher than presented here.

A significant decrease in incidence was observed over the ten year study period (from 90 per 100,000 in 2006 to 78 per 100,000 in 2015, trend test $p < 0.0001$). This may reflect a decrease in patients presenting with acute appendicitis and/or a decrease in the number of patients treated surgically. The decrease in incidence observed in this study seems to be in line with results from a recently published population-wide study among children in Sweden that demonstrated a significant decline in incidence of appendicitis

over time.[31] Then again, a nationwide epidemiological study on appendicitis in the USA published in 2012 reported a significant increase in incidence between 1993 and 2008.[32] The literature on incidence of appendicitis is not clear.[31,33-35] In a systematic review on the global incidence of appendicitis, pooled incidence of appendicitis or appendectomy in the Western World was estimated at 151 per 100 000 person years and reported to be stable in most Western countries.[23] The finding in this cohort that incidence peaks among persons aged 10 to 19 years, and is greater among men compared to women, is consistent with previous epidemiological literature.[1,32,36,37] In 2010 a new Dutch guideline on treatment of appendicitis was published, which incorporates ultrasound or CT imaging in the standard diagnostic process.[38,39] It is plausible that fewer patients were operated as a result due to better diagnosis and a fall in the proportion of appendectomy for appendix sana. A large Dutch cohort study (n=1943) performed in 2014 demonstrated a low negative appendectomy rate of 3%.[38,39] Another factor that might play a role is the growing popularity of non-operative treatment and fading dogma 'when in doubt, take it out'. With a growing number of papers presenting good results for the non-operative approach, surgeons may already be less inclined to take patients straight to theater.[10-12,40] As discussed before, the DIS database does not allow for accurate identification of non-operative treatment of appendicitis. Neither does it contain information on histopathological examination of the appendices. Therefore it is impossible to estimate the potential effect of a supposedly decreased negative appendectomy rate and increased non-operative treatment rate in this study.

The use of minimally invasive appendectomy significantly increased over time. This seems justified since minimally invasive appendectomy was consistently associated with a shorter hospital stay and similar costs from 2012 onwards. Patients were admitted to the hospital approximately 3.5 days after laparoscopic appendectomy and slightly (but significantly) longer after open surgery (3.8 days). This finding has been reported before in a national cohort from the US for 2004 to 2011, as well as other studies.[36] Interestingly, for five per cent of patients not one hospital admission day was registered, which may reflect a proportion of *same-day discharge* patients. Several recent studies have indicated that same-day discharge is safe after appendectomy for simple appendicitis. Both the proportion of minimally invasive surgery and same-day discharge can be expected to increase in the future, which may reduce the costs. No clear trend in hospital costs was observed during the study period. Within the DIS registration, patients are categorized into three groups based on length of stay, which may explain that hospital costs do not seem to increase or decrease directly following changes in length of stay. It appears as though mean hospital costs fluctuated considerably in the early years of the DIS database and stabilized somewhat towards the end of the study period. Whereas from 2006 to 2011 hospital costs were significantly higher for patients that underwent minimally invasive appendectomy, from 2012 onwards this was not the case anymore. Moreover, in 2014

the hospital costs were significantly higher for patients that underwent open appendectomy. This is of interest, since most previous studies demonstrated lower or comparable costs.[19,21,41] Furthermore, this study only evaluated differences in direct hospital costs, whereas there may likely be additional benefit of minimally invasive surgery in terms societal costs (i.e. faster recovery resulting in less sick leave).[41,42] With an abundance of evidence showing that a laparoscopic technique surpasses open surgery in clinical outcomes,[22,41,43,44] at similar cost as presented here, laparoscopic appendectomy should likely be the first-choice surgical approach.

In the Netherlands and several other Western countries healthcare costs have risen over the past decades, with over 10% of the gross domestic product being spent on healthcare.[45-47] In general, long-term care for the elderly and the dying form the greater part of healthcare costs.[45] Nevertheless acute appendicitis forms a substantial economic burden. This study indicates that appendicitis and appendectomy produced almost €47 million in hospital costs in 2015, which is 0.8% of the total €5915.6 million in hospital costs for diseases of the digestive tract in the same year according to the Central Bureau for Statistics in the Netherlands.[48] Wherever possible, the aim should be to reduce costs without compromising clinical outcomes. Based on the present results, treatment of appendicitis in general hospitals is preferable over treatment in top-clinical and university hospitals, both in terms of hospital costs and length of stay. A minor proportion (5%) of patients in the present cohort was treated in university hospitals. Presumably these patients represent a selected sample of more complex, high-risk patients and therefore require longer hospital admission and higher cost of care compared to patients in other hospital settings. Differences in length of stay and hospital costs between top-clinical hospitals and general hospitals were smaller, yet significant. In this cohort already the majority of cases (64%) was treated in general hospitals and, assuming equivalent outcomes, this may be further encouraged. Non-operative treatment of appendicitis has also been proposed to be an economical choice,[17] at no compromise in safety according to several recent studies.[11,49,50] Patients treated non-operatively were excluded from this study and the DBC reimbursement system does not allow for discrimination of operating costs from admission day costs. Hence, no direct conclusions can be drawn with regards to the cost of operative vs non-operative management of acute appendicitis based on this cohort.

Limitations and strengths

Some important limitations to this cohort study should be acknowledged. First, in a large administrative database like the DIS database some level of erroneous registration and miscoding may occur. The finding of a fairly large proportion of patients with a registered diagnosis of appendicitis without a surgical procedure of the appendix may be an indicator of this. Secondly, we were unable to further discriminate (and correct for)

relevant potential confounders such as comorbidities, the type of appendicitis (simple / complex) and postoperative complications, which are known to influence length of stay and hospital costs. Unfortunately the DIS-database does not contain all these parameters. Nevertheless, the main strength of the study is that we were able to analyze data from all Dutch hospitals in a nationwide cohort. And despite its limitations, we believe the present study provides an adequate estimation of the substantial burden of appendicitis and appendectomy.

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DISCLOSURES

Authors Elisabeth de Wijkerslooth, Anne Loes van den Boom and Bas Wijnhoven declare no conflict of interest.

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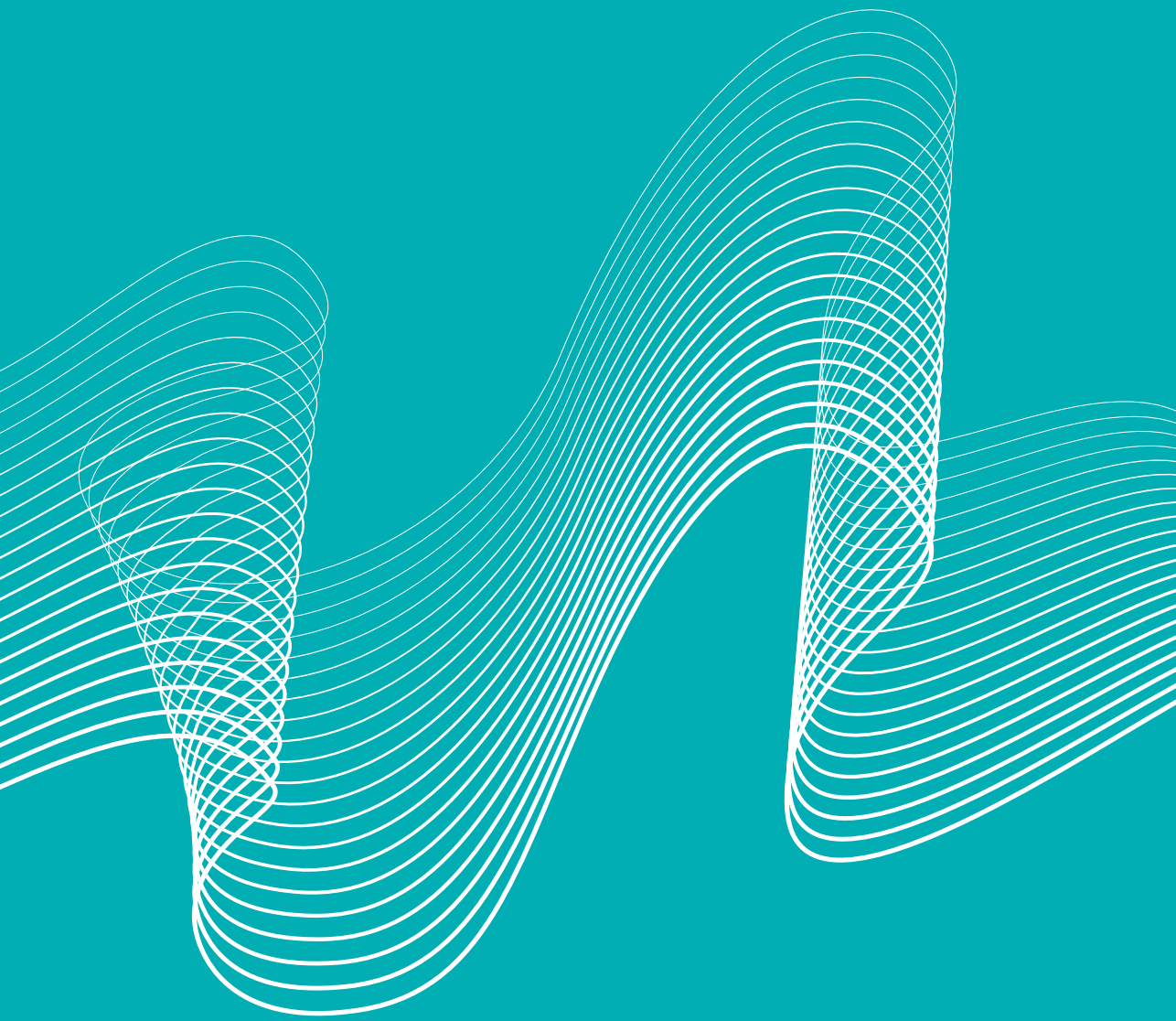

A.L. van den Boom, E.M.L. de Wijkerslooth, K.A.L. Mauff, I. Dawson, C.C. van Rossem, B.R. Toorenvliet, B.P.L. Wijnhoven

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3

INTEROBSERVER VARIABILITY IN THE CLASSIFICATION OF APPENDICITIS DURING LAPAROSCOPY

ABSTRACT

Background:

The intraoperative classification of appendicitis dictates the patient's postoperative management: prolonged antibiotic prophylaxis is recommended for complex appendicitis (gangrenous, perforated, abscess), whilst preoperative prophylaxis suffices for simple appendicitis. Distinguishing these two conditions can be challenging. The aim of this study was to assess the interobserver variability in the classification of appendicitis during laparoscopy.

Methods:

Short video-recordings taken during laparoscopy for suspected appendicitis were shown to surgeons and surgical residents. They were to 1) classify the appendix as no, simple or complex appendicitis, 2) categorize it as normal, phlegmonous, gangrenous, perforated and/or abscess, and 3) decide whether they would prescribe postoperative antibiotics. Answers to the second question were recategorised into complex appendicitis and not complex appendicitis according to the definition by Bhangu *et al*. (Lancet 2015). Interrater reliability was evaluated using Fleiss' kappa (K) score and the S* statistic.

Results:

Eighty assessors participated in the study. Video-recordings of twenty patients were used. Interobserver agreement was minimal for both the classification of appendicitis (K 0.398, 95% CI 0.385 – 0.410) and the choice for postoperative antibiotic treatment (K 0.378, 95% CI 0.362 – 0.393). Agreement was slightly higher when Bhangu's definition of complex appendicitis was applied (K 0.552, 95% CI 0.537 – 0.568).

Conclusions:

The present study indicates that there is considerable variability in the intraoperative classification of appendicitis and the decision to prescribe postoperative antibiotic treatment.

INTRODUCTION

Acute appendicitis is a highly prevalent gastrointestinal disorder among both children and adults. It is the most common abdominal surgical emergency worldwide.[1-4] Its severity can be classified into two distinct types based on operative findings: simple and complex appendicitis.[5] In the literature, 25 to 30 percent of all acute appendicitis is considered complex.[6-11] A classification to distinguish simple and complex appendicitis was provided by Bhangu *et al.*[5] In this classification, a phlegmonous appendix is considered simple appendicitis, whereas gangrenous appendicitis, perforated appendicitis, and periappendiceal abscess formation are regarded as complex appendicitis. Previous studies have shown that the intraoperative assessment of the appendix often does not concur with the histopathological assessment.[12-15] Intraoperative findings were found to be more predictive of the postoperative course (complications) than the histopathological classification.[12] Hence, postoperative management should probably be guided by intraoperative classification of appendicitis.

For simple appendicitis perioperative antibiotic prophylaxis should suffice,[16] whereas for complex appendicitis postoperative antibiotic treatment (or 'prolonged prophylaxis') is recommended.[17,18] However, distinguishing a simple from a complex appendicitis during laparoscopy can be challenging. To date, only one study has evaluated the interobserver variation in the intraoperative classification of acute appendicitis. The authors concluded that agreement on perforated versus non-perforated appendicitis was poor.[9] Such significant interobserver variation may account for variation in perioperative management and postoperative outcomes reported in the literature. An important shortcoming of that study is that static images were used. No study has yet been performed using video footage from laparoscopic appendectomies to evaluate interobserver reliability in the classification of appendicitis.

The aim of this study was to obtain further insight into the interobserver variability amongst surgeons in the intraoperative classification of appendicitis, using laparoscopic video fragments.

METHODS

A cross-sectional interrater reliability study was performed to assess variation in classification of appendicitis. Short video fragments of the appendix, recorded during laparoscopy for suspected appendicitis, were constructed from patient files and shown to surgeons and surgical residents in a survey. Since very little evidence was available in literature to supply us with information to calculate a target sample size from, we

first performed a pilot study. In this pilot, objectives were to obtain preliminary data on interrater reliability and to test face-validity of the video-survey system. Twenty surgeons and residents from the surgical departments of one university hospital and three teaching hospitals in the Rotterdam area participated in this pilot. Fifteen video-fragments were used. By means of the pilot study results, it was calculated (via simulation) that a target sample size of 20 videos, each assessed by forty different participants, should yield an adequate level of precision for the Fleiss Kappa estimate. To enhance the participation, two video-surveys were constructed, each containing ten videos. Eighty participants were recruited in total, forty for each survey. Surgeons and surgical residents in-training from all regions of the Netherlands were invited to participate in this survey during a two-day national surgical congress that took place in May 2017 ('Chirurgendagen 2017').

Video-assessments

Each video-assessment consisted of one or two short fragments (10-20 seconds) followed by three multiple choice questions. The video-fragments came from patients that underwent laparoscopy for suspected appendicitis in one of the aforementioned teaching hospitals between May 2016 and May 2017. A diverse selection of appendices was shown in the videos, varying in size, colour and degree of peritonitis in their surroundings.

Outcomes

Participants were first asked to classify the appendix in the video as *no appendicitis*, *simple appendicitis* or *complex appendicitis* ("classification 1"). No definition of simple and complex appendicitis was given beforehand. Participants were also asked to rank the appendix as *normal*, *phlegmonous*, *gangrenous*, *perforated* and/or *abscess* ("classification 2"). Afterward, these answers were categorized following the definition by Bhangu *et al.* published in the Lancet in 2015 ("classification 3") [5]. In case *gangrenous*, *perforated* and/or *abscess* was checked, the answer was categorized as *indicating complex appendicitis*. If only *normal* or *phlegmonous* was selected, the answer was categorized as *not indicating complex appendicitis (table 1)*. Finally, participants were asked to choose whether they would prescribe postoperative antibiotic treatment "yes" or "no". After assessing the videos, participants were asked to answer some questions about local hospital protocols and their personal opinion on the indications for postoperative antibiotic treatment, and on the duration and route of administration of this treatment.

Table 1. Classification of acute appendicitis*.

Simple appendicitis	Complex appendicitis
Phlegmonous appendix	Gangrenous appendix Perforated appendix Abscess (pelvic/abdominal)

*simplified from classification system by Bhangu et al. [5]

Statistics

Interrater reliability was evaluated using Fleiss' kappa (K) coefficient and the S* statistic [20-24] for classification 1, classification 3 and the decision on postoperative antibiotics. Since multiple answers were allowed for classification 2, these could not be considered strictly independent and no direct interobserver correlation could be calculated. Only percentage agreement results are reported for this classification. Kappa statistics are useful to assess reproducibility and grossly estimate the degree of agreement between observers, beyond that expected by chance alone. Fleiss' K score is related to Cohen's K score, and is meant for measuring reliability among more than two observers.[24,25] K values classify the level of agreement into the following seven categories: 0.01 – 0.20 none; 0.21 – 0.39 minimal; 0.40 – 0.59 weak; 0.60 – 0.79 moderate; 0.80 – 0.90 strong; > 0.90 almost perfect agreement.[23] A P-value below 0.05 indicates the estimated kappa itself is not due to chance.[26]

K statistics were calculated for the following subsets of participants: all participants, surgeons and surgical residents. The S* statistic (a weighted S index for ordinal variables [20,21]) was calculated for participants specialized in abdominal/oncological surgery and participants that performed appendectomy at least once per month, owing to the varying numbers of participants per survey for these two groups.

Additionally, simple descriptives were used to evaluate intra-observer concordance per video-assessment. A video classified as *complex appendicitis* in classification 1 should positively concur with a *complex appendicitis* in classification 3 (based on classification 2) and the prescription of postoperative antibiotics. Likewise, a simple appendicitis in classification 1 should concur with no complex appendicitis in classification 3 and a decision against postoperative antibiotics.

Table 2. Basic demographics of the study participants.

Profession	**N (%)**
Surgeons	46 (58)
• Operating on adults	39 (49)
• Operating on children	1 (1)
• Operating on both	6 (8)
Surgical residents	34 (43)
• 4th – 6th year of training	12 (15)
• 1st – 3rd year of training	22 (28)
Differentiation	**N (%)**
Differentiated into specialty	57 (71)
• Abdominal/oncological surgery	35 (44)
• Trauma surgery	9 (11)
• Vascular surgery	9 (11)
• Other	4 (5)
No differentiation (yet)	23 (29)
Frequency of appendectomies	**N (%)**
Often (>3 per month)	33 (41)
Regularly (≥1 per month)	54 (68)
Rarely (<1 per month)	26 (33)

RESULTS

Eighty surgeons and residents from 35 different hospitals participated in the study. Some 29 participants (36%) worked in the Rotterdam area, 48 (60%) worked in hospitals in other regions of the Netherlands and the remaining three participants worked abroad (in Curacao, Norway and Belgium). Basic demographic information is listed in table 2.

Interobserver agreement

For classification 1 percent agreement ranged from 53% to 98% across the videos (supplementary table S1). Fleiss' K (0.398) reflects minimal agreement among the participants (table 3). For classification 2 percent agreement ranged from 53%–100%, 50%–100%, 50%–100%, 60%–100% and 63%–100%, respectively (suppl. table S1). For classification 3 percent agreement ranged from 53% to 100% (suppl. table S1). Interobserver agreement was weak (K 0.552). The decision to prescribe postoperative antibiotics resulted in percent agreement ranging from 55% to 100%. Interobserver agreement was also minimal (K 0.378).

Kappa scores for reliability were higher for the residents compared to the surgeons (table 3). Kappa scores for subgroups 'abdominal/oncological specialists' and 'participants that performed appendectomy at least monthly' were similar, reflecting minimal to weak interobserver agreement (suppl. table S2).

Table 3. Interobserver agreement Fleiss' K analysis.

Dataset	K-value [95% CI]	P-value
Classification 1: No, simple or complex appendicitis?		
All participants (40)	0.398 [0.385 – 0.410]	<0.0001
Surgeons (23)	0.361 [0.338 – 0.383]	<0.0001
Residents (17)	0.459 [0.429 – 0.489]	<0.0001
Classification 3: Complex appendicitis or not according to Bhangu system*		
All participants (40)	0.552 [0.537 – 0.568]	<0.0001
Surgeons (23)	0.521 [0.493 – 0.548]	<0.0001
Residents (17)	0.608 [0.571 – 0.646]	<0.0001
Decision for postoperative antibiotics, yes or no?		
All participants (40)	0.378 [0.362 – 0.393]	<0.0001
Surgeons (23)	0.352 [0.324 – 0.379]	<0.0001
Residents (17)	0.444 [0.406 – 0.481]	<0.0001

*as displayed in table 1.

Intra-observer concordance

In 119 (15%) of all 800 assessments (20 videos each assessed by 40 participants) classification 1 did not match classification 3. In 75 of those 119 (63%), participants assessed the video as simple appendicitis while also ranking it as a gangrenous appendicitis. In 99 of 800 assessments (12%) classification 1 did not match the decision on postoperative antibiotics. In about half these cases antibiotics were not prescribed even though the

rater did assess the video as complex appendicitis and in the other half antibiotics were prescribed even though the video was assessed as simple appendicitis.

Postoperative antibiotic treatment

Tables 4 and 5 show the participants' answers on postoperative antibiotic treatment for complex appendicitis according to local hospital protocol and their personal preferences. Some 39% and 62.5% of participants felt that prolonged antibiotic prophylaxis was not indicated for appendicitis with localized pus and for gangrenous appendicitis, respectively. Prolonged prophylaxis for less than three days was uncommon in hospital protocols (3%), while 31% of participants indicated this to be their personal preference. The majority of participants preferred a combination of intravenous and oral administration, whereas only 35% indicated this was the route of administration as defined by protocol in their hospital.

Table 4. Indications for postoperative antibiotics after appendectomy (n=80).

	Local hospital protocol, n (%) *		Personal preference, n (%)	
	Indicated	**Not indicated**	**Indicated**	**Not indicated**
Appendicitis with localized pus	39 (49)	21 (26)	49 (61)	31 (39)
Gangrenous appendicitis	23 (29)	34 (43)	30 (37.5)	50 (62.5)
Perforated appendicitis	77 (96)	2 (3)	76 (95)	4 (5)
Appendicitis in presence of abscess	70 (88)	1 (1)	72 (90)	8 (10)
Appendicitis with purulent peritonitis	74 (93)	2 (3)	76 (95)	4 (5)

*remaining participants indicated they were uncertain if it was or was not indicated in the local protocol

Table 5. Preferred (minimum) duration of treatment and route of administration (n=80).

		Local hospital protocol, n (%)	Personal preference, n (%)
Duration	5 days	32 (40)	16 (20)
	3 days	46 (57.5)	39 (49)
	< 3 days	2 (2.5)	25 (31)
Route*	Completely intravenous (IV)	51 (64)	26 (33)
	Intravenous and oral (IV/PO)**	28 (35)	50 (63)

*1 missing answer for hospital protocol on route of administration, 4 missing answers for personal preference
**intravenous administration initially, switched to oral formula if the patient's condition allows

DISCUSSION

The present study demonstrated minimal interobserver agreement in the intraoperative classification of appendicitis. There was also minimal agreement on the choice whether or not to prescribe postoperative antibiotics. These results suggest that the current classification of appendicitis is highly unreliable and that the indications for the administration of postoperative antibiotic treatment vary greatly among surgeons and residents.

For some part, a varying definition of complex appendicitis may account for the variation in classification. As confirmed in the survey results, some surgeons do not classify a gangrenous appendicitis as complex while others do. Likewise, differences in protocols

and opinions may partly account for variability in the decision for or against postoperative antibiotic treatment. This is especially true for appendicitis with localized pus and for gangrenous appendicitis, as indicated by our participants. Kappa scores for reliability remained weak even after categorizing the participants' assessments according to the definition by Bhangu *et al*. This implies that the terms in this classification system might still be too vague. Interrater reliability was slightly better for surgical residents. Kappa scores were consistently higher among the residents, as compared to all participants or the surgeons only. This finding may be attributed to the fact that residents, whilst still in training, are perhaps more focused on adhering to definitions. Reliability was similarly poor for the subgroups of participants differentiating into abdominal/oncological surgery and participants that performed appendectomy at least monthly, compared to all study participants. This implies that even among more experienced surgeons there is considerable variability in the classification.

If a variable simply has two clearly defined outcomes, rater reliability is likely to be high.[23] As soon as multiple outcome measures are in play and the distinction between them is more challenging, this can negatively affect reliability.[23] An accurate intraoperative classification of appendicitis requires the assessors to make fine discriminations and many factors may affect their judgement. Some smaller perforations are not easily detected, but may well be clinically relevant. Signs of necrosis in gangrenous appendicitis may be difficult to distinguish from colour changes due to vascular obstruction. During surgery the appearance of the appendix and its surroundings may change. Furthermore, the level of detail perceived by the surgeon is also dependent on the quality of the laparoscopy equipment. In most studies on appendicitis a specific type of appendicitis is investigated or outcome is compared between different types. The validity of these studies however, may be questionable due to inaccurate classification of the appendicitis, as indicated by the present study. For example, a previous study has shown increased risk of infectious complications after appendectomy for complex appendicitis, when compared to simple appendicitis.[27] If postoperative management depends on the surgeon's intraoperative classification of appendicitis, which seems to be arbitrary, these results may be invalid. This was also stated by Ponsky *et al*. in 2009.[19] They reported considerable variability comparable to the present results (Inter Class Coefficient scores 0.27 – 0.36 (same interpretation as for K-score) for distinguishing perforated from non-perforated appendicitis).[19] Their conclusion was that the available classification by the International Statistical Classification of Diseases and Health Problems (ICD) was too limited and more objective assessment points should be defined.

In this study, agreement improved slightly after converting the participants' answers according to Bhangu's more detailed definition of complex appendicitis. Interrater reliability remained weak however, suggesting that even if surgeons would strictly adhere to this

definition, the diagnosis of complex appendicitis would still be unreliable. An intraoperative classification tool consisting of more clear-cut, objective factors, could perhaps improve interobserver agreement in classification and postoperative management. However, it is questionable whether any intraoperative assessment will be reliable enough. Maybe the emphasis should not rely (solely) on intraoperative findings, but on more quantifiable variables, such as preoperative biochemical blood analyses (e.g. C-reactive protein, white bloodcell count).[28] Several radiological and laboratory factors have been associated with adverse outcomes after appendectomy.[29-34] A combination of these and intraoperative findings may result in more consistent postoperative management.[35]

Interestingly, a third of the participants in this study would prefer to restrict postoperative antibiotics to less than 3 days after appendectomy, while only 3% answered this was standard practice at their hospital. Moreover, 40% of the participants indicated that the standard treatment duration at their hospital was 5 days. This implies that if it were up to the surgeons themselves, prolonged antibiotic prophylaxis could be reduced substantially. An interesting thought, taking into account the alarming emergence of hospital costs and antimicrobial resistance worldwide that warrants optimization of antibiotic use.

The present study was limited by only showing the participants 10 to 20 seconds of video-footage to base their classification on. In reality the surgeon has the entire length of the operation to decide on the type of appendicitis and postoperative treatment. This may have resulted in underestimation of rater reliability. Agreement on the classification and postoperative treatment may have been better, if it were tested under circumstances better resembling the real situation. A follow-up study incorporating more and/or longer videos, according to a standardized format that specifies the required content of the video fragments, could be interesting.

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Authors' contributions
All authors were involved in the design of the study. EW created the online video surveys, collected the data and wrote this manuscript. KM performed all statistical analyses. AB and BW revised the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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SUPPLEMENTARY TABLES

Table S1. Percent agreement analysis.

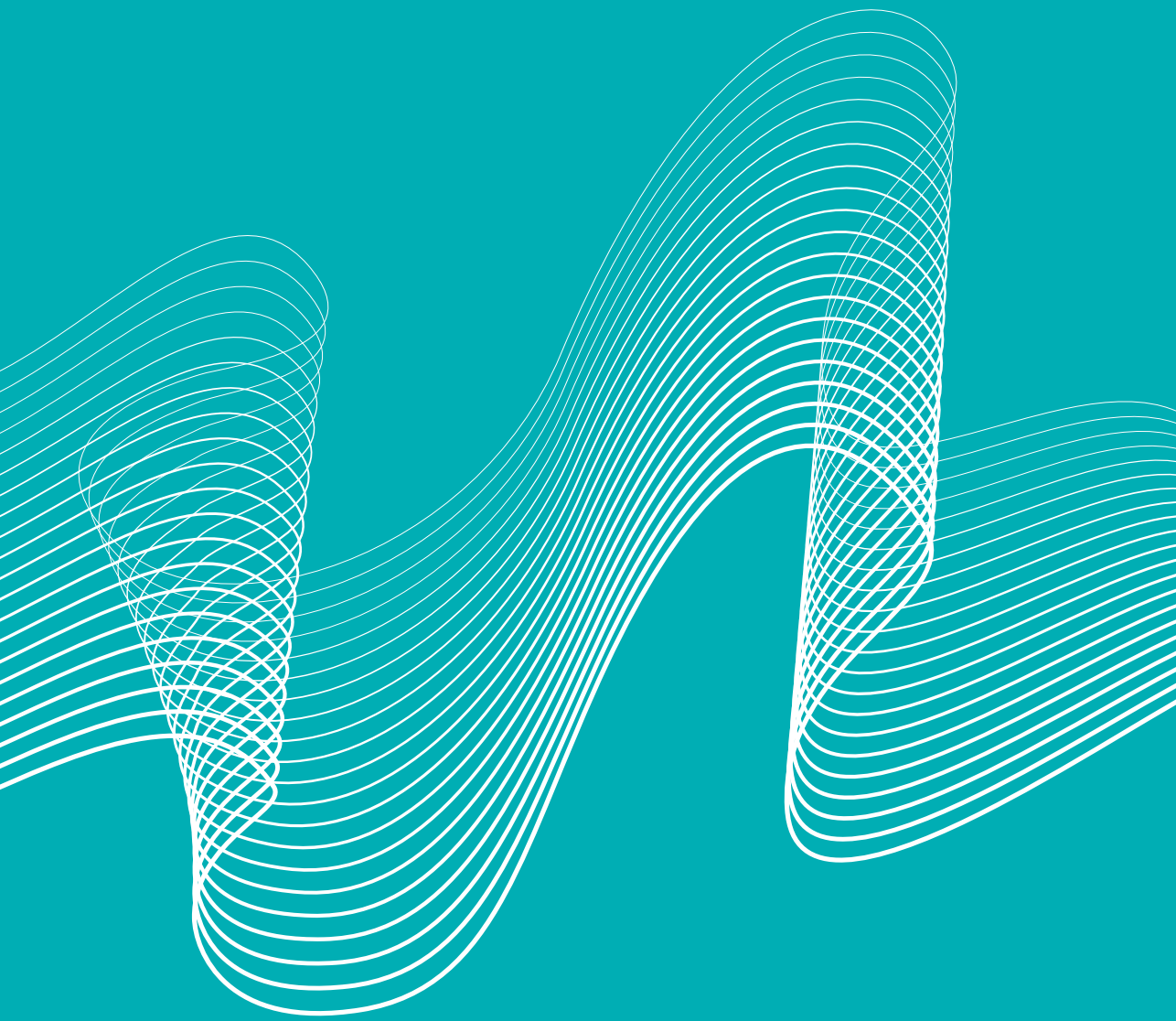
Video	No, simple or complex?[1]	Sana?[2]	Phlegmonous?[2]	Gangrenous?[2]	Perforated?[2]	Abscess?[2]	Bhangu complex?[2]	Postop. antibiotics?[2]
1	83% (S)	100% (N)	88% (Y)	90% (N)	98% (N)	93% (N)	83% (N)	85% (N)
2	65% (C)	100% (N)	60% (N)	58% (N)	80% (N)	85% (N)	68% (Y)	70% (Y)
3	70% (C)	100% (N)	83% (N)	93% (N)	60% (Y)	73% (N)	85% (Y)	83% (Y)
4	60% (S)	100% (N)	93% (N)	93% (Y)	98% (N)	100% (N)	95% (Y)	55% (N)
5	85% (S)	93% (N)	83% (Y)	93% (N)	100% (N)	98% (N)	90% (N)	98% (N)
6	95% (N)	95% (Y)	98% (N)	100% (N)	100% (N)	100% (N)	100% (N)	100% (N)
7	90% (C)	100% (N)	100% (N)	93% (Y)	83% (N)	93% (N)	100% (Y)	75% (Y)
8	85% (S)	100% (N)	50% (Y)	53% (Y)	100% (N)	98% (N)	53% (Y)	93% (N)
9	68% (C)	100% (N)	58% (Y)	93% (N)	70% (N)	70% (N)	58% (Y)	68% (Y)
10	53% (C)	100% (N)	68% (Y)	98% (N)	73% (N)	78% (N)	50% (Y)	65% (Y)
11	98% (S)	95% (N)	98% (Y)	100% (N)	100% (N)	100% (N)	100% (N)	100% (N)
12	68% (S)	85% (N)	83% (Y)	98% (N)	100% (N)	100% (N)	98% (N)	80% (N)
13	85% (C)	100% (N)	93% (N)	50% (N)	70% (Y)	100% (N)	98% (Y)	85% (Y)
14	90% (S)	98% (N)	83% (Y)	88% (N)	98% (N)	98% (N)	83% (N)	83% (N)
15	80% (C)	100% (N)	78% (N)	58% (Y)	75% (N)	93% (N)	85% (Y)	60% (Y)
16	53% (C)	100% (N)	55% (N)	68% (N)	80% (N)	88% (N)	60% (Y)	55% (Y)
17	55% (S)	53% (N)	53% (Y)	98% (N)	100% (N)	100% (N)	98% (N)	95% (N)
18	85% (C)	100% (N)	98% (N)	90% (Y)	80% (N)	88% (N)	98% (Y)	70% (Y)
19	63% (C)	100% (N)	63% (N)	63% (N)	80% (N)	63% (N)	78% (Y)	73% (Y)
20	80% (S)	90% (N)	88% (Y)	100% (N)	100% (N)	98% (N)	98% (N)	88% (N)

[1]S = simple, C = complex, N = no appendicitis. [2]N = no; Y = yes.

Table S2. Kappa coefficient analysis per subgroup.

Question	Dataset	Videos	Participants	Fleiss' K	LCL[1]	UCL[2]	p
No, simple or complex appendicitis?	All	20	40	0,398	0,385	0,410	<0.0001
	Surgeons	20	23	0,361	0,338	0,383	<0.0001
	1st – 3rd yr. residents	20	11	0,474	0,426	0,522	<0.0001
	4th – 6th yr. residents	20	6	0,480	0,390	0,569	<0.0001
	All residents	20	17	0,459	0,429	0,489	<0.0001
	Abd-Onco. specialized[3]	20	16/19[5]	0,477[7]	0,374	0,578	<0.0001
	≥ 1 appendectomy/month[4]	20	24/30[6]	0,511[7]	0,408	0,616	<0.0001
Complex according to Bhangu definition?	All	20	40	0,552	0,537	0,568	<0.0001
	Surgeons	20	23	0,521	0,493	0,548	<0.0001
	1st – 3rd yr. residents	20	11	0,585	0,526	0,645	<0.0001
	4th – 6th yr. residents	20	6	0,701	0,588	0,815	<0.0001
	All residents	20	17	0,608	0,571	0,646	<0.0001
	Abd-Onco specialized[3]	20	16/19[5]	0,517[7]	0,346	0,695	<0.0001
	≥ 1 appendectomy/month[4]	20	24/30[6]	0.382[7]	0,233	0,541	<0.0001
Prescribe postoperative antibiotics or not?	All	20	40	0,378	0,362	0,393	<0.0001
	Surgeons	20	23	0,352	0,324	0,379	<0.0001
	1st – 3rd yr. residents	20	11	0,449	0,390	0,508	<0.0001
	4th – 6th yr. residents	20	6	0,411	0,298	0,525	<0.0001
	All residents	20	17	0,444	0,406	0,481	<0.0001
	Abd-Onco specialized[3]	20	16/19[5]	0,414[7]	0,265	0,582	<0.0001
	≥ 1 appendectomy/month[4]	20	24/30[6]	0,382[7]	0.233	0,541	<0.0001

[1] LCL = lower confidence interval limit;
[2] UCL = upper confidence interval limit;
[3] surgeons and residents who specialized in gastrointestinal/oncological surgery;
[4] surgeons and residents who perform appendectomy at least once monthly;
[5] Half the videos assessed by 16 participants, half by 19, in this analysis;
[6] Half the videos assessed by 24 participants, half by 30, in this analysis;
[7] S*test performed, using normal/Monte-Carlo approximation, due to the different number of participants per subject. [20,21]



Elisabeth M.L. de Wijkerslooth, Anne Loes van den Boom, Bas P.L. Wijnhoven

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4

VARIATION IN CLASSIFICATION AND POSTOPERATIVE MANAGEMENT OF COMPLEX APPENDICITIS: A EUROPEAN SURVEY

ABSTRACT

Background:

Data on common practice in the management of patients with complex appendicitis is scarce, especially for the adult population. Variation in the definition of complex appendicitis, indications for and the type of prolonged antibiotic prophylaxis has not been well-studied yet. The aim of this study was to document current practice of the classification and postoperative management of complex appendicitis on an international level.

Methods:

An online survey was dispersed among practicing surgeons and surgical residents. Survey questions pertained to the definition of a complex appendicitis, indications for antibiotic prophylaxis after appendectomy, the duration, route of administration and antibiotic agents used.

Results:

A total of 137 survey responses were eligible for analysis. Most respondents were from Northern or Western Europe and were specialized in gastrointestinal surgery. Opinion varied substantially regarding the management of appendicitis, in particular for phlegmonous appendicitis with localized pus, gangrenous appendicitis and iatrogenic rupture of appendicitis. The most common duration of postoperative antibiotics was evenly spread over <3, 3, 5 and 7 days. Whereas most respondents indicated a combined intravenous and oral route of administration was common practice, 28% answered a completely intravenous route of administration was standard practice.

Conclusions:

Current practice patterns in the classification and postoperative management of complex appendicitis are highly variable.

INTRODUCTION

Acute appendicitis is a highly prevalent surgical emergency in both children and adults.[1-4] Yet, the optimum management of this disease remains a subject of controversy. The non-operative management is increasingly being studied, but emergency appendectomy remains the cornerstone of treatment in most hospitals.[5-7] If the surgeon classifies the type of appendicitis as complex, antibiotic prophylaxis should be continued after surgery.[8-11] This aims to prevent infectious complications, including recurrent intra-abdominal infections. The available guidelines recommend to extend prophylaxis for 3 to 7 postoperative days.[8-13] The alarming emergence of antimicrobial resistance worldwide warrants optimization of antibiotic use, as presented as a key focus by the WHO.[14] Therefore it is key to carefully select patients that benefit from prolonged prophylaxis and to define the optimal regimen.

A survey among Dutch surgeons demonstrated that a clear standard of care is missing both in patient selection and determining the length of treatment.[15] The definition of complex appendicitis used in studies varies. Apart from its common component: perforated appendicitis, it may or may not also include unperforated gangrenous appendicitis, appendicitis in presence of a faecolith and/or appendicitis in presence of pus, or purulent peritonitis, or abscess.[16-20] Postoperative antibiotic use is left to the discretion of the surgeon. Five days of antibiotics, switched from an intravenous to oral route as early as 48 hours after surgery, is common use in many centers in the Netherlands.[16,21] Another strategy, which is gaining ground, consists of three days of intravenous antibiotics only.[16,21,22] Intravenous regimens most used are cefuroxime or ceftriaxone in combination with metronidazole.[23] Amoxicillin-clavulanate is often chosen as oral antibiotic. Little is reported in literature regarding the common practice of prolonged prophylaxis after appendectomy in other countries. Some studies have reported variability in care for patients with complex appendicitis.[24-30] Most studies included only pediatric patients and few focused on the postoperative management of appendicitis. In pursuit of the optimum antibiotic regimen for complex appendicitis, a variety of treatment protocols has been reported.[16,22,31-34] Limiting antibiotic use to five days at most is widely accepted, but no specific duration of postoperative antibiotic use has proven most advantageous. Previous research has shown that standardization of practice can be beneficial in terms of clinical outcomes after appendectomy (i.e. postoperative abscess formation and length of hospital stay).[30,35] Identifying variation in practice may therefore reveal opportunities for quality improvement.

The aim of this study was to determine the variation in the classification and postoperative management of complex appendicitis on an international level.

MATERIAL AND METHODS

The present study was a cross-sectional, international, anonymous online survey among surgeons and surgical residents, which took place from June until September 2017. Several surgical associations and research collaboratives (European Digestive Surgery; East Midlands Surgical Academic Network; GlobalSurg; National Research Collaborative (UK/Ireland); Scottish Surgical Research Group; South Yorkshire Surgical Research Group; West Midlands Research Collaborative) kindly dispersed the survey among their members. Through email surgeons and residents were invited to participate by clicking a link to enter the online survey module. Three to four weeks after the first email, a second reminder was sent out. Participation was voluntary. Due to widespread dispersion of the survey through association newsletters and personal forwarding the response-rate could not be assessed.

The survey consisted of thirteen questions in total. Data on the respondents' backgrounds were collected in the first five questions. Next, respondents were to answer two questions *based on their personal professional opinion:* concerning the definition of a complex appendicitis and indications for prolonged antibiotic prophylaxis after appendectomy. Lastly, respondents were to answer five questions *based on common practice at their hospital*: these were questions regarding the duration, route of administration and antibiotic agents used as prolonged prophylaxis after appendectomy. All survey questions were multiple-choice questions. Only 4 questions allowed for a free text answer if answer option 'Other' was ticked. The full survey question list can be found in supplementary file S1.

Statistics

All survey data were analyzed by means of simple descriptive statistics using Excel® 2010 (Microsoft, Redmond, Washington, USA) and SPSS version 21 (IBM, Armonk, New York, USA). Included in the analysis are results from all European respondents that completed at least the survey items on the definition of a complex appendicitis.

RESULTS

A total of 150 European respondents submitted their surveys within the 2-month timeframe. Ten responses were excluded from the analysis due to insufficient completion. Another three were excluded, as the respondents were not surgeons or surgical residents. The remaining 137 surveys were analyzed. The respondents were employed in 82 different hospitals in 19 countries. Background characteristics of the respondents are shown in table 1. Eighty-four percent of them performed appendectomy at least monthly.

Definition of complex appendicitis and indications for prolonged prophylaxis (table 2).

Eighty-eight percent of respondents was familiar with the classification of appendicitis into simple and complex appendicitis; fifty percent indicated they most often used the classification in practice. For the 8 types of appendicitis used in this survey, the proportion of surgeons that considered it a complex appendicitis type and the proportion that considered it an indication for prolonged prophylaxis are shown in table 2. Disagreement among the respondents, especially regarding phlegmonous appendicitis with localized pus/peritonitis, gangrenous appendicitis and iatrogenic rupture of appendicitis, is further illustrated in figure 1.

Table 1. Study participants (n=137).

Region*	**n (%)**
Northern Europe	76 (55)
Western Europe	48 (35)
Other	13 (10)
Profession	**n (%)**
Surgeon	84 (61)
Senior resident (4th – 6th yr.)	28 (20)
Junior resident (1st – 3rd yr.)	25 (18)
Field of specialization†	**n (%)**
Gastrointestinal/oncological surgery	110 (80)
Trauma surgery	12 (9)
Vascular surgery	6 (4)
General surgery	6 (4)
Other‡	7 (5)
No differentiation (yet)	16 (12)
Type of hospital	**n (%)**
Academic or university hospital	83 (61)
General hospital	30 (22)
Teaching hospital	22 (16)
Other§	2 (1)
Performs appendectomy	**n (%)**
Rarely (< 1 per month)	22 (16)
Sometimes (1-2 per month)	34 (25)
Often (> 2 per month)	81 (59)

* Number of respondents per country is available in supplementary table S1.
† More than one answer was allowed.
‡ Other specializations included: 4x emergency surgery, 1x hand surgery, 1x orthopedics and 1x pediatric surgery.
§ Other answer included: 1x private clinic, 1x general pediatric teaching hospital.

Table 2. Respondents' answers on the definition of complex appendicitis and indication for postoperative antibiotic use, n (%).

Do you consider the following types of appendicitis complex? ***Answer 'yes'***	**All** ***n=137***	**Northern Eur.** ***n=76***	**Western Eur.** ***n=48***	**Other** ***n=13***
Phlegmonous appendicitis	23 (17)	10 (13)	10 (21)	3 (23)
Phlegmonous appendicitis with localized pus/peritonitis	74 (54)	34 (45)	32 (67)	8 (62)
Gangrenous appendicitis	65 (47)	31 (41)	26 (54)	8 (62)
Gangrenous appendicitis with localized pus/peritonitis	110 (80)	57 (75)	41 (85)	12 (92)
Perforated appendicitis	129 (94)	73 (96)	44 (92)	12 (92)
Iatrogenic rupture of appendicitis	50 (36)	33 (43)	12 (25)	5 (38)
Appendicitis with an intraabdominal abscess	133 (97)	74 (97)	47 (98)	12 (92)
Appendicitis with purulent peritonitis	134 (98)	76 (100)	46 (96)	12 (92)
Do the following patients need postoperative antibiotic treatment? ***Answer 'yes'***	**All** ***n=133***	**Northern Eur.** ***n=73***	**Western Eur.** ***n=47***	**Other** ***n=13***
Patient with phlegmonous appendicitis	13 (10)	2 (3)	9 (19)	2 (15)
Patient with phlegmonous appendicitis with localized pus/peritonitis	77 (58)	37 (51)	30 (64)	10 (77)
Patient with gangrenous appendicitis	65 (49)	31 (42)	23 (49)	11 (85)
Patient with gangrenous appendicitis with localized pus/peritonitis	109 (82)	59 (81)	37 (79)	13 (100)
Patient with perforated appendicitis	126 (95)	71 (97)	43 (91)	12 (92)
Patient with iatrogenic rupture of appendicitis	76 (57)	38 (52)	28 (60)	10 (77)
Patient with appendicitis with an intraabdominal abscess	127 (95)	69 (95)	46 (98)	12 (92)
Patient with appendicitis with purulent peritonitis	128 (96)	70 (96)	46 (98)	12 (92)

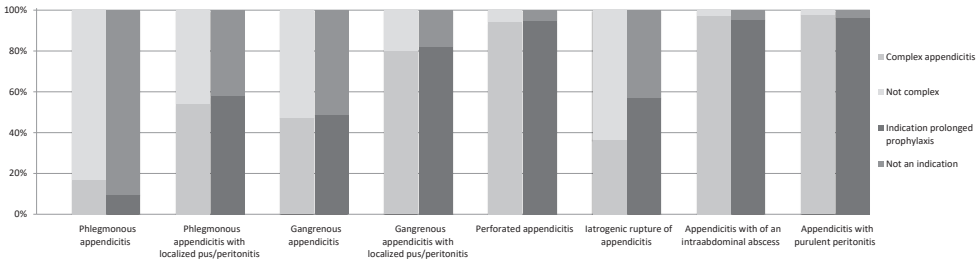

Figure 1. The definition of a complex appendicitis and indications for prolonged antibiotic prophylaxis

Duration, route of administration and antibiotic agents

Table 3 shows the variation in treatment duration and route of administration, according to the respondents' answers on policy at their hospital. Forty-five per cent of respondents answered that the minimum duration of prolonged prophylaxis at their hospital was 24 or 48 hours. Subsequently, 23 per cent indicated that this was the most common duration (fig. 2). Most respondents that indicated 24 hours as minimum were from the UK (49%) or Finland (24%) (fig. 2). The majority answered that a combined intravenous and oral course was most prescribed at their hospital (table 3). The most popular intravenous antibiotic regimens were cefuroxime in combination with metronidazole (27%), amoxicillin/clavulanate (22%) and piperacillin in combination with tazobactam (12%). And the most preferred oral agents were amoxicillin/clavulanate (37%), ciprofloxacin in combination with metronidazole (24%) and cephalexin in combination with metronidazole (11%).

Table 3. Respondents' answers on duration and administration of postoperative antibiotic use for complex appendicitis at their hospital, n (%).

Minimum duration	**All** ***n=127***	**Northern Eur.** ***n=68***	**Western Eur.** ***n=46***	**Other** ***n=13***	**Denmark** ***n=16***	**Finland** ***n=19***	**Ireland** ***n=10***	**Lithuania** ***n=12***	**Norway** ***n=13***	**UK** ***n=29***
24 hours	45 (35)	15 (22)	27 (59)	3 (23)	1 (6)	11 (58)	5 (50)	1 (8)	1 (8)	22 (76)
48 hours	13 (10)	3 (4)	5 (11)	5 (38)	0	2 (11)	1 (10)	1 (8)	0	3 (10)
3 days	46 (36)	37 (54)	5 (11)	4 (31)	15 (94)	3 (16)	1 (10)	5 (42)	11 (85)	2 (7)
5 days	18 (14)	10 (15)	7 (15)	1 (8)	0	3 (16)	2 (20)	4 (33)	1 (8)	1 (3)
7 days	5 (4)	3 (4)	2 (4)	0	0	0	1 (10)	1 (8)	0	1 (3)
Most common duration	**All** ***n=127‡***	**Northern Eur.** ***n=67‡***	**Western Eur.** ***n=45***	**Other** ***n=13***	**Denmark** ***n=16***	**Finland** ***n=19***	**Ireland** ***n=10***	**Lithuania** ***n=12§***	**Norway** ***n=13§***	**UK** ***n=28***
24 hours	19 (15)	10 (12)	8 (18)	1 (8)	1 (6)	4 (20)	0	3 (25)	0	8 (29)
48 hours	10 (8)	2 (2)	6 (13)	2 (15)	0	1 (5)	1 (10)	1 (8)	0	5 (18)
3 days	34 (27)	24 (39)	5 (11)	5 (38)	15 (94)	1 (5)	1 (10)	2 (17)	4 (31)	4 (14)
5 days	35 (28)	13 (19)	18 (40)	3 (23)	0	5 (26)	6 (60)	3 (25)	4 (31)	8 (29)
7 days	26 (20)	15 (25)	8 (18)	2 (15)	0	8 (40)	2 (20)	2 (17)	4 (31)	3 (11)
Common administration	**All** ***n=130***	**Northern Eur.** ***n=70***	**Western Eur.** ***n=47***	**Other** ***n=13***	**Denmark** ***n=17***	**Finland** ***n=19***	**Ireland** ***n=10***	**Lithuania** ***n=12***	**Norway** ***n=13***	**UK** ***n=30***
Intravenous (IV)	36 (28)	23 (30)	8 (17)	5 (38)	8 (47)	3 (16)	3 (30)	5 (42)	4 (31)	5 (17)
Combined (IV/PO)	93 (72)	46 (61)	39 (81)	8 (62)	8 (47)	16 (84)	7 (70)	7 (58)	9 (69)	25 (83)
Oral (PO)	1 (1)	1 (1)	0	0	1 (6)	0	0	0	0	0

Results shown for all respondents, per region and per country with at least 10 respondents that completed the relevant survey items.

‡ three other responses: 2x 4 days and 1x 10 days.

§ one other response: 4 days

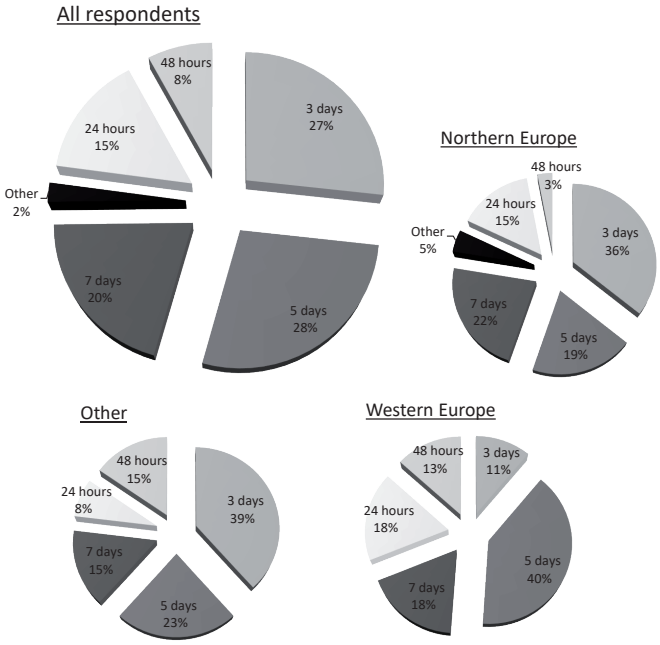

Figure 2. Most common duration of prolonged antibiotic prophylaxis for complex appendicitis

Northern Europe Denmark, Finland, Lithuania, Norway and Sweden. Western Europe Belgium, Germany, Ireland, Switzerland and the United Kingdom. Other Bulgaria, Croatia, Greece, Italy, Poland, Romania, Spain, Turkey.

DISCUSSION

The present study was designed to provide an overview of current practice in the postoperative management of complex appendicitis. There was a considerable variation in the definition of a complex appendicitis, indications for prolonged antibiotic prophylaxis after appendectomy and the antibiotic regimens used. Such variation in practice may have an effect on clinical outcomes, and standardization may impact the appropriate use of antibiotics worldwide given the rising antimicrobial resistance.

The vast majority of surgeons in this survey agreed that appendicitis with perforation, intra-abdominal abscess or purulent peritonitis can be defined as complex appendicitis for which prolonged antibiotic prophylaxis is indicated. Most respondents (80%) also classified a gangrenous appendicitis with localized pus as complex appendicitis. Opinion was divided regarding a gangrenous appendicitis without localized pus: only about half considered this type a complex appendicitis. In their guideline on intra-abdominal infections, the Surgical Infection Society and Infectious Diseases Association of America recommend to restrict antibiotic prophylaxis to 24 hours after appendectomy for gangrenous unperforated appendicitis.[10] Nevertheless, as confirmed in this survey, some clinicians feel that a gangrenous appendicitis increases the patient's risk of an infectious complication and there is some evidence that supports this.[36] Responses were ambiguous for phlegmonous appendicitis with localized pus as well. It appears that the presence of (localized) pus in the abdomen could be a decisive factor for some surgeons to classify appendicitis as complex. However, none of the available guidelines take into account the presence of pus in the decision of prescribing postoperative antibiotics (nor do they mention abscess or purulent peritonitis).[9-11] Strikingly, 36% of respondents felt that a iatrogenic rupture of appendicitis fell within the definition of a complex appendicitis, yet 57% indicated that postoperative antibiotics were needed. Such variation in opinion among surgeons may originate from a lack of consensus in literature, especially literature on adult patients.[12,13,37,38] These results imply that depending on the type of appendicitis, a patient might be treated completely different by one surgeon compared to another. The present analyses showed that this standard care differs substantially for several types of appendicitis, both between and within countries.

The most common duration of prolonged prophylaxis for complex appendicitis was almost evenly spread over less than 3 days, 3, 5 and 7 days. About half the respondents answered that prophylaxis was most often extended *beyond* 3 postoperative days. A large prospective cohort study demonstrated that 3 and 5 days of postoperative antibiotics result in similar rates of infectious complications.[22] Thus, substantial overtreatment may exist. Another sign of potential overuse of antibiotics is that there was quite a large difference between the minimum durations in hospital protocols and the most commonly

practiced durations. Randomized studies will have to confirm whether a reduced course is indeed safe and effective. In this survey, responses from Denmark were unambiguous: all but one indicated that three days of postoperative antibiotics was the minimum as well as the most common duration. This duration has become the standard in Denmark.[39] For the remainder, responses on duration varied greatly within and between geographical regions. Again, this implies considerable variation in care. For one individual patient this may affect their length of stay in the hospital and perhaps their risk of an infectious complication. Moreover, on a national or international level, a reduced or prolonged antibiotic course may have a significant impact on antibiotic use, antimicrobial resistance and hospital costs.

A recent survey among Dutch surgeons and residents demonstrated similar ambiguity concerning appendicitis with localized pus and gangrenous appendicitis: 61% and 38% of 80 respondents indicated they considered these types an indication for postoperative antibiotics, respectively.[21] Most commonly postoperative antibiotics were given for 3 days (58%) or 5 days (40%). Restricting postoperative antibiotics to less than 3 days was much less common (2,5%), compared to the 23% of respondents in this international survey that indicated this was the most common duration of prolonged prophylaxis. Two survey studies among pediatric surgeons in North-America (published in 2003 and 2004) also addressed the postoperative management of complex (perforated) appendicitis.[27,40] Both studies reported a highly variable duration of antibiotic therapy for perforated appendicitis. At that time, more than 90 percent of the pediatric surgeons extended intravenous prophylaxis beyond 3 postoperative days and added 4 to 10 days of oral antibiotics.[27]

The lack of consistency in classification and management of appendicitis demonstrated in this survey, was also addressed by Reid *et al*. in 2017. They proposed a uniform intraoperative scoring system to more accurately define the type of appendicitis and predict the risk of recurrent abdominal infection.[41] Likewise, a standardized definition of complex appendicitis is warranted to aid stratification of risk and guide postoperative antibiotic use.[42] According to the Surgical Infection Society, there are very little data on standardized approaches to prolonged prophylaxis for patients with complex appendicitis.[10,43] It is suggested that standardized approaches to source control could improve outcomes. In pursuit of the shortest effective course, we recently started the APPIC trial, hypothesizing that 48 hours of antibiotics is non-inferior to 5 days in terms of preventing infectious complications after surgery for complex appendicitis.[44] The present survey results imply that non-inferiority of the short 48 hours course may significantly impact current practice.

One important limitation to this study is that it is unsure whether the respondents in this survey are a representative sample, therefore the results may only be interpreted as an indication of variation in practice. To assess true variation in international current practice, one would have to perform an audit of appendicitis on a larger scale. This survey was built to encourage many responses in a short timeframe. The questions were designed to minimize free-text responses and the total number of questions was kept small. The focus was on different types of appendicitis as potential indications for prolonged prophylaxis and on the specifics of the antibiotic regimen. Other factors that may also influence postoperative management of complex appendicitis – such as preoperative and postoperative clinical characteristics or inflammatory biochemical results – were not addressed in this survey.

Despite these limitations, the results firmly suggest that there is considerable variability in the classification and postoperative management of patients with complex appendicitis. Future research should focus on identifying patients that benefit from prolonged antibiotic prophylaxis, determining the shortest effective course and standardizing the approach.

Authors' contributions

EW, AB and BW designed this study. EW created the survey and wrote this manuscript. AB and BW revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY TABLES

Table S1. Work origin of respondents.

Country	n	Region
Belgium	5 (4)	Western Europe
Bulgaria	1 (1)	Eastern Europe
Croatia	1 (1)	Eastern Europe
Denmark	17 (12)	Northern Europe
Finland	21 (15)	Northern Europe
Germany	1 (1)	Western Europe
Greece	1 (1)	Southern Europe
Ireland	11 (8)	Western Europe
Italy	4 (3)	Southern Europe
Lithuania	13 (9)	Northern Europe
Norway	15 (11)	Northern Europe
Poland	2 (1)	Eastern Europe
Romania	1 (1)	Eastern Europe
Spain	1 (1)	Southern Europe
Sweden	10 (7)	Northern Europe
Switzerland	1 (1)	Western Europe
Turkey	1 (1)	Eastern Europe
Ukraine	1 (1)	Eastern Europe
United Kingdom	30 (22)	Western Europe
Total	137	

Table S2. Familiar with classification into simple and complex appendicitis? (n=137).

	n (%)
Unfamiliar	16 (16)
Familiar but don't regularly use it	26 (19)
Sometimes do, sometimes don't use it	27 (20)
(Almost) always use it	68 (50)

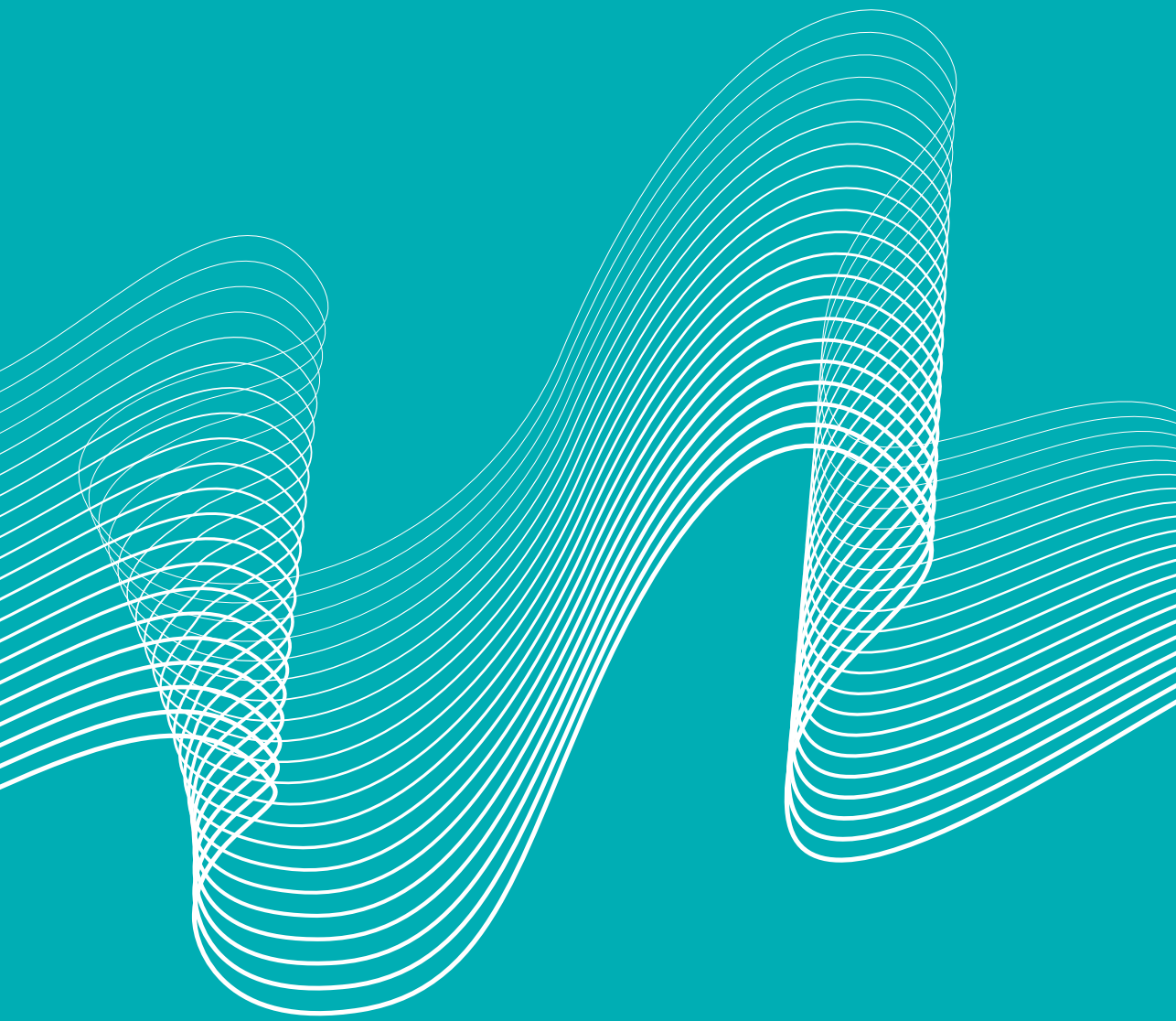
Table S3. Preferred antibiotic agents.

Preferred for intravenous administration, n=128*	n (%)
Amoxicillin + clavulanate	31 (22)
Other amoxicillin combination	13 (10)
Cefuroxime + metronidazole	38 (27)
Other cephalosporin + metronidazole	13 (10)
Gentamicin + metronidazole	8 (6)
Piperacillin + tazobactam	17 (12)
Other piperacillin combination	6 (5)
Other‡	3 (2)
Preferred for oral administration, n=127	**N (%)**
Amoxicillin + clavulanate	47 (37)
Other amoxicillin combination	11 (9)
Cephalexin + metronidazole	14 (11)
Other cephalosporin combination	7 (6)
Ciprofloxacin + metronidazole	31 (24)
Trimethoprim + sulfamethoxazole + metronidazole	12 (9)
Other§	5 (4)

* 1 double answer in free text.

‡ Other answers included: ciprofloxacin + metronidazole (2) and trimethoprim + sulfamethoxazole + metronidazole.

§ Other answers included: clavulanate + metronidazole (1), levofloxacin + metronidazole (3) and tazobactam (1).



Elisabeth M.L. de Wijkerslooth*, Joske de Jonge*, Anne Loes van den Boom, Anna A.W. van Geloven, Willem A. Bemelman, Bas P.L. Wijnhoven, Charles C. van Rossem, for the Snapshot Appendicitis Study Group.

* shared first authorship

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5

POSTOPERATIVE OUTCOMES OF PATIENTS WITH NON-PERFORATED GANGRENOUS APPENDICITIS: A NATIONAL MULTICENTER PROSPECTIVE COHORT ANALYSIS

ABSTRACT

Background:

Controversy exists regarding the use of postoperative antibiotics for non-perforated gangrenous appendicitis.

Objective:

The aim of this study was to evaluate the rate of postoperative infectious complications and the effect of postoperative antibiotic use among patients with non-perforated gangrenous appendicitis.

Patients:

All consecutive patients who had surgery for suspected acute appendicitis. Patients were excluded if no appendectomy was performed or appendectomy was performed for pathology other than acute appendicitis.

Main Outcomes Measures:

Type of appendicitis was categorized as phlegmonous, gangrenous or perforated. The primary endpoint was the rate of infectious complications (intra-abdominal abscess and surgical site infection) within 30 days after appendectomy. Univariable and multivariable logistic regression analyses were performed to identify predictors of infectious complications.

Results:

A total of 1863 patients were included: 1321 (70.9%) with phlegmonous appendicitis, 181 (9.7%) with gangrenous appendicitis and 361 (19.4%) with perforated appendicitis. Infectious complications were more frequent in patients with gangrenous vs. phlegmonous appendicitis (7.2% vs. 3.8%, p = 0.03). This association was no longer statistically significant in multivariable analysis (OR 1.09, 95% CI 0.49 – 2.44). There was no significant difference in infectious complications between ≤ 24h (n=57) of postoperative antibiotics compared to > 24hrs (n=124) (3.6% vs. 8.9%, p = 0.35) in patients with gangrenous appendicitis.

Conclusion:

Patients with non-perforated gangrenous appendicitis are at higher risk of infectious complications than patients with phlegmonous appendicitis, yet gangrenous disease is not an independent risk factor. Postoperative antibiotic use over 24 hours was not associated with decreased infectious complications.

INTRODUCTION

The treatment of gangrenous non-perforated appendicitis is controversial.[1,2] Routine administration of postoperative antibiotics to reduce the rate of infectious complications remains a topic of debate. Most guidelines lack clear recommendations on gangrenous appendicitis (*gangrenous* implies *non-perforated gangrenous* unless specified otherwise).[3-7] The guideline by the Surgical Infection Society (SIS), however, recommends to limit postoperative use of antibiotics to 24 hours.[8] Although the authors state that this is based on level 1A evidence,[8] adherence to the guideline is poor. Many surgeons consider gangrenous appendicitis as a complex appendicitis similar to a perforated appendicitis or appendicitis with abscess and/or purulent peritonitis. For these patients, antibiotic prophylaxis is usually given for 3 to 5 postoperative days.[7,9,10] On the contrary, others do not prescribe any postoperative antibiotic treatment or just a short course (24 or 48 hours).[9,10] It has been reported in literature that standardization of practice leads to improved surgical outcomes, for appendicitis and several other indications.[11-16] Therefore, it is key to address this variation in medical care and develop a standardized strategy for this type of appendicitis. To our knowledge, previous literature focused on a population of both phlegmonous and gangrenous appendicitis [17,18] and little is known with respect to merely the latter. Therefore, we aimed to evaluate postoperative outcomes for gangrenous appendicitis exclusively. The primary aim of this study was to compare the rate of postoperative infectious complications between patients with gangrenous and phlegmonous appendicitis. Secondly, to compare the effect of postoperative antibiotic use on the rate of infectious complications.

METHODS

Study design, setting and participants

In 2014, data from all consecutive patients that had surgery for suspected acute appendicitis (AA) in 62 Dutch hospitals was prospectively collected during a predefined two-month study period (June and July). The study protocol was reviewed and approved by the medical ethics committee in the Academic Medical Center in Amsterdam. Owing to the observational, non-interventional study design, informed consent requirement was waived. One or two surgical residents per participating hospital were responsible for the data registration. Further details on the study design can be found in previously publications from this cohort.[19,20] For this analysis, patients that had an appendectomy (open of laparoscopic) for AA were selected from the database. Both adult and pediatric patients were included.

Collected data

Baseline patient characteristics (i.e. gender, age, ASA-classification) were registered as well as several pre- intra- and postoperative variables: temperature, white blood cell count (WBC) and C-reactive protein (CRP) at presentation, time between onset and operation (hours), preoperative antibiotic prophylaxis (yes or no), type of appendicitis, extent of peritonitis (none, local, diffuse), type (laparoscopic or open) and duration of surgery (min), duration of postoperative antibiotic treatment (intravenous and oral), overall 30-day postoperative complications, intra-abdominal abscess (IAA), surgical site infection (SSI), length of hospitalization (days from operation), readmission, percutaneous drainage, reoperation, 30-day mortality.

Outcome measures

The main outcomes in this study were type of appendicitis, duration of postoperative antibiotic use and rate of infectious complications (including IAA and SSI) within 30 days after appendectomy. The type of appendicitis was classified as phlegmonous, gangrenous or perforated based on the operative report. Gangrenous appendicitis was defined as appendicitis with signs of necrosis or gangrene without mention of macroscopic perforation. Duration of postoperative antibiotic use was recorded as the total duration of intravenous and oral antibiotics together, in postoperative days. IAA was defined as a fluid collection in the abdomen, diagnosed postoperatively by cross-sectional imaging and necessitating treatment (antibiotics treatment or (radiological or surgical) drainage). SSI was recorded only if this resulted in restart or prolongation of antibiotic treatment, or surgical drainage of the wound (under local or generalized anesthesia).

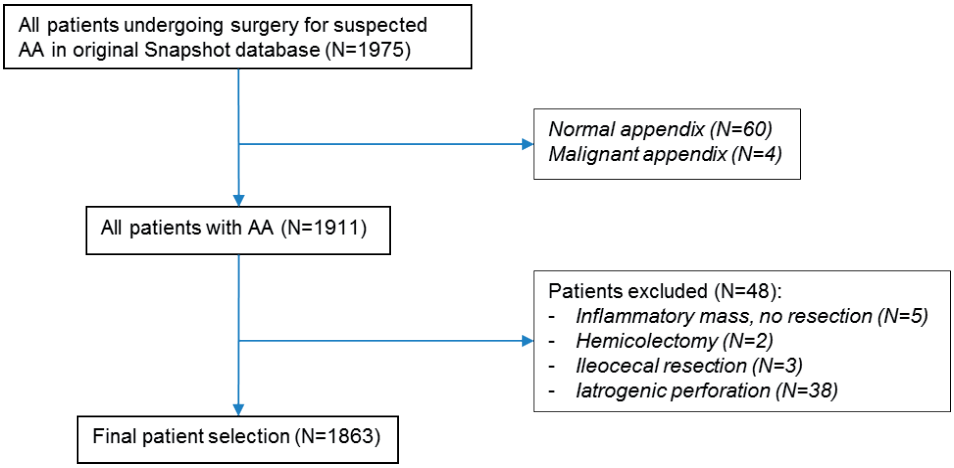

Figure 1. Patients included in present analysis.
Abbreviations: AA, acute appendicitis.

Secondary outcomes were length of hospital stay (LOS), the rate of overall complications, readmission, percutaneous drainage and/or reoperation (all within 30 days after appendectomy).

Statistical analysis

In univariable analysis, outcomes were compared between gangrenous and other types of appendicitis. The independent samples Student's t-test and Mann-Whitney test were used in case of continuous variables and the Chi-square and Fisher's exact test were used in case of categorical variables, as appropriate. To evaluate the effect of duration of postoperative antibiotic treatment on the infectious complication rate, groups of different duration were compared with the same statistical tests as described for the primary endpoint. Furthermore logistic regression analysis was performed to compare outcomes in multivariable analysis. A 2-sided $P < 0.05$ was considered significant. All data analysis was performed in SPSS version 21 (IBM, Armonk, New York, USA).

This manuscript was written using the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement checklist.[21]

RESULTS

In June and July 2014, 1975 patients had surgery for suspected AA. The details of these patients have been described in previous reports.[19,20] After exclusion of 112 patients (*Figure 1)*, 1863 remained eligible for analysis. The median age was 29 years (interquartile range (IQR) 16-47) and 514 (27.6%) were under the age of 18. Fifty-three per cent (980/1863) were male. Type of appendicitis was scored as phlegmonous in 1321 (70.9%), gangrenous in 181 (9.7%) and perforated in 361 (19.4%) patients. In total, there were 237 (12.7%) postoperative complications, 137 (7.4%) were infectious complications. The rate of infectious complications was 20.5% in patients with perforated appendicitis vs. 7.2% in patients with gangrenous appendicitis and 3.8% in patients with phlegmonous appendicitis ($p < 0.001$). Patients with perforated disease were excluded from further analyses.

Phlegmonous (PA) versus gangrenous appendicitis (GA)

Significant differences in baseline and perioperative characteristics were observed between patients with GA and PA. Patients with GA had a higher median (IQR) age (40 (19-56) vs. 27 years (16-42); $p <0.001$) and had higher WBC and CRP levels at presentation (*Table 1*). Postoperative antibiotics were administered significantly more often to patients with GA vs. PA (74.6% vs. 9.7% ($p < 0.001$)). The rate of infectious complications was significantly higher among patients with GA compared to PA (7.2% vs. 3.8%, $p = 0.033$), as

Table 1. Baseline and perioperative characteristics of the study population, n=1502.

Variable	GA, n=181	PA, n=1321	*P* value
Age, y, med (IQR)	40 (19;56)	27 (16;42)	< 0.001
Sex, male, n (%)	103 (56.9)	687 (52)	0.216
ASA, n (%)			0.076 (f)
I – II	173 (95.6)	1292 (97.8)	
III – IV	8 (4.4)	29 (2.2)	
Temperature, °C, mean (sd)	37.6 (0.8)	37.3 (0.7)	< 0.001
WBC, 10^9/L, mean (sd)	15 (4.7)	13.7 (4.6)	< 0.001
CRP, mg/L, med (IQR)	64 (26;124)	24 (9;54)	< 0.001
Time to surgery, h, med (IQR)	6.5 (4;14)	6.5 (4;13)	0.331
Preop. AB prophylaxis, n (%)	175 (96.7)	1260 (95.4)	0.426
Type of surgery, n (%)			0.954
Laparoscopic	133 (73.5)	968 (73.3)	
Open	48 (26.5)[a]	353 (26.7)[b]	
Degree of peritonitis, n (%)			< 0.001
None	102 (56.4)	1216 (92.1)	
Localized	67 (37)	91 (6.9)	
Diffuse	12 (6.6)	14 (1.1)	
Duration of surgery, m, med (IQR)	44 (32;56)	38 (30;50)	< 0.001
Postop. AB use, n (%)	135 (74.6)	128 (9.7)	< 0.001
Duration postop. AB use, n (%)			< 0.001
none	46 (25.4)	1192 (90.2)	
24h	11 (6.1)	33 (2.5))	
2 – 3d	37 (20.4)	28 (2.1)	
4 – 5d	64 (35.4)	48 (3.7)	
> 5d	23 (12.7)	19 (1.4)	

Abbreviations: PA, phlegmonous appendicitis; GA, gangrenous appendicitis; y, years; med, median; IQR, interquartile range; ASA, American Society of Anesthesiologists classification; f, fisher's exact test; sd, standard deviation; WBC, white bloodcell count; CRP, c-reactive protein; h, hours; AB, antibiotics; m, minutes.
[a] A total of 7 gangrenous appendicitis patients (3.8%) had laparoscopy converted to open surgery.
[b] A total of 15 phlegmonous appendicitis patients (1.1%) had laparoscopy converted to open surgery.

were the rates of IAA and complications overall (*Table 2*). And median (IQR) LOS was 3 (2;5) days for GA compared to 2 (1;2) days for PA, p < 0.001.

Risk factors for infectious complications

In univariable analysis, risk factors for the development of an infectious complication in patients with GA and PA were: increasing age, elevated temperature at presentation, higher level of WBC at presentation, presence of localized or diffuse peritonitis (vs. none) and gangrenous disease (vs. phlegmonous). In multivariable logistic regression analysis only age, WBC and duration of surgery showed a statistically significant association with infectious complications (*Table 3*).

Postoperative antibiotics for gangrenous appendicitis

Among 181 patients with gangrenous appendicitis, postoperative antibiotic use was limited to ≤ 24 hours in 57 (31.5%) patients and given longer than 24 hours in 124 (68.5%) patients. Patients with extended antibiotic use were older (median (IQR) age 44 (24-59) vs. 31 years (13-59); p = 0.006), had higher median CRP levels at presentation (78 mg/L (29-144) vs. 46 mg/L (17-86); p = 0.003) and more frequently showed local or diffuse peritonitis

during surgery (14% vs. 57.3%, p < 0.001). Infectious complications occurred more often among patients with extended antibiotic use but the difference was not statistically significant (3.5% vs. 8.9%, p = 0.233) (*Table 4)*. The median (IQR) LOS was prolonged by the extended antibiotic use (4 (3;6) vs. 2 days (1;2), p < 0.001).

Table 2. Univariable outcome analysis, n=1502.

Variable	GA, n=181	PA, n=1321	*P* value
LOS, d, med (IQR)	3 (2;5)	2 (1;2)	< 0.001
Any complication, n (%)	31 (17.1)	101 (7.6)	< 0.001
Infectious complication, n (%)	13 (7.2)	50 (3.8)*	0.033
IAA, n (%)	11 (6.1)	23 (1.7)	0.001
SSI, n (%)	2 (1.1)	32 (2.4)	0.421 (f)
Readmission, n (%)	11 (6.1)	56 (4.2)	0.261
Re-intervention, n (%)	6 (3.3) ¥¥	20 (1.5) ¥	0.117 (f)
Percutaneous drainage, n (%)	4 (2.2)	15 (1.1)	0.273 (f)
Reoperation, n (%)	4 (2.2)	14 (1.1)	0.260
Mortality, n (%)	1 (0.6)	1 (0.08)	0.227

Abbreviations: LOS, length of stay, PA, phlegmonous appendicitis; GA, gangrenous appendicitis; d, days; IAA, intra-abdominal abscess; SSI, surgical site infection; f, fisher's exact test;*5 patients suffered IAA ánd SSI; ¥ 9; ¥¥ 2 patients underwent drainage ánd reoperation.

Table 3. Multivariable outcome analysis, n=1502.

	Univariable analysis			Multivariable analysis		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age, year	1.01	1.0 - 1.03	0.04	1.02	1.00 - 1.03	0.046
Temperature, ˚C	1.51	1.08 - 2.1	0.015	1.32	0.91 - 1.91	0.146
WBC, 10^9/L	1.06	1.01 - 1.12	0.016	1.07	01.00 - 1.13	0.038
CRP, mg/L	1.0	0.99 - 1.01	0.1	1.0	0.99 - 1.0	0.47
Peritonitis (vs. none)	1.93	1.03 - 3.62	0.042	1.28	0.55 - 2.94	0.567
GA (vs. PA)	1.97	1.05 - 3.69	0.036	0.88	0.37 - 2.1	0.768
Open procedure (vs. laparoscopic)	1.5	0.88-2.55	0.135	1.68	0.89-3.14	0.107
Duration of surgery, min	1.02	1.01-1.03	0.006	1.02	1.01-1.04	0.004
Postop. AB use (vs. none)	2.29	1.32 - 3.95	0.003	1.55	0.65 – 3.69	0.318

Abbreviations: OR, odds ratio; CI, confidence interval; WBC, white bloodcell count; CRP, c-reactive protein; GA, gangrenous appendicitis; PA, phlegmonous appendicitis; AB, antibiotic.

Table 4. Postoperative antibiotics for gangrenous appendicitis, n=181.

Variable	≤ 24h, n=57	> 24h, n=124	*P* value
LOS, d, med (IQR)	2 (1;2)	4 (3;6)	<0.001
Any complication, n (%)	4 (7)	27 (21.8)	0.014
Infectious complication, n (%)	2 (3.5)	11 (8.9)	0.233
IAA, n (%)	2 (3.5)	9 (7.3)	0.506(f)
SSI, n (%)	-	2 (1.6)	1.0 (f)
Readmission, n (%)	4 (7)	7 (5.6)	0.743(f)
Re-intervention, n (%)	1 (1.8)	5 (4)	0.667 (f)
Percutaneous drainage, n (%)	1 (1.8)	3 (2.4)	1.0 (f)
Reoperation, n (%)	1 (1.8)	3 (2.4)	1.0 (f)
Mortality, n (%)	-	1 (0.8)	1.0 (f)

Abbreviations: h, hours; LOS, length of stay; d, days; IQR, interquartile range; IAA, intra-abdominal abscess; SSI, surgical site infection.

DISCUSSION

This prospective cohort study demonstrated that patients with non-perforated gangrenous appendicitis are at higher risk of postoperative infectious complications than patients with phlegmonous appendicitis. However, having gangrenous (vs. phlegmonous) appendicitis was not identified as an independent risk factor for developing infectious complications. Postoperative antibiotic use longer than 24 hours after appendectomy was not associated with a decreased rate of infectious complications, but did correlate with a longer length of stay.

Patients with gangrenous appendicitis were shown to differ from patients with phlegmonous appendicitis on various levels. They are older, they have higher CRP and WBC levels at arrival to the hospital and they present with localized or diffuse peritonitis in the abdomen more often than patients with phlegmonous appendicitis. The rate of intra-abdominal abscess was more than three times as high in patients with gangrenous appendicitis compared to patients with phlegmonous appendicitis. This confirms in a multicenter prospective setting, what was previously reported by Romano *et al*. in their retrospective single-center study including 372 patients.[22] In this study, age, WBC and duration of surgery were identified as independent risk factors for infectious complications, whereas a gangrenous type of appendicitis was not. A previous study on non-perforated appendicitis (n=728) by Coakley *et al*. identified open surgery and gangrenous appendicitis (both the surgical and histopathological assessment) as risk factors.[17] Only patients with a histopathological confirmation of non-perforated appendicitis were included in their study and the rate of infectious complications observed was 8.4% (61/728). In contrast, the rate in this study was 4.2%, 63 infectious complications among 1502 patients, whereas inclusion was solely based on the intraoperative classification appendicitis. Open surgery showed a slight trend towards significance, which might reflect a type II error here. Had the study population or the infectious complication rate been larger, a significant association with infectious complications might have arisen.

As expected, the majority of patients with gangrenous appendicitis received antibiotics postoperatively, whereas 25% were not given any antibiotics after appendectomy. If the surgeon chose to prescribe postoperative antibiotic treatment, this lasted longer than 24 hours in 92% of the patients. This did not decrease the infectious complications rate, compared patients with 24 hours of postoperative antibiotics or none. However, length of stay was longer in patients with extended antibiotic use: median length of stay was doubled compared to patients that received max. 24 hours treatment. This finding is consistent with the results from a small cohort study (n=58) by Shbat *et al.*[1] They reported an almost 50% reduction in length of stay without increase in complications for patients with gangrenous appendicitis given 2 postoperative doses of antibiotics instead of the

conventional longer treatment duration based on clinical criteria.[1] This further supports the recommended duration of 24 hours of postoperative antibiotics in the SIS/IDSA guideline, currently based on only one study on non-perforated appendicitis by Mui *et al.*[18] In this randomized controlled trial prolonged antibiotic use was associated with an increase of complications related to antibiotic treatment without reduction of infectious complications. This is in line with a recent single-center (n=1007) study by Nordin *et al.* as well. The authors reported outcomes before and after a protocol change towards classifying gangrenous appendicitis as simple appendicitis and omitting postoperative antibiotics.[23] A significant decrease in hospitalization and antibiotic use was observed for patients with gangrenous disease (n=69), without increase in complications.

In clinical practice and research, phlegmonous appendicitis is usually classified as simple appendicitis, whereas gangrenous appendicitis and perforated appendicitis are most often categorized together as complex appendicitis. This study emphasizes that these three types of appendicitis have a different risk of infectious complications: 3.8%, 7.2% and 20.5%, respectively. This implies that gangrenous appendicitis should perhaps be considered a separate entity, instead of being categorized together with either phlegmonous or perforated appendicitis. Gangrenous appendicitis was more often accompanied by localized or diffuse pus than phlegmonous appendicitis was (37% vs. 7%, respectively). Though the degree of peritonitis was not proven an independent risk factor for infectious complications in the present analysis, it is likely this does play a role to some extent. Previous studies have reported a correlation between peritonitis and postoperative complications.[24,25] Therefore, apart from the aspect of the appendix, the degree of peritonitis should perhaps also be part of the classification system.[26] Surgeons are already familiar with using this in their decision whether or not to prescribe postoperative antibiotics.[9,10] The optimum classification of appendicitis that correlates well with clinical outcomes has yet to be developed.[27,28] This may help standardization of practice in the future.

Strengths and limitations

The strengths of the present study are the prospective nature, national study participation and the large number of patients included. Nonetheless some important limitations need to be mentioned. First of all, patient inclusion in this study was based on the intraoperative classification of appendicitis by surgeons. This surgical classification is known to be more predictive of postoperative outcomes than the histopathological classification,[29] but it is also associated with interobserver variability and its reliability may therefore be questioned.[10,30] This concerns the distinction between perforated and non-perforated appendicitis, as well as assessment of gangrenous discoloration. Moreover, (assessment of) the extent of necrosis may vary: an appendix could show phlegmonous inflammation for the greater part with necrosis at the tip. This may be differently classified and treated

depending on the surgeon operating, which may in turn have influenced results. Secondly, concerning the analysis of postoperative antibiotic use, one may argue that some bias may be present as patients at higher risk of complications may have been prescribed more antibiotics than the 'fitter' patients.

Despite its limitations, this study shows that patients with non-perforated gangrenous appendicitis differ from patients with phlegmonous appendicitis in baseline characteristics and risk of postoperative infectious complications. Non-perforated gangrenous appendicitis should be considered its own distinctive entity, separate from phlegmonous (simple) and perforated (complex) appendicitis. Future research should focus on a universal and reliable classification system for appendicitis and standardization of postoperative antimicrobial policy.

Author Contributions

EdW, JdJ, BW and CvR designed this study. JdJ and CvR had full access to the study data and take responsibility for the integrity of the data and accuracy of the data analysis. EdW wrote this manuscript together with JdJ. All authors read and approved the final manuscript.

Disclosure/conflict of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Group Information

The Snapshot Appendicitis Collaborative Study Group members, who provided study patients and collected data, included: G.J.D. van Acker, MD, PhD (Medical Center Haaglanden, Den Haag), B. Akkermans, MD (Bronovo Hospital, Den Haag), G.J.M. Akkersdijk, MD, PhD (Spaarne Hospital, Hoofddorp), G.D. Algie, MD (M. C. Groep Zuiderzee, Lelystad), J.H. Allema, MD, PhD (Haga-Juliana Children's Hospital, Den Haag), C.S. Andeweg, MD, PhD (St Jansdal Hospital, Harderwijk), N. Appeldorn (Ropcke-Zweers Hospital, Hardenberg), J.G. van Baal, MD, PhD (Ziekenhuisgroep Twente, Almelo), C.M. den Bakker, MD (Kennemer Gasthuis, Haarlem), S.A.L. Bartels, MD, PhD (Albert Schweitzer Hospital, Dordrecht), C. van den Berg, MD (Diaconessenhuis, Leiden), B. Boekestijn (Groene Hart Hospital, Gouda), F.C. den Boer, MD, PhD (Zaans Medical Center, Zaandam), D. Boerma, MD, PhD (St Antonius Hospital, Nieuwegein), A.L. van den Boom, MD (Reinier de Graaf Groep, Delft), M.C. Boute, MD (Westfriesgasthuis, Hoorn), S.A.W. Bouwense, MD (Canisius-Wilhelmina Hospital, Nijmegen), J. Bransen, MD (Catharina Hospital, Eindhoven), F.A. van Brussel, MD (Spaarne Hospital, Hoofddorp), O.R.C. Busch, MD, PhD (Academic Medical Center, Amsterdam), S.M.M. de Castro, MD, PhD (Sint Lucas Andreas Hospital, Amsterdam), H.A. Cense, MD, PhD (Rode Kruis Hospital, Beverwijk), C. Croese, MD (Medical Center Haaglanden, Den Haag), T. van Dalen, MD,

PhD (Diakonessenhuis, Utrecht), I. Dawson, MD, PhD (IJsselland Hospital, Capelle aan Den IJssel), E. van Dessel, MD (ZorgSaam Zeeuws-Vlaanderen, Terneuzen), R. Dettmers, MD (Rijnland Hospital, Leiderdorp), N. Dhar, MD (BovenIJ Hospital, Amsterdam), F.Y.M. Dohmen (St Jans Gasthuis, Weert), K.W. van Dongen, MD, PhD (Diaconessenhuis, Leiden), P. van Duijvendijk, MD, PhD (Gelre Hospital, Apeldoorn), R.R. Dulfer, MD (Sint Franciscus Gasthuis, Rotterdam), B.J. Dwars, MD, PhD (Slotervaart Hospital, Amsterdam), J.P. Eerenberg, MD, PhD (Tergooi Hospital, Hilversum), M. van der Elst, MD, PhD (Reinier de Graaf Groep, Delft), E.D. van den Ende, MD, PhD (Ropcke-Zweers Hospital, Hardenberg), L.M.M. Fassaert, MD (Orbis Medical Center, Sittard), J.T. Fikkers, MD (Haga Hospital, Den Haag), J.W. Foppen (St Jansdal Hospital, Harderwijk), E. J.B. Furnee, MD, PhD (Diakonessenhuis, Utrecht), F.P. Garssen, MD (Amstelland Hospital, Amstelveen), M.F. Gerhards, MD, PhD (Onze Lieve Vrouwe Gasthuis, Amsterdam), H. van Goor, MD, PhD (Radboud University Medical Center, Nijmegen), R.R. Gorter, MD (Emma Children's Hospital–Academic Medical Center/Free University Medical Center, Amsterdam and Rode Kruis Hospital, Beverwijk), J.S. de Graaf, MD, PhD (Medical Center Leeuwarden, Leeuwarden), L.J. Graat, MD (Elisabeth-TweeSteden Hospital, Tilburg), J. Groote, MD (Wilhelmina Hospital, Assen), A.C. van der Ham, MD, PhD (Sint Franciscus Gasthuis, Rotterdam), J.F. Hamming, MD, PhD (Leids University Medical Center, Leiden), J.T.H. Hamminga, MD(University Medical Center Groningen and Beatrix Children's Hospital, Groningen), E. van der Harst, MD, PhD (Maasstad Hospital, Rotterdam), J. Heemskerk, MD(Laurentius Hospital, Roermond), H.A. Heij, MD, PhD (Emma Children's Hospital–Academic Medical Center/Free University Medical Center, Amsterdam), A. Heijne, MD (Zaans Medical Center, Zaandam), J.T. Heikens, MD, PhD (Rivierenland Hospital, Tiel), E. Heineman, MD, PhD (University Medical Center Groningen and Beatrix Children's Hospital, Groningen), R. Hertogs, MD (Wilhelmina Hospital, Assen), E. van Heurn, MD, PhD (Maastricht University Medical Center, Maastricht), L.C. L. van den Hil, MD (Laurentius Hospital, Roermond), A.G.M. Hoofwijk, MD, PhD (Orbis Medical Center, Sittard), C.C.C. Hulsker, MD (Wilhelmina Children's Hospital–University Medical Center Utrecht, Utrecht), D.R.M. Hunen, MD (Elkerliek Hospital Helmond), M.S. Ibelings, MD, PhD (TweeSteden Hospital, Tilburg), J.M. Klaase, MD, PhD (Medical Spectrum Twente, Enschede), R. Klicks, MD, PhD (BovenIJ Hospital, Amsterdam), L. Knaapen, MD (Radboud University Medical Center and Amalia Children's Hospital, Nijmegen), R.T.J. Kortekaas, MD, PhD (Vlietland Hospital, Schiedam), F. Kruyt, MD, PhD (Gelderse Vallei Hospital, Ede), S. Kwant (Zuwe Hofpoort Hospital, Woerden), S.S. Lases, MD (Isala Hospital, Zwolle), T. Lettinga, MD (St Jans Gasthuis, Weert), A. Loupatty, MD (Leids University Medical Center, Leiden), R.A. Matthijsen, MD, PhD (Academic Medical Center, Amsterdam), R.C. Minnee, MD, PhD (Onze Lieve Vrouwe Gasthuis, Amsterdam), B. Mirck, MD (Medical Center Alkmaar, Alkmaar), L. Mitalas, MD (Maastricht University Medical Center, Maastricht), D.E. Moes, MD (Slotervaart Hospital, Amsterdam), A.M. Moorman, MD (Ziekenhuisgroep Twente, Almelo), V.B. Nieuwenhuijs, MD, PhD (Isala Hospital, Zwolle), G.A.P. Nieuwenhuijzen, MD, PhD (Catharina Hospital, Eindhoven), P.D. Nijk, MD (Diakonessenhuis, Utrecht), J.M.T. Omloo, MD, PhD (Gelre Hospital, Apeldoorn), A.G. Ottenhof, MD (Flevo Hospital, Almere), H.W. Palamba, MD (Gelre Hospital, Zutphen), D.L. van der Peet, MD, PhD (Free University Medical Center, Amsterdam), I.T.A. Pereboom, MD, PhD (Medical Center Leeuwarden, Leeuwarden), P.W. Plaisier, MD, PhD (Albert Schweitzer Hospital, Dordrecht), A.P.T. van der Ploeg, MD, PhD (Maasstad Hospital, Rotterdam), M.H. Raber, MD

(Medical Spectrum Twente, Enschede), M.M.P.J. Reijnen, MD, PhD (Rijnstate Hospital, Arnhem), H. Rijna, MD, PhD (Kennemer Gasthuis, Haarlem), C. Rosman, MD, PhD (Canisius-Wilhelmina Hospital, Nijmegen), R.M.H. Roumen, MD, PhD (Maxima Medical Center, Veldhoven), R.F. Schmitz, MD, PhD (Groene Hart Hospital, Gouda), A.P. Schouten van der Velden, MD, PhD (Maas Hospital Pantein, Boxmeer), W.H. Schreurs, MD, PhD (Medical Center Alkmaar, Alkmaar), T.A. Sigterman, MD (Atrium Medical Center, Heerlen), H.J. Smeets, MD, PhD (Bronovo Hospital, Den Haag), D.J.A. Sonneveld, MD, PhD (Westfriesgasthuis, Hoorn), M.N. Sosef, MD, PhD (Atrium Medical Center, Heerlen), S.F. Spoor (M.C. Groep Zuiderzee, Lelystad), L.P.S. Stassen, MD, PhD (Maastricht University Medical Center, Maastricht), L. van Steensel, MD, PhD (Ikazia Hospital, Rotterdam), E. Stortelder, MD (Rijnstate Hospital, Arnhem), J. Straatman, MD (Free University Medical Center, Amsterdam), H.J. van Susante, MD (Amstelland Hospital, Amstelveen), D.E.N.M. Suykerbuyk de Hoog, MD (Maxima Medical Center, Veldhoven), C.E.J. Terwisscha van Scheltinga, MD (Sophia Children's Hospital–Erasmus Medical Center, Rotterdam), B.R. Toorenvliet, MD, PhD (Ikazia Hospital, Rotterdam), B.M. Verbeek, MD (Vlietland Hospital, Schiedam), P.C.M. Verbeek, MD, PhD (Flevo Hospital, Almere), M. Verseveld, MD (IJsselland Hospital, Capelle aan Den IJssel), J.H. Volders, MD (Gelderse Vallei Hospital, Ede), M.R. Vriens, MD, PhD (University Medical Center Utrecht, Utrecht), P.W.H.E. Vriens, MD, PhD (St Elisabeth Hospital, Tilburg), B.C. Vrouenraets, MD, PhD (Sint Lucas Andreas Hospital, Amsterdam), B.J.M. van de Wall, MD, PhD (University Medical Center Utrecht, Utrecht), J.A. Wegdam, MD (Elkerliek Hospital, Helmond), E. Westerduin, MD (Tergooi Hospital, Hilversum), J.J. Wever, MD, PhD (Haga Hospital, Den Haag), N.A.T. Wijffels, MD, PhD (Zuwe Hofpoort Hospital, Woerden), B.P.L. Wijnhoven, MD, PhD (Erasmus Medical Center, Rotterdam), T.A. Winkel, MD (Erasmus Medical Center and Sophia Children's Hospital, Rotterdam), D.C. van der Zee, MD, PhD (Wilhelmina Children's Hospital–University Medical Center Utrecht, Utrecht), A.M. Zeillemaker, MD, PhD (Rijnland Hospital, Leiderdorp), and C. Zietse, MD (St Antonius Hospital, Nieuwegein).

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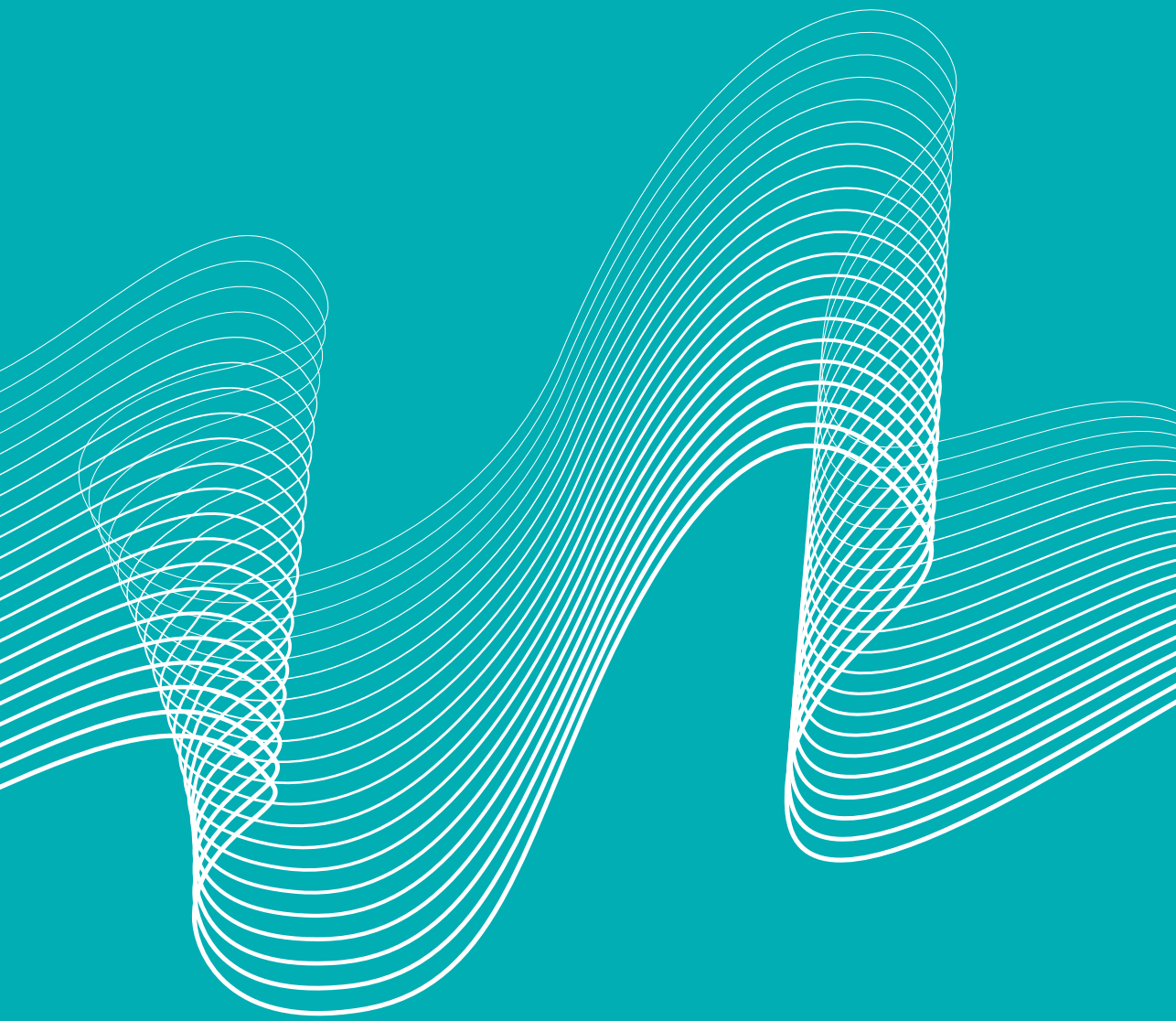

Elisabeth M. L. de Wijkerslooth, Jay M. Bakas, Joost van Rosmalen, Anne Loes van den Boom, Bas P. L. Wijnhoven

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6

SAME-DAY DISCHARGE AFTER APPENDECTOMY FOR ACUTE APPENDICITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Purpose:

Patients presenting with acute appendicitis are usually hospitalized for a few days for appendectomy and postoperative recovery. Shortening length of stay may reduce costs and improve patient satisfaction. The purpose of this study was to assess the safety of same-day discharge after appendectomy for acute appendicitis.

Methods:

A systematic review was performed according to PRISMA guidelines. A literature search of EMBASE, Ovid MEDLINE, Web of Science, Cochrane central and Google scholar was conducted from inception to April 14, 2020. Two reviewers independently screened the literature and selected studies that addressed discharge on the same calendar day as the appendectomy. Risk of bias was assessed with the ROBINS-I tool. Main outcomes were hospital readmission, complications and unplanned hospital visits in the postoperative course. A random effects model was used to pool risk ratios for the main outcomes.

Results:

Of 1912 articles screened, 17 comparative studies and 8 non-comparative studies met the inclusion criteria. Most only included laparoscopic procedure for uncomplicated appendicitis. Most studies were considered at moderate or serious risk of bias. In meta-analysis same-day discharge (*vs*. overnight hospitalization) was not associated with increased rates of readmission, complication and unplanned hospital visits. Non-comparative studies demonstrated low rates of readmission, complications and unplanned hospital visits after same-day discharge.

Conclusion:

This study suggests that same-day discharge after laparoscopic appendectomy for uncomplicated appendicitis is safe without an increased risk of readmission, complications or unplanned hospital visits. Hence, same-day discharge may be further encouraged in selected patients.

INTRODUCTION

Acute appendicitis is one of the most frequent surgical emergencies worldwide and is associated with a substantial clinical and financial burden. Appendectomy is mostly performed through laparoscopy, enabling quick recovery of the patient. Reducing length of stay (LOS) may relieve pressure on hospital bed capacity, reduce healthcare costs and improve treatment satisfaction.[1-5] Many studies have evaluated the safety and feasibility of expedited discharge after appendectomy. However, the terminology and definitions used for early discharge vary greatly.[1-11] Usually, outpatient appendectomy is defined as discharge after appendectomy without hospital admission and ambulatory appendectomy as postoperative LOS of 12 hours at most (with or without overnight hospitalization).[1,3] Day-case and same-day suggest discharge on the day of surgery, but are often defined as a maximum postoperative LOS of 24 hours.[2,12] Criteria for patient selection and discharge vary as well. Most often only patients with laparoscopic procedure for simple appendicitis (without perforation or necrosis) are considered eligible for same/day discharge. Some studies also selected for patients without concerns of comorbidities or social/organizational contraindications. A recent review of five studies on ambulatory laparoscopic appendectomy among adults demonstrated its feasibility but the authors were concerned about the methodological quality of the included studies.[13] Several other studies have shown the feasibility of same-day discharge (SDD), defined as discharge on the same *calendar* day as appendectomy.[5,8,9,14,15] Nevertheless, consensus on the safety of same-day discharge after appendectomy has yet to be established[16,17] and most patients are still hospitalized for 1 or 2 nights after appendectomy for simple appendicitis.[5,18-20] The aim of this study was to assess the safety of same-day discharge after appendectomy for acute appendicitis by performing a systematic review and critical appraisal of the available literature.

METHODS

Protocol

A study protocol was established and entered in the International Prospective Register of Systematic Reviews PROSPERO network (registration no. CRD42018115948).[21] This systematic review was conducted according to the PRISMA guidelines.[22] In addition, the Cochrane Handbook for Systematic Reviews of Interventions[23] and the AMSTAR 2 Checklist were used.[24]

Search strategy

A comprehensive search was performed in EMBASE, Ovid MEDLINE, Web of science, Cochrane Central, Google scholar and ClinicalTrials.gov from inception to April 14, 2020.

The initial query was developed in consultation with a library scientist. Among other, search terms included 'appendicitis', 'appendectomy', 'hospital discharge', 'ambulatory', 'outpatient' and 'day case'. The complete search strategy is outlined in Online Resource 'Appendix A'. The search was limited to articles published in the English language. Manual reference checks were performed in relevant articles.

Study selection

Studies presenting outcome data for patients with same calendar day discharge (SDD) after appendectomy were eligible. In this study, SDD included ambulatory appendectomy, day-case appendectomy and any other protocol of discharge on the day of appendectomy without overnight hospital stay.[2,1,3] The following study types were included: randomized controlled trial, prospective observational (cohort) study, retrospective observational (cohort) study, case-control study and case series. Studies were included if at least one of the main outcomes was reported. Titles and abstracts were first screened for eligibility. Articles were excluded if the abstract revealed no relevance to the subject or if they concerned one of the following: conservative/nonoperative treatment of appendicitis, case reports, editorials without evaluation data. Two reviewers (EdW and JB) independently assessed all non-duplicate articles for inclusion. Disagreements were resolved via negotiated consensus. Subsequently, full-text articles of potentially eligible studies were reviewed and a final selection of studies was agreed on. If full-text was unavailable, the corresponding author was contacted to request access. Reasons for exclusion after full-text screening are reported in the flowchart (figure 1).

Risk of bias assessment

Two reviewers independently assessed the risk of bias in each comparative study, using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool.[25] The ROBINS-I tool evaluates the risk of bias in 7 domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported results.

Outcomes

The main outcomes were hospital readmission, complications and unplanned hospital visits within 30 days after appendectomy. Complications were defined as any complication overall or any surgical site complication. Unplanned hospital visits were defined as visits to the Emergency Room (ER) and/or to the outpatient clinic (excluding planned postoperative follow-up appointments).

Secondary outcomes were (radiological or surgical) reinterventions, length of hospital stay, costs and treatment satisfaction.

Data extraction and statistical analysis

Outcome data were extracted as well as data on study period and origin, study design, patient selection, number of patients, characteristics of study group and follow-up time. Data were collected by one reviewer and verified by another. Outcomes are either displayed as reported originally or calculated from the raw reported data. Uncomplicated acute appendicitis was defined as acute appendicitis without findings of necrosis/gangrene or perforation, unless otherwise specified.

Only comparative studies were considered for meta-analysis. Assessment of the study characteristics identified three methodological categories. Some studies compared SDD in a prospective cohort with a historical cohort. Three studies compared SDD to discharge on postoperative day (POD) 1 or 2 and excluded patients discharged after 2 days. This was done to exclude patients with prolonged hospital stay due to immediate complications and/or medical reasons. The third category comprises of studies that compared patients with SDD to patients with overnight stay (for one or more nights) during the same study period. This group of studies was felt to be conceptually different from the other studies, since the control groups included patients that stayed overnight for various reasons that may have affected their chance of adverse outcomes: medical reasons (i.e. nausea, pain, comorbidities, complex type appendicitis), social and organizational reasons (i.e. late surgery, home > 1h from hospital, no accompanying adult). It was decided to exclude these studies from meta-analysis. The other study categories were considered appropriate for meta-analysis but inappropriate for pooling together due to heterogeneity in study design. Hence, meta-analyses were conducted separately for studies comparing patients in a SDD protocol to historical controls and studies comparing SDD to discharge on POD1-2.

Meta-analyses were performed for the risk ratio (RR) of three outcomes (readmission, complications and unplanned hospital visits), using a random-effects meta-analysis model. In this model, the Sidik-Jonkman method was used to estimate the between-study variance.[26,27] The I^2-statistic and Cochran's Q test were used to assess statistical heterogeneity between studies. Meta-analysis was also applied to present results with adjustment for covariates, based on the published adjusted odds ratios (OR) and confidence intervals in two studies (Cairo *et al*. adjusted for: age, ASA-class, sex, race and ethnicity [5]; Grigorian *et al*. adjusted for age, wound classification, ASA-class, several comorbidities, steroid use [15]). Results are presented in forest plots. Analyses were performed in R version 3.5.2.[28]

RESULTS

Study selection

Literature search identified 1912 non-duplicate articles. After abstract and full-text review, 25 studies, 17 comparative and 8 non-comparative observational studies, were included. The flowchart of the study selection is presented in figure 1. The rate of same-day discharge among the cohorts ranged from 22% to 96%. Ten studies included pediatric patients only and ten studies adults only. Five studies included patients from all ages.

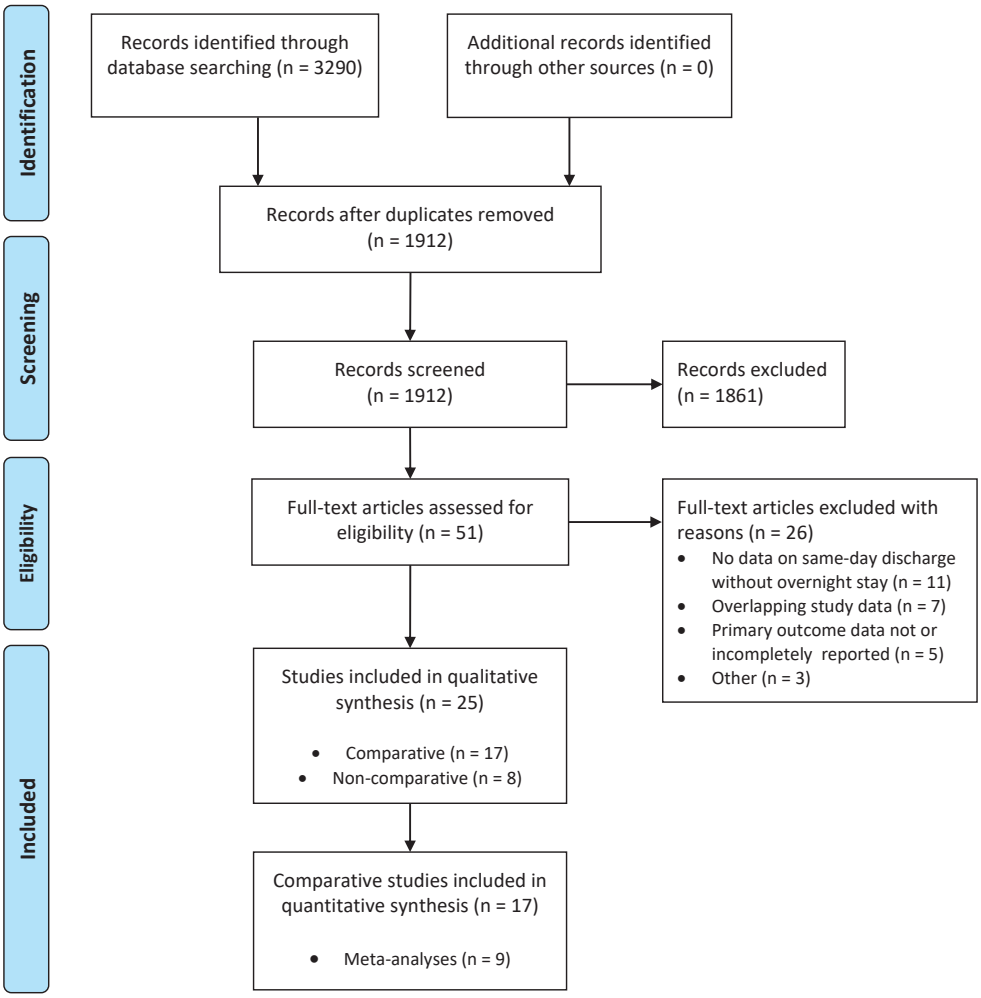


Figure 1. PRISMA flow diagram
From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:*10.1371/journal.pmed1000097*.

Comparative studies

Characteristics of all comparative studies are shown in table 1, grouped into three categories according to study design. Five studies compared patients in a prospective SDD protocol to patients from a historical control cohort (with a lower percentage of SDD).[12,29-32] Three multicenter retrospective studies compared SDD to discharge on POD 1 or 2 at the latest.[5,15,33] The remaining nine studies compared successful SDD to overnight hospitalization for one or more nights.[7,9,34-40] Overnight hospitalization occurred for varying reasons of medical, social and organizational nature. Since these factors may well have affected the outcomes of interest, the latter group of studies was excluded from meta-analysis. Variations in cohort selection criteria, discharge criteria and reasons for failing SDD are further illustrated in supplementary table S1 (Online Resource 'Appendix B').

Risk of bias assessment

The ROBINS-I results are highlighted in supplementary table S2 (Online Resource 'Appendix B'). The overall risk of bias was considered moderate in five studies, serious in ten studies and critical in two studies.

Table 2 outlines the main outcomes for the comparative studies.

Hospital readmission

Fifteen studies with varying duration of follow-up reported readmission rates (table 2). Readmission after SDD ranged from 0 to 4.6%. One study reported a significantly higher readmission rate for the SDD protocol cohort.[12] Meta-analysis with pooled data from four studies comparing readmission rates for SDD protocol patients *vs*. historical controls demonstrated a RR of 1.47, 95% CI 0.56 to 3.84 (figure 2a). Meta-analysis with pooled data from 3 studies comparing readmission rates for SDD *vs*. discharge on POD1-2 demonstrated a RR of 0.76, 95% CI 0.67 to 0.88 (figure 2b). Meta-analysis with pooled adjusted data from two of the latter studies showed a similar association: OR 0.81, 95% CI 0.68 to 0.97 (figure 2c). No statistically significant between-study heterogeneity or between-study variance was observed in any of the meta-analyses (I^2 and Cochran's Q results shown in figure 2).

Postoperative complications

All 17 studies reported postoperative complications. Rates varied between 0% and 19% (table 2). There was inconsistency in the definitions used for complications (table S1, Appendix B). One study reported a significantly higher rate of complications for SDD protocol patients.[30] Meta-analysis with pooled data from five studies comparing complication rates for SDD protocol patients *vs*. historical controls demonstrated a RR of 1.18, 95% CI 0.73 to 1.91 (figure 3a). Meta-analysis with pooled data from 3 studies comparing complication rates for SDD *vs*. discharge on POD1-2 demonstrated a RR of 0.77, 95% CI 0.65 to 0.90 (figure 3b). Meta-analysis with pooled adjusted data from two

Table 1. Characteristics of comparative studies.

Study	Country *Study period*	Study design	Patient selection					SDD group, n (%)	Control group, n (%)	Outcomes
			LA/OA	Appendicitis	Age, yrs	Exclusions	N			
Studies comparing patients in a SDD protocol to historical controls										
Cash *et al.* 2012 [1]	U.S.A. *2009-2011*	Prospective cohort	LA	UAA	≥18	Pregnancy	235	116 (49) *85% SDD-PACU*	119 (51)[a] *35% SDD*	Readmission Complications
Dubois *et al.* 2010 [2]	Canada *2005-2007*	Retrospective cohort	LA	UAA+CAA	All ages	-	317	161 (51) *45% SDD-PACU* *pLOS 13.1h (4.8;42.3)*	156 (49)[a] *% SDD nr* *pLOS 29.7h (13.9;47.5)*	Complications Unplanned visits Costs
Lefrancois *et al.* 2015 [3]	France *2013*	Prospective cohort	LA	UAA+CAA	All ages	-	652	184 (28) *20% SDD* *pLOS 41.8h ±59.0*	468 (72)[a] *0 % SDD* *pLOS 47.1h ±55.4*	Readmission Complications
Putnam *et al.* 2014 [4]	U.S.A. *2009-2013*	Prospective cohort	LA+OA *93% LA*	UAA	<18	-	794	478 (60) *32% SDD* *pLOS 42h (17; 31)*	316 (40) *7.6% SDD* *pLOS median 15-18h*	Readmission Complications Unplanned visits Costs
Rosen *et al.* 2017 [5]	U.S.A. *2014-2016*	Prospective cohort	LA	UAA	>18	Pregnancy, penitentiary ward patients	351	173 (49) *65% SDD-PACU* *pLOS 9.3h ±12.9*	178 (51)[a] *% SDD nr* *pLOS 19.3h ±13.2*	Readmission Complications Unplanned visits Patient satisfaction
Studies comparing SDD to discharge on postoperative day 1 or 2										
Cairo *et al.* 2017 [6]	U.S.A. *2012-2015*	Retrospective cohort[M]	LA+OA *95% LA*	UAA	<18	-	20,981	4662 (22)	16,319 (78) *Max. 2 nights*	Readmission Complications
Grigorian *et al.* 2019 [7]	U.S.A. *2016-2017*	Retrospective cohort[M]	LA	UAA[b]	≥18	-	16,931	3988 (24)	12,943 (76) *Max. 2 nights*	Readmission Complications
Scott *et al.* 2017 [8]	U.S.A. *2010-2014*	Retrospective cohort[M]	LA	UAA[b]	>18	-	12,703	6710 (53) *SDD-PACU*	5993 (47) *Max. 48 hrs*	Readmissions Wound complications Unplanned visits Costs
Studies comparing SDD to overnight stay for one or more nights										
Aguayo *et al.* 2014 [9]	U.S.A. *2012-2013*	Retrospective cohort	LA	UAA[b]	Children[c]	-	588	128 (22) *pLOS 7.3h ±2.5*	460 (78)[a] *pLOS 22h ±11.3*	Readmission Complications Unplanned visits
Alkhoury *et al.* 2012 [10]	U.S.A. *2010-2011*	Prospective cohort	LA	UAA + interval	Children[c]	-	158	162 (78) *SDD-PACU* *pLOS 5h ± nr*	45 (22)[a] *pLOS 16h ± nr*	Readmission Complications Unplanned visits Parent satisfaction

Benedict *et al.* 2018 [11]	U.S.A. *2015-2017*	Retrospective cohort	LA	UAA[b]	<18	-	569	495 (87) *pLOS 4h (3;5)*	74 (13)[a] *pLOS 19h (15;25)*	Readmissions Complications
Farach *et al.* 2014 [12]	U.S.A. *2014*	Prospective cohort	LA+OA *76% LA*	UAA+CAA	<21	Pre-existing complex medical conditions, late surgery, inadvertent admission to inpatient unit, social indications	349	185 (53) *pLOS 3.1h ±1.4*	164 (47)[a] *pLOS 66.1 ± 84.8*	Complications Costs
Gignoux *et al.* 2018 [13]	Switzerland *2015-2016*	Retrospective cohort	LA	UAA+CAA	All ages	-	185	109 (59) *tLOS 8.5h (3.3;20.5)*	76 (41)[a] *tLOS nr*	Readmission Complications Unplanned visits
Gurien *et al.* 2017 [14]	U.S.A. 2015	Retrospective cohort	LA	UAA	≤18	-	171	63 (37) *SDD-PACU tLOS 3.1h ± nr*	108 (63)[a] *≥ 1 nights tLOS 14.6h ± nr*	Readmission Complications Unplanned visits Costs
Halter *et al.* 2016 [15]	U.S.A. *2012-2015*	Retrospective cohort	LA	UAA	1-18	Pre-existing medical requirement for admission	236	121 (51) *SDD-PACU tLOS 11.8h ±2.7*	115 (49) *Max. 1 night tLOS 24.8h ±21.2*	Readmission Complications Unplanned visits Costs Family satisfaction
Hussain *et al.* 2014 [16]	India nr	Prospective cohort	LA	UAA	14-60	Multiple comorbidity, coagulation disorders, adverse anesthetic history, malignancy, ASA-III(uncontrolled) or IV, BMI > 35	30	26 (87) *pLOS 9.6h ± nr*	4 (13)[a] *Max. 1 night pLOS 22.0h ± nr*	Readmission Complications Unplanned visits Patient satisfaction
Yu et al. *2017 [17]*	U.S.A. *2016-2017*	Prospective cohort	LA	UAA	5-18	Pre-existing medical or social requirement for admission	602	185 (31) *pLOS 4.4h (3.1;6.2)*	417 (69)[a] *pLOS 17.4h (14.3;21.8)*	Readmission Complications Unplanned visits Costs

Abbreviations: SDD, same-day discharge; LA, laparoscopic appendectomy; OA, open appendectomy; UAA, uncomplicated acute appendicitis; CAA, complicated acute appendicitis; SDD-PACU, discharge directly from the postanesthesia care unit (recovery room); ASA, American Society of Anesthesiologists; pLOS, length of stay from operation to discharge (expressed as mean ± sd or median (interquartile range)); tLOS, total length of stay from admission to discharge; nr, not reported.

[a] Reasons for overnight stay summarized in supplementary table S1 (Appendix B)

[b] Uncomplicated acute appendicitis included all unperforated appendicitis in this study (gangrenous or necrotic appendicitis not excluded)

[c] No age limit(s) specified in Methods

[M] Multicenter study

Table 2. Primary outcomes of comparative studies.

Study	Follow-up duration	Readmissions, n (%)			Complications, n (%)			Unplanned hospital visits, n (%)		
		SDD group	Control group	*p*	SDD group	Control group	*p*	SDD group	Control group	*p*
Studies comparing patients in a SDD protocol to historical controls										
Cash *et al.* 2012 (1)	2 weeks	0	2 (1.7)	-	6 (5.2)	10 (8.4)	ns[a]	nr	nr	-
Dubois *et al.* 2010 (2)	30 days	nr	nr	-	17 (10.6)	21 (13.5)	0.490	22 (13.7)	24 (15.4)	0.66
Lefrancois *et al.* 2015 (3)	30 days	16 (8.7)	25 (5.3)	ns[a]	35 (19)	58 (12.9)	0.029[a]	nr	nr	-
Putnam *et al.* 2014 (4)	30 days	17 (3.6)	4 (1.2)	0.049[a]	13 (2.7)	5 (1.6)	ns[a]	24 (5.0)	6 (1.9)	0.024[a]
Rosen *et al.* 2017 (5)	2 weeks	3 (1.7)	3 (1.7)	1	6 (3.4)	4 (2.2)	0.54	11 (6.3)	10 (5.6)	0.83
Studies comparing SDD to discharge on postoperative day 1 or 2										
Cairo *et al.* 2017 (6)	30 days	88 (1.9)	380 (2.3)	0.07	57 (1.2)	261 (1.6)	0.06	nr	nr	-
Grigorian *et al.* 2019 (7)	30 days	71 (1.8)	297 (2.3)	0.051	41 (10.3)	196 (15.1)	0.022[a]	nr	nr	-
Scott *et al.* 2017 (8)	30 days	149 (2.2)	183 (3.1)	< 0.005	147 (2.2)[b]	160 (2.7)[b]	ns	847 (12.6)[c]	742 (12.4)[c]	ns
Studies comparing SDD to overnight stay for one or more nights										
Aguayo *et al.* 2014 (9)	nr	1 (0.8)	6 (1.3)	ns[a]	2 (1.6)	11 (2.4)	ns	6 (4.7)	25 (2.4)	ns
Alkhoury *et al.* 2012 (10)	2 weeks	4 (2.5)	1 (2.2)	ns	13 (8.0)	3 (6.6)	ns	12 (7.4)	2 (4.4)	ns
Benedict *et al.* 2018 (11)	nr	8 (2)	3 (4)	0.16	nrd	nrd	-	nr	nr	-
Farach *et al.* 2014 (12)	2 weeks	nr	nr	-	5 (2.7)	18 (11)	0.002	nr	nr	-
Gignoux *et al.* 2018 (13)	30 days	5 (4.6)	7 (9.2)	0.24	13 (11.9)	19 (25)	0.03	13 (11.9)	17 (22.4)	0.07
Gurien *et al.* 2017 (14)	nr	0	1 (0.9)	-	1 (1.6)	0	-	5 (7.9)	8 (7.4)	0.98
Halter *et al.* 2016 (15)	30 days	1 (0.8)	3 (2.6)	0.68	1 (0.8)	3 (2.6)	0.35	8 (6.7)	3 (2.6)	0.17
Hussain *et al.* 2014 (16)	10 days	0	0	-	0	0	-	0	0	-
Yu *et al.* 2017 (17)	30 days	1 (0.5)	10 (2.4)	0.19	3 (1.6)	13 (3.1)	0.29	8 (4.3)	25 (6)	0.41

Abbreviations: SDD, same day discharge; ns, not statistically significant; nr, not reported.

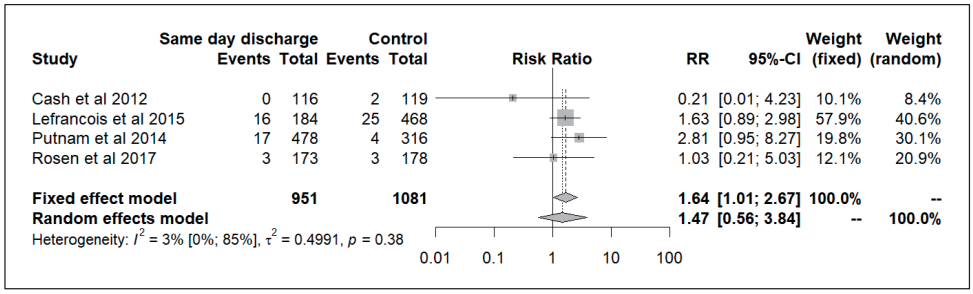
[a] Proportions tested for significance (simple X2 test) based on extracted raw data reported, with α level of 0.05

[b] Wound-related complication instead of any postoperative complication

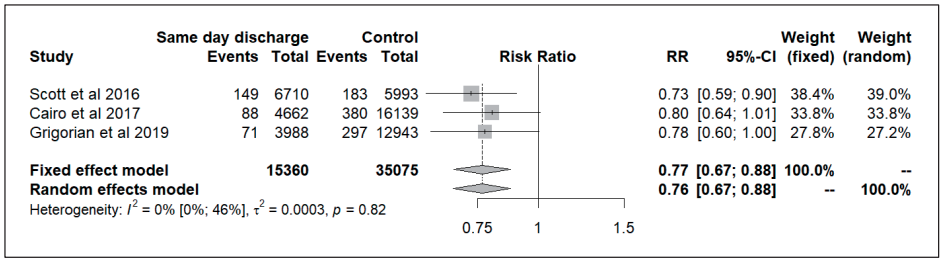
[c] No statistically significant difference in unplanned ER visits. Rate of postoperative clinic visits (planned + unplanned) did differ: 5460 (81.4%) vs 5121 (85.5%) in the SDD vs. control group ($p < 0.0001$).

[d] Complications reported in the manuscript text, but incomplete data.

2a. Meta-analysis with unadjusted data of studies comparing patients in a SDD protocol to historical controls



2b. Meta-analysis with unadjusted data of studies comparing SDD to discharge on POD1-2



2c. Meta-analysis with adjusted data of studies comparing SDD to discharge on POD1-2

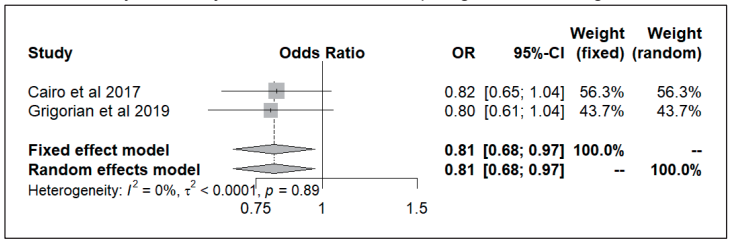


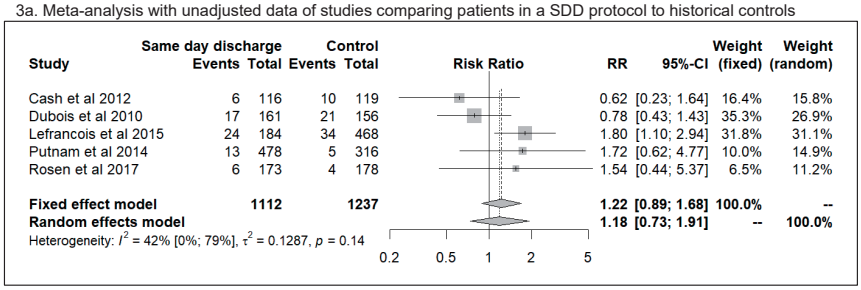
Figure 2. Meta-analyses on the association between SDD and rate of readmission

of the latter studies showed a significant association as well: OR 0.64, 95% CI 0.42 to 0.97 (figure 3c). No statistically significant between-study heterogeneity was observed in any of the meta-analyses (I^2 and Cochran's Q results shown in figure 3).

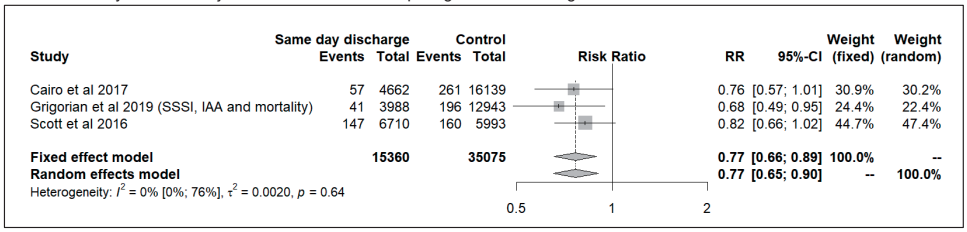
Unplanned hospital visits

Eleven studies described unplanned visits to the hospital, ranging from 0% to 12.6% after SDD (table 2). One study found a significantly higher rate for the SDD protocol group.[12] The remaining studies found no difference in the rate of unplanned visits. Meta-analysis with pooled data from three studies comparing complication rate for SDD protocol patients *vs*. historical controls showed a RR of 1.30, 95% CI 0.68 to 2.49 (figure 4). No statistically significant between-study heterogeneity was observed (I^2 53%, 95% CI 0%-87%, Cochran's Q test $p = 0.12$).

3a. Meta-analysis with unadjusted data of studies comparing patients in a SDD protocol to historical controls



3b. Meta-analysis with unadjusted data of studies comparing SDD to discharge on POD1-2



3c. Meta-analysis with adjusted data of studies comparing SDD to discharge on POD1-2

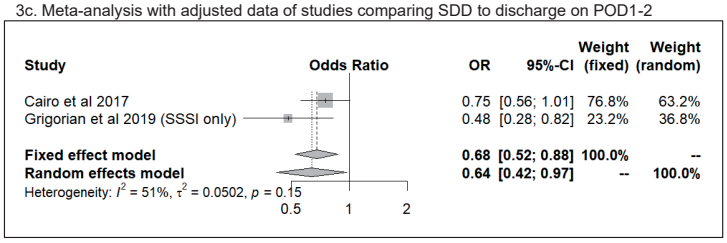


Figure 3. Meta-analyses on the association between SDD and rate of complications

Meta-analysis with unadjusted data of studies comparing patients in a SDD protocol to historical controls

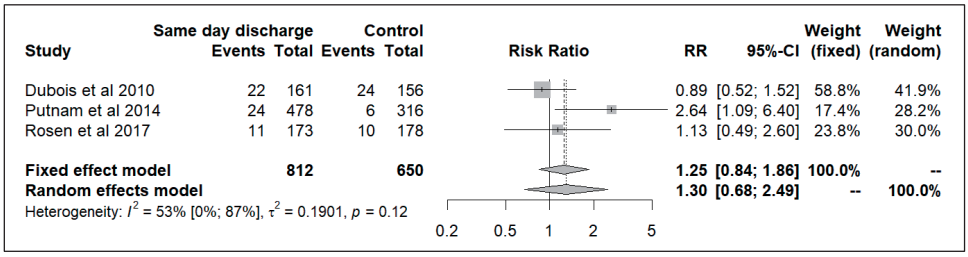


Figure 4. Meta-analysis on the association between SDD and rate of unplanned hospital visits

Other outcomes

Reinterventions – Six comparative studies reported reinterventions to some extent, all showing reoperation occurrence below 1% after SDD.[9,15,32,38-40] There were no significant differences in reoperation rate between SDD and control group patients (details in table S3, Appendix B). Another six studies that reported complications, did not present any reintervention in their study cohorts.[7,29,34-37]

Length of stay – Thirteen studies reported length of stay, as displayed in table 1 in hours. Mean postoperative length of stay after SDD ranged from 3.1 ± 1.4[39] to 9.6 (standard deviation not given)[37] hours. Nine studies tested for significance, all reporting a statistically significant reduction in LOS for SDD compared to control groups. [7,9,12,31,32,35,37-39]

Costs – Seven studies performed a cost analysis.[7,12,32,33,36,38,39] Methods of cost analysis were reported in only four studies and concerned direct hospital-costs, societal costs were outside the scope (details in table S4, Appendix B). All seven studies reported a cost reduction in the SDD group compared to controls, ranging from $323 [32] to $4111.[39] Three studies showed a statistically significant cost reduction (table S3, Appendix B).

Treatment satisfaction – Five studies reported treatment satisfaction to some extent. [7,31,35,37,38] Various short, non-validated surveys were used at different postoperative points in time (details in table S5, Appendix B). Overall, the studies reported high patient satisfaction after SDD. One study presented satisfaction scores for both SDD protocol patients and historical controls and showed no differences.[31]

Non-comparative studies

Eight non-comparative, observational studies reported outcomes after implementation of an SDD protocol.[4,8,14,41-45] Their characteristics and main results are shown in table 3. Seven studies reported successful SDD in 80% or more of their selected population. One study reported only 40% SDD.[8] This study only included patients aged 2-18 years. Reported readmission and complication rates ranged from 0 to 6.9% and 0 to 12.8%, respectively. Unplanned hospital visits were observed in 8.1 to 13.2% of patients.

With regards to secondary outcomes: reintervention rates ranged from 0 to 3.6% in 7 studies (table S3, Appendix B), none analyzed costs and only one study evaluated treatment satisfaction and quality of life (table S5, Appendix B).

Table 3. Characteristics and primary outcomes of non-comparative studies.

Study	Country *Study period*	Study design	Patient selection					SDD n (%)	Follow-up duration	Primary outcomes n (%)		
			LA/OA	Appendicitis	Age, yrs	Exclusions	N			Readmissions	Complications	Unplanned visits
Aubry et al. 2017 (38)	France 2013-2015	Prospective cohort	LA+OA 99% LA	UAA (pre-operatively assessed)	≥ 15	ASA ≥3, pregnancy, physical/ mental condition preventing participation	102	89 (87)[a]	30 days	2/102 (2)	6/102 (6)	nr
Frazee et al. 2016 (1)	U.S.A. 2010-2014	Retrospective cohort	LA	UAA	≥ 18	Pregnancy	563	484 (86)[a]	nr	7/484 (1.5)	38 /563 (7)	nr
Frazee et al. 2017 (2)	U.S.A. nr	Retrospective cohort	LA	UAA	≥ 18	Pregnancy	376	299 (80)[a]	nr	12/376 (3)	18/376 (5)	nr
Gee et al. 2018 (3)	U.S.A. 2016	Prospective cohort	LA	UAA	2-18		961	382 (40)	2 weeks (median)	2/382 (0.5)	2/382 (0.5)	45/382 (12)
Grelpois et al. 2016 (4)	France 2013-2015	Prospective cohort	LA	UAA	>18	ASA ≥3, pregnancy or breastfeeding, incarceration, legal guardianship	83	76 (92)[a]	30 days	3/76 (4)	13/83 (16)	10/76 (13)
Hobeika et al. 2017 (5)	France 2013-2015	Prospective cohort	LA for	UAA+CAA	All ages	St. Antoine score[c] < 4, no patient consent	102	92 (90)[a]	30 days	7/102 (7)	7/102 (7)	9/102 (9)
Hrad et al. 2015 (6)	U.S.A. 2010-2013	Retrospective cohort	LA	UAA[b]	All ages	Pathological UAA	74	71 (96)[a]	11 days	0	0	6/74 (8)
Sabbagh et al. 2019 (7)	France 2016-2017	Retrospective cohort	LA	UAA	All ages	ASA ≥3, clinical signs of CAA, living alone or far from a hospital	102	54 (95)[a]	nr	2/54 (3.7)	nr	8/54 (15)

Abbreviations: SDD, same-day discharge; LA, laparoscopic appendectomy; OA, open appendectomy; UAA, uncomplicated acute appendicitis; ASA, American Society of Anesthesiologists; nr, not reported; CAA, complicated acute appendicitis.

[a] Reasons for overnight stay summarized in supplementary table S1 (Appendix B)

[b] Uncomplicated acute appendicitis included all unperforated appendicitis in this study (gangrenous or necrotic appendicitis not excluded)

[c] Score of 1 point per each of the following factors (associated with early discharge in prior retrospective study): BMI < 28 kg/m2, WBC < 15.0/µL, C-reactive protein < 30 mg/L, no radiological signs of perforation, and appendix diameter of ≤10mm.

DISCUSSION

This systematic review demonstrated no increased risk of adverse outcomes following same-day discharge (SDD) after appendectomy. Meta-analyses revealed either no significant association between SDD and rates of readmission, complication and unplanned visits, or a statistically signification association in favor of SDD. Due to substantial clinical and methodological between-study heterogeneity, pooling of data for meta-analysis was limited.

Fifteen of 17 included comparative studies showed no increase in any adverse outcome after SDD. Two studies reported a statistically significant increase in one or two adverse outcomes after SDD. The differences presented may not be clinically relevant. Hence, same-day discharge seems safe and may be encouraged after careful selection of patients. Results on secondary outcomes (very low rate of reinterventions, significantly reduced postoperative length of stay, indication of reduced costs, no indication of reduced treatment satisfaction), further support SDD. If SDD after appendectomy would be applied more frequently in the future, this will likely reduce hospitalization and associated healthcare costs. With the results of this review in mind, it may be of interest to perform appendectomies early during the day, thereby enabling SDD. Protocols designed to facilitate SDD may be helpful to reduce the need for hospital beds and health care workers, especially during the night.

In contrast to previously published reviews, the present study focused on discharge on the same *calendar* day as the operation and excluded studies that did not explicitly report SDD.[15-17] Sabbagh *et al*. performed a review on the feasibility of ambulatory surgery (<12h length of stay) for several gastrointestinal emergencies in adults.[16] Only three of 12 included studies on early discharge after appendectomy concerned ambulatory surgery, two of which explicitly reported SDD and are therefore included in the present review. The authors concluded that there is probably a place for ambulatory surgery in clinical practice. Cosse *et al*. conducted a review on the feasibility of day-case appendectomy for acute appendicitis in adults.[2] They included the same studies as Sabbagh *et al.* as well as a duplicate publication by Cash *et al*.[29,46] Seven studies reported day-case appendectomy, defined as <24h length of stay (hence none were included in the present review). The authors stated that day-case appendectomy was safe and feasible, but more prospective studies should be performed before accepting day-case appendectomy as standard care. Genser *et al*. also reviewed ambulatory appendectomy and included only three studies, all of which are included in the present review as well. They concluded that ambulatory appendectomy for uncomplicated appendicitis is feasible and may be implemented.[17] Most studies included in these reviews were of retrospective nature. Best evidence would come from prospective trials. A randomized study would be ideal but may not be feasible or

ethical. Trejo-Avila *et al.* recently published a randomized trial related to this topic.[10] In this study, 108 patients were randomized to an enhanced recovery protocol (ERAS) or standard care. Ambulatory management (defined as postoperative LOS <12h) was achieved in 90% in the ERAS group *vs*. 3.4% for standard care.[10] Though this RCT could not be included in the present review as there was no explicit report of (the proportion of) discharge on the same *calendar* day, it does support the findings of the present study. The same authors also performed a systematic review and meta-analysis on ambulatory appendectomy for adult patients.[13] The results are in concordance with ours and represent the best currently available evidence on early discharge after appendectomy. Remarkably, many studies have misleading titles: incorporating the words 'same-day discharge', 'outpatient' and/or 'ambulatory', whilst not actually reporting discharge without overnight stay [1]. This was a main reason for excluding full text articles in the present review. Nevertheless, an additional 10 comparative studies were included that were not assessed in the previous reviews, reporting data from both pediatric and adult study populations. Furthermore, eight non-comparative studies were included to summarize evidence on same-day discharge completely. Clinical outcomes after implementation of an SDD protocol in the non-comparative studies were similar to those in the comparative studies.

SDD is feasible and safe in a large proportion of patients. Based on the heterogeneous sample of studies in this review, it is difficult to establish one optimum set of patient selection and discharge criteria for SDD. Selection criteria used in most studies are uncomplicated/unperforated appendicitis and laparoscopic surgery. Twenty-one of 25 studies in this review excluded open procedures from their cohort. In four studies that included both laparoscopic and open procedures, the proportion of open procedures was low and no separate outcome data were available. Hence, no conclusions can be drawn concerning the safety of SDD after open appendectomy. Both adult and pediatric patients can be considered eligible for SDD after laparoscopic appendectomy. Exclusion of ASA-class III-IV and pregnant patients was often applied as well and seems appropriate. Discharge criteria should entail normal vital signs, ability to tolerate oral intake, ability to ambulate and pain controlled by oral analgesics. Ultimately, the goal will not be to discharge *all* patients on the day of appendectomy, but to improve treatment efficiency by facilitating same-day discharge in a larger proportion of *eligible* patients. A same-day discharge protocol preferably entails a concise set of eligibility criteria that can be assessed preoperatively for the most part. Patients discharged this quickly after surgery should be well informed of relevant signs and symptoms of complications. And adequate (reporting of) follow-up is essential to evaluate the effects of adapting such a protocol.

This study has some limitations. Only non-randomized observational studies were included, which are prone to bias, e.g. due to confounding and selective reporting of results. Meta-analysis was only justified for a limited number of studies. Due to the small

number of studies in the meta-analyses, funnel plots for identifying publication bias were not felt to be of added value and statistical between-study heterogeneity (though not observed) cannot be ruled out. Many of the included studies compared SDD patients to a non-matched control group of patients with overnight stay (determined by different medical, social and organizational reasons). Moreover, there was substantial clinical heterogeneity (varying patient selection criteria) as well as methodological heterogeneity (varying study design) among the studies. Lastly, variation in duration of follow-up may have resulted in underreported events. Nonetheless, strengths of the present study are its systematic and extensive nature. A preregistered protocol was adhered to and the PRISMA guidelines were followed,[14] resulting in a large number of recently published studies that was included.

CONCLUSION

Current literature provides no indication that same-day discharge is unsafe. Adequate patient selection may be the key to stimulate same-day discharge. It appears safe for most patients undergoing laparoscopic appendectomy for uncomplicated acute appendicitis that meet discharge criteria. Data on costs and treatment satisfaction presented in this review were rather limited. Further implementation of same-day discharge after appendectomy may lower expenses and enhance patient satisfaction.

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APPENDIX I: SEARCH STRATEGY OUTLINE

Search date: April 14, 2020

DATABASE	# of refs	after de-duplication
Embase.com	1569	1544
Medline ovid	772	109
Web of science	619	125
Cochrane CENTRAL	130	54
Google scholar	200	80
Total	**3290**	**1912**

Embase.com

('appendectomy'/exp OR 'appendicitis'/de OR (appendectom* OR appendicectom* OR postappendectom* OR postappendicectom* OR appendicit*):ab,ti) AND ('same day discharge'/de OR 'ambulatory surgery'/de OR 'outpatient'/de OR 'hospital discharge'/de OR 'outpatient department'/de OR 'ambulatory care'/de OR (((same-day OR early OR 24h OR 24-h OR 24-hour* OR 12h OR 12-h OR 12-hour* OR within OR timely OR direct*) NEAR/3 discharge*) OR ambulat* OR outpatient* OR out-patient* OR day-surg* OR (day NEXT/1 (case OR care)) OR fast-track OR (short* NEAR/3 stay*)):ab,ti) NOT ([Conference Abstract]/lim) AND [english]/lim

Medline ovid

(Appendectomy/ OR Appendicitis/ OR (appendectom* OR appendicectom* OR postappendectom* OR postappendicectom* OR appendicit*).ab,ti.) AND (Ambulatory Surgical Procedures/ OR Outpatients/ OR Patient Discharge/ OR Ambulatory Care/ OR (((same-day OR early OR 24h OR 24-h OR 24-hour* OR 12h OR 12-h OR 12-hour* OR within OR timely OR direct*) ADJ6 discharge*) OR ambulat* OR outpatient* OR out-patient* OR day-surg* OR (day ADJ (case OR care)) OR fast-track OR (short* ADJ3 stay*)).ab,ti.) AND english.lg.

Web of science

TS=(((appendectom* OR appendicectom* OR postappendectom* OR postappendicectom* OR appendicit*)) AND ((((same-day OR early OR 24h OR "24-h" OR "24-hour*" OR 12h OR "12-h" OR "12-hour*" OR within OR timely OR direct*) NEAR/2 discharge*) OR ambulat* OR outpatient* OR "out-patient*" OR "day-surg*" OR (day NEXT (case OR care)) OR fast-track OR (short* NEAR/2 stay*)))) AND DT=(article) AND LA=(english)

Cochrane CENTRAL

((appendectom* OR appendicectom* OR postappendectom* OR postappendicectom* OR appendicit*):ab,ti) AND ((((same-day OR early OR 24h OR "24-h" OR "24-hour*" OR 12h OR "12-h" OR "12-hour*" OR within OR timely OR direct*) NEAR/3 discharge*) OR ambulat* OR outpatient* OR "out-patient*" OR "day-surg*" OR (day NEXT (case OR care)) OR fast-track OR (short* NEAR/3 stay*)):ab,ti)

Google scholar

appendectomy|appendicectomy|postappendectomy|postappendicectomy|appendicitis "day|early|24h|hour|12h|timely|direct discharge"|"discharge within"|ambulatory|outpatient|"day-surgery|case|care"|"fast-track"|"short stay"

APPENDIX II

Table S1. Details of included studies.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Aguayo (1)	• Laparoscopic surgery • Nonperforated AA • Children	Excluded: Perforation defined as a hole in the appendix or fecalith in the abdomen	Not reported	59 (13%) medical 18 (3.9%) late arrival 2 (0.4%) social 381 (83%) clinical care habits	Not specified
Alkhoury (2)	• Laparoscopic surgery • Acute or interval • UAA • Children	Excluded: perforation or gangrene, or residual abscess or faecolith found at operation	Not reported	5 (11%) medical 35 (78%) late operation 5 (11%) social	Not specified
Benedict (3)	• Laparoscopic surgery • Nonperforated AA • Age <18yrs	Excluded: perforation defined as either a hole in the appendix or a fecalith in the abdomen	Not reported	5 (6%) late surgery 10 (14%) pain 10 (14%) nausa/emesis 12 (16%) significant comorbidities 37 (50) no specific reason	Not specified
Cairo (4)	• Laparoscopic or open • UAA • Age <18yrs • Excluding: - Discharge on day ≥ 3	Excluded: Perforated or complicated appendicitis	Not reported	Not reported	Wound complications: eg. superficial surgical site infection (SSI), deep surgical-space infection, deep organ-space infection, and wound disruptions, such as dehiscence)
Cash (5)	• Laparoscopic surgery • UAA • Age ≥18yrs • Excluding: - pregnancy	Excluded: intraoperative findings of perforation, abscess, or gangrenous appendicitis	• Ability to tolerate liquid intake • Ability to ambulate • Pain controlled with oral analgesics • Hemodynamic stability • Adequate respiratory effort • No alteration in mental status from baseline • Ability to urinate • Nausea and vomiting controlled • Physician approval • Appropriate supervision and assistance at home	7 (41%) unrelated medical conditions 2 (12%) intraoperative complications 8 (47%) physician discretion *(all further specified in the paper)*	Not specified
Dubois (6)	• Laparoscopic and open • UAA+CAA • All ages Considered for SDD if: - Laparoscopic - UAA - age ≥ 16 and ≤ 65yrs - not pregnant, insulin dependent or immunosuppressed - adult available to monitor for the first 24h - live <30min of a hospital	Complicated appendicitis was defined as perforation or gangrenous.	• Stable vital signs • Able to tolerate oral intake • Able to void urine • Pain controlled by oral analgesia	27 (17) open/converted surgery 6 (4) age <16 or >65 2 (1) no responsible adult at home 1 (0.6) insulin dependent 23 (14) CAA 5 (3) postoperative fever 2 (1) pain uncontrolled by oral analgesia 2 (1) other (numbers above account for the SDD protocol group)	Any complication within 30 days of the operation, as documented in the patient's health record.

Table S1. Continued.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Farach (7)	• Laparoscopic or open • AA or interval • Age <21yrs • Excluded: - pre-existing complex medical conditions not suitable for outpatient surgery - inadvertent admission to the inpatient unit - social indications - late operation	AA was defined as appendiceal hyperemia, dilation, or inflammation without presence of fibrinous exudate, turbid peritoneal fluid, or perforation. CAA: intraoperative findings of suppurative, gangrenous or perforated appendicitis.	• Afebrile < 38°C • Hemodynamically stable • Able to tolerate liquids • Adequate pain control • Able to void	46 (28%) excluded preoperatively 97 (59%) complex appendicitis 9 (5.5%) late operation 3 (1.8%) inadequate pain control 3 (1.8%) unable to tolerate PO 3 (1.8%) fever 2 (1.2%) social indications 1 (0.6%) medical condition	Not further specified in methods Results show 4 categories: superficial wound infection, intra-abdominal abscess, ileus/bowel obstruction and other.
Gignoux (8)	• Laparoscopic surgery • AA • All ages • Excluding: - could not be operated before 5pm or could not be postponed to the next day - home-hospital journey over 1h - patient living alone - severe comorbidities requiring monitoring	All AA. Patients with generalized peritonitis or abscess requiring administration of intravenous antibiotics were considered ineligible for SDD.	• No anaphylaxis • Pain that controlled with oral analgesics • No fever • No vomiting	68 (89%) excluded preoperatively 3 (4.0%) severe infections 1 (1.3%) anaphylaxis 2 (2.6%) generalized peritonitis 2 (2.6%) excessive pain	Not specified Complications were classified according to the modified Clavien system.
Grigorian (9)	• Laparoscopic surgery • Nonperforated AA • Age ≥18yrs • Excluding: - Discharge on day ≥ 3	Excluded: Intraoperative findings of perforation or abscess	Not reported	Not reported	Superficial surgical-site infections (SSSI), post-operative intra-abdominal abscess, mortality
Gurien (10)	• Laparoscopic surgery • UAA • Age ≤ 18yrs	Excluded: if perforated or gangrenous	Not reported	94 (87%) observation <24h 6 (5.6%) surgeon preference 4 (3.7%) medical reasons 4 (3.7%) social reasons	Not specified
Halter (11)	• Laparoscopic • UAA • Age 1-18yrs • Excluding: - medical indication for postoperative admission	Excluded: evidence of perforation or gangrenous appendicitis	"Patients were deemed safe for discharge home from the recovery room using the same discharge criteria applied to patients discharged following elective same-day outpatient procedures In the Ambulatory Surgery Unit."	Not reported	Not specified

Table S1. Continued.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Hussain (12)	• Laparoscopic surgery • UAA • Age 14-60yrs • Excluding: -multiple comorbid diseases -coagulation disorders -adverse anaesthetic history -suspected/proven malignancy -ASA-III or IV - unavailability of competent adult to accompany the patient -BMI >35 -Long distance from home (>30min travel)	Uncomplicated symptomatic appendicitis, that is, without abscess, perforation, sepsis and phlegmon formation	a)Stable vital signs >30min b)No new signs/symptoms after the operation c)No active bleeding or oozing d)Minimal nauseau and persistent emesis for <30min e)Orientation in person, time and place f)Pain controllable with oral analgesics g)Passed urine h)No surgical complication i)Minimal dizziness after sitting for <10min j)A responsible escort	1 (25%) medical reasons 3 (75%) social reasons	Not specified
Lefrancois (13)	• Laparoscopic surgery • UAA+CAA • All ages • Excluded: - interval surgery - stump appendicitis Considered for SDD if: St. Antoine score* ≥ 4; UAA; no pregnancy, severe comorbidity or previous pelvic surgery; no severe sepsis or excessive pain; accompanying person; home located <1h transport; sufficient understanding.	All AA	• >No fever • >No pain • >No nausea/vomiting	81 (44) score >4 45 (69) SDD unit unavailable 10 (5.4) not proposed 7 (3.8) social/medical contraindication 3 (1.6) refusal (numbers above account for the SDD protocol group)	Any complication within 30 days of operation.
Putnam (14)	• Laparoscopic or open • UAA • Age <18yrs • Excluded: - interval surgery	Excluded: gagrenous or perforated appendicitis at the time of operation.	Not reported	Not reported	Postoperative superficial, deep and organ/space SSIs were recorded.
Rosen (15)	• Laparoscopic surgery • UAA • Age ≥ 18yrs • Excluded: - pregnant - wards of the county penitentiary	No evidence of gangrene or perforation.	• Normal vital signs • Adequate pain control • Ability to urinate • Ability to ambulate • Ability to tolerate oral intake • Physician approval *(further specified in the paper)*	24 (40) medical reasons 23 (38) social reasons 13 (22) concern for intraoperative findings *(further specified in the paper)*	Not specified

Table S1. Continued.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Scott (16)	• Laparoscopic surgery • Nonperforated AA • Age >18yrs • Excluded: - incidental appendectomy - appendectomy concomitant with other procedure - admission >48h	Not specified	Discharge based on a >12 score on the Procedural and Anesthesia Scoring System which is a scoring tool used region-wide to discharge directly from the recovery room after any operation.	Not reported	Only wound infection reported, no definition specified.
Yu (17)	• Laparoscopic surgery • Uncomplicated • Age 5-18yrs • Excluding: - pre-existing medical conditions requiring inpatient admission - social indications (extensive travel, lack of resources to provide acute care after surgery) - surgery performed between midnight and 7am	Excluded: patients with complex appendicitis (gangrenous or perforated).	Not reported	32 (39) failed to meet discharge criteria 15 (18) surgeon preference for additional IV antibiotics	Any postsurgical condition requiring ED visit, readmission or reoperation. Surgical site infections were defined according to the Centers for Disease Control and Prevention guideline.
Non-comparative studies					
Aubry (18)	• Laparoscopic or open • UAA • Age ≥ 15yrs • ASA I-II • accompanying adult • place of residence within 1h • Excluding: - physical/mental condition preventing participation - pregnancy Considered for SDD if: - no CAA at surgery - no complication from anesthesia	Excluded:presence ofappendiceal or pelvic abscess on radiological examination, radiological pneumoperitoneum and/or general peritoneal effusion. CAA defined as abscess, local or general peritonitis discovered during surery.	Not reported.	7 (7) CAA 3 (50%) medical reasons 3 (50%) social reasons *(further specified in the paper)*	Not specified. Postoperative complications were graded according to the Clavien-Dindo classification.

Table S1. Continued.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Frazee 2016 (19)	• Laparoscopic surgery • UAA • Age ≥ 18yrs • Excluding: - interval surgery - pregnancy	Excluded: gangrenous and ruptured appendicitis	• Ability to tolerate liquid intake • Ability to ambulate • Pain controlled with oral analgesics using VAS • HD stability • adequate respiratory effort • no alteration in mental status from baseline • Ability to urinate • Nausea/vomiting controlled • Physician approval • Appropriate supervision and assistance at home	32 (41) pre-existing conditions 10 (13) postoperative morbidity 6 (8) physician discretion 31 (39) social reasons *(further specified in the paper)*	Not specified
Frazee 2017 (20)	• Laparoscopic surgery • UAA • Age ≥ 18yrs • Excluding: - interval surgery - pregnancy	Excluded: findings of gangrenous or perforated appendicitis	• Ability to tolerate liquid intake • Ability to ambulate • Pain controlled with oral analgesics using VAS • HD stability • adequate respiratory effort • no alteration in mental status from baseline • Ability to urinate • Nausea/vomiting controlled • Physician approval • Appropriate supervision and assistance at home	20 (26) pre-existing conditions 21 (27) medical reasons 22 (29) social reasons 12 (16) physician discretion	Not specified
Gee (21)	• Laparoscopic surgery • UAA • Age 2-18yrs • Excluding: - interval surgery - additional intra-abdominal pathology (i.e. torsed ovarian cyst)	Excluded: perforated or gangrenous appendicitis	Not reported	Not reported	All complications including surgical site infection, abscess, nausea and/or vomiting, intractable pain, readmissions, return to the ER and non-scheduled clinic visits were recorded.
Grelpois (22)	• Laparoscopic surgery • UAA • Age >18yrs • ASA I-II • Excluding: - contraindications for operation or SDD - diagnosis between midnight and 7am or during weekend - pregnancy, breastfeeding - incarceration - living alone or >1 h from a hospital - not easy contactable	Excluded: imaging and/or intraoperative findings of abscess, localized or generalized fluid, fecaliths/ coproliths	Not reported	6 (86) medical 1 (14) discharge against medical advice	Morbidity (Clavien-Dindo classification)

Table S1. Continued.

First author	Patient selection & eligibility for SDD	Type of appendicitis	Discharge criteria	Reasons for overnight stay	Definition complications
Hobeika (23)	• Laparoscopic surgery • UAA • All ages • St Antoine score ≥ 4 (based on BMI, WBC, CRP, no radiological signs perforation, diameter ≤ 10mm) • Excluding: - absence of accompanying adult - inavailability day surgery room	Not specified	Not reported	4 (4) medical reasons 3 (3) patient refusal or end of surgery after 18:00 3 (3) no available reason *(further specified in the paper)*	Any complication within 30 days of operation.
Hrad (24)	• Laparoscopic surgery • UAA • All ages	Excluded, based on pathology report: normal appendix, chronic, perforated, necrotic/gangrenous appendicitis	• A Modified Aldrete Post Anesthesia Score of 10-12, which does not include the need to void before discharge. *(further specified in paper)*	2 (67) medical reasons 1 (33) social reasons *(further specified in the paper)*	Not reported
Sabbagh (25)	• Laparoscopic surgery • UAA • Age >18yrs • ASA I-II • Excluding: - diagnosis between midnight and 7am or during weekend - intraoperative finding of an alternative diagnosis - associated surgical procedure (colectomy, cecectomy, adnexectomy) - insufficient understanding - inavailability of another person to spend the night at the patient's home in the event of an emergency - living > 1h from a hospital - unable to be contacted	Excluding: CAA on the basis of clinical features (sepsis), laboratory signs (renal failure), radiologic or intraoperative signs (abscess, localized or generalized peritonitis, fecaliths, or pneumoperitoneum)	• Ability to tolerate a liquid diet	3 (5) medical reasons	Not reported

Abbreviations: CAA, complicated acute appendicitis; UAA, uncomplicated acute appendicitis; NA, not applicable.
* St. Antoine score was based on BMI, WBC, CRP, no radiological sign of perforation and appendix diameter ≤10mm).

Table S2. ROBINS-I results of comparative studies.

Risk of bias domains

	D1	D2	D3	D4	D5	D6	D7	Overall
Cash *et al.* 2012	x	+	+	+	+	-	-	x
Dubois *et al.* 2010	-	+	+	+	+	-	-	-
Lefrancois *et al.* 2015	x	+	+		+	-	-	x
Putnam *et al.* 2014		+	+		+	-	-	-
Rosen *et al.* 2017	x	+	+	+	+	-	-	x
Cairo *et al.* 2017	-	+	+	+	+	-	-	-
Grigorian *et al.* 2019	-	+	+	+	+	-	-	-
Scott *et al.* 2017	x	+	+	+	+	-	-	x
Aguayo *et al.* 2014	x	+	+	+	+	-	-	x
Alkhoury *et al.* 2012	x	+	+	+	+	-	-	x
Benedict *et al.* 2018	x	+	+	+	+	-	-	x
Farach *et al.* 2014	X	+	+	+	+	-	-	X
Gignoux *et al.* 2018	-	+	+	+	+	-	-	-
Gurien *et al.* 2017	x	+	+	+	+	-	-	x
Halter *et al.* 2015	x	+	+	+	+	-	-	x
Hussain *et al.* 2014	X	+	+	+	+	-	-	X
Yu *et al.* 2017	x	+	+	+	+	-	-	x

Domains
D1 = Bias due to confounding*
D2 = Bias due to selection of participants
D3 = Bias in classification of interventions
D4 = Bias due to deviations from intended interventions†
D5 = Bias due to missing data§
D6 = Bias in measurement of outcomes
D7 = Bias in selection of the reported resultsΩ

Judgement
+ Low
- Moderate
x Serious
X Critical

* Confounding to some extent expected in all studies, few studies performed analysis to adjust for confounders
† In most studies patients were retrospectively included in the intervention or control group based on their date of discharge, which inherently could not be deviated from (patients were either discharged or admitted on the day of surgery).
§ In none of the studies loss of follow-up was described. Primary outcomes being readmissions, complications and unplanned hospital visits, it is expected not to be a substantial risk of bias.
Ω None of the included studies referred to a prespecified statistical analysis plan. Though no specific indication was found that reported results were selected from larger datasets, this cannot be ruled out.

Table S3. Reinterventions.

First author *Follow-up*	Subgroups (n)	Reintervention n (%)	*p* value
Studies comparing patients in a SDD protocol to historical controls			
Cash *2 weeks*	SDD protocol (116) Historical controls (119)	0	-
Dubois *30 days*	SDD protocol (161) Historical controls (156)	1 (0.6) reoperation reported in the SDD protocol group (laparotomy and small bowell resected due to iatrogenic small bowell injury), no report on possible percutaneous drainage of reported intra-abdominal abscesses.	-
Lefrançois *30 days*	SDD protocol (184) Historical controls (468)	Not reported	-
Putnam *30 days*	SDD protocol (478) Historical controls (316)	Not reported	-
Rosen *2 weeks*	SDD protocol (173) Historical controls (178)	Not reported	-
Studies comparing SDD to discharge on postoperative day 1 or 2			
Cairo *30 days*	SDD (4662) Control group (16139)	Not reported	-
Grigorian *30 days*	SDD (3988) Control group (12943)	14 (0.3) percutaneous drainages and 0 reoperations 37 (0.3) percutaneous drainages and 0 reoperations	ns
Scott *30 days*	SDD (6710) Control group (5993)	Not reported (though in the Methods it is stated that reoperation was examined).	-
Studies comparing SDD to overnight stay for one or more nights			
Aguayo *nr*	SDD (128) Control group (460)	0	-
Alkhoury *2 weeks*	SDD (162) Control group (45)	0	-
Benedict *nr*	SDD (495) Control group (74)	1 (0.2) diagnostic laparoscopy for small bowel obstruction 0	-
Farach *2 weeks*	PACU (185) Control group (164)	1 (0.5) exploratory laparotomy with lysis of adhesions for small bowel obstruction, among those completing the protocol	-
Gignoux *30 days*	SDD (109) Control group (76)	1 (0.9) reoperation 3 (4.0) reoperations	0.306
Gurien *nr*	PACU discharge (63) Control group (108)	0	-
Halter *30 days*	SDD (121) Control group (115)	0	-
Hussain *10 days*	SDD (26) Control group (4)	0	-
Yu *30 days*	SDD (185) Control group (417)	1 (0.5) reoperation 4 (1.0) reoperations	0.69
Non-comparative studies			
Aubry *30 days*	N = 102	1 (1) patient with a pelvic abscess reoperated for drainage.	-
Frazee 2016 *nr*	N = 563	0	-
Frazee 2017 *nr*	N = 376	1 (0.3) diagnostic laparoscopy to exclude missed enterotomy because of significant postoperative abdominal tenderness	-
Gee *2 weeks*	N = 961	0	-
Grelpois *30 days*	N = 83	3 (3.6) deep abscesses classified as Clavien-Dindo IIIa (2) and IIIb (1)	-
Hobeika *30 days*	N =102	2 (2) patients: 1 transrectal surgical drainage and 1 laparoscopic lavage of pelvic abscesses.	-
Hrad *11 days*	N = 74	0	-
Sabbagh *nr*	N = 57	Unclear from data as presented in paper.	-

SDD, same day discharge; PACU, postanesthesia care unit (recovery room).

Table S4. Costs.

First author *Follow-up*	Subgroups (n)	Costs - METHOD	Costs - OUTCOME *p value*	
Studies comparing patients in a SDD protocol to historical controls				
Dubois *30 days*	SDD protocol (161) Historical controls (156)	nr	"After adjusting for inflation to 2007 costs in Canadian dollars, the average cost per patient discharged from the recovery room was $4,845 ± 686; the average cost per patient in the matched control group was $5,168 ± 1,216. This translates to a mean difference of -$323 (95% CI -$670, $23, p = 0.067) per patient."	
Putnam *30 days*	SDD protocol (478) Historical controls (316)	"Cost data were obtained through the hospital cost accounting system. Direct costs were used as the pathway only affected this portion of the total hospital costs, The direct cost of the OR was excluded because the pathway did not change intraoperative practices. The remaining direct costs were averaged for the pre-pathway and pathway cohorts to determine the cost per encounter. Importantly, the costs of readmission and post-discharge events such as SSIs were not obtainable for this study and may limit the applicability of the results."	"the average cost per encounter during the prepathway period was $3,090 ± 996, which decreased to $2719 ± 926 at the time of audit #1 but subsequently increased to $2,988 ± 1,024 at the time of the second audit. Yearly cost savings during the pathway period was $49,053."	
Studies comparing SDD to discharge on postoperative day 1 or 2				
Scott *30 days*	SDD (6710) Control group (5993)	"The cost of treatment is the sum of the hospital's fixed direct cost amount and the hospital variable direct cost amount. Costs for both included both labor and non-labor costs per service cost code allocated in the cost accounting system."	$1,994 $2,343	< 0.001
Studies comparing SDD to overnight stay for one or more nights				
Farach *2 weeks*	PACU discharge (185) Control group (164)	nr	"This decrease in inpatient resources resulted in a median reduction in hospital charges of $4111 per patient discharged from the PACU after appendectomy. This resulted in total savings of $760,535 during the 1-year study period."	
Gurien *nr*	PACU discharge (63) Control group (108)	nr	Not reported (reference) +$1007 for admission <24h +$2237 for admission >24h	nr
Halter *30 days*	SDD (121) Control group (115)	"Cost analyses were performed using the hospital cost accounting system and were based on total charges for the entire hospital encounter, including emergency room evaluation, diagnostics, OR and surgical charges, and hospital admission where applicable. No adjustments were made to correct for inflation during the study period."	$10,551 ± 2165 $12,691 ± 3507	< 0.001
Yu *30 days*	SDD (185) Control group (417)	"Costs were compared for the initial admission alone and for an episode of care, which included the initial admission and a period of 30 days after discharge. Direct variable costs, total costs, and payments received (revenue) were analyzed. Margins were estimated by subtracting hospital accounting costs from the payments received. Physician and outpatients pharmacy costs were not included in our economic analysis; nor were education and implementation costs. The institution's internal costing system provided patient-level costs."	$8073 (6748-9093) $8424 (7207-9725)	0.002
Non-comparative studies				
Hobeika *30 days*	N = 102	nr	"This study did not measure direct costs or charges. Potential cost savings of this approach were estimated using a similar analysis as that used by Frazee. This analysis relied on measurements of the Henry J. Kaiser Family Foundation that reported in 2010 that median cost of 1 day in the hospital was approximately $1910 US. Multiplying this cost by the number of uncomplicated laparoscopic appendectomies performed each year (1910 x 280,000 cases) results in a potential cost savings of $534,800,000/y in the United States."	

SDD, same day discharge; PACU, postanesthesia care unit (recovery room); nr, not reported

Table S5. Treatment satisfaction.

First author *Follow-up*	Subgroups (n)	Treatment satisfaction - METHOD	Treatment satisfaction - OUTCOME
Studies comparing patients in a SDD protocol to historical controls			
Rosen *2 weeks*	SDD protocol (173) Historical controls (178)	"Satisfaction surveys using a Likert scale (range 1 to 4, with a score of 1 indicating extreme disagreement and 4 denoting extreme agreement) were distributed to all patients at their 2-week follow-up appointment or via phone."	"Responses from both groups showed no statistically significant difference and the median response scores of both groups were identical. The survey covered ability to resume daily activities (median 3 for both groups), pain control (median 4), and understanding of their treatment plan (median 4). Same-day discharge patients were asked if they were nervous about the protocol (median 3), if they were happy with the protocol (median 3), and if they would want a same-day discharge if they could do it over again (median 3). Overall ranking of the hospital (scale 1 to 10) yielded a median score of 9 in both the control and outpatient groups. Response rate for the satisfaction surveys was 55%."
Studies comparing SDD to overnight stay for one or more nights			
Alkhoury *2 weeks*	SDD (162) Control group (45)	"At the postoperative visit 2 to 3 weeks later, parents completed a 1-page survey that asked about their satisfaction with same-day discharge, in addition to information about pain control, return to normal activities, and postoperative problems. The pertinent portion of the survey that relates to parental satisfaction with same-day discharge is given in Table 1." Parent satisfaction survey questions: 1. Immediately after surgery, how did you feel about going home on the same day? A) Happy to go home, b) Nervous, but we did fine, c) I wouldn't want to do it again. 2. In retrospect, how do you feel now? A) It was the right thing to do, b) It was OK to go home on the same day, but I'm not sure it was best, c) I would not want to do it again. 3. Feel free to add other comments regarding your child's surgery."	"Overall, parents were satisfied with their child's expeditious discharge. At the postoperative office visit, 141 of 162 parents (87.0%) said that immediately following the surgery they had been pleased with same-day discharge, whereas 13 parents (8.0%) indicated they felt nervous but were ultimately satisfied; 8 parents (4.9%) were not sure early discharge was best. In retrospect, satisfaction rose to 95.0% at the time of the postoperative office visit, with 154 parents stating that same-day discharge was desirable. Only 1 parent would insist on admission if faced with the situation again."
Halter *30 days*	SDD (121) Control group (115)	"All patients' families were contacted by phone within 2 weeks of surgery to conform there had been an uneventful recovery and to inquire about any issues that might require a follow-up visit in the office. For those patients discharged from the recovery room, families were also mailed a six-question survey regarding their experience."	"With respect to patient satisfaction, surveys were sent to families of all SDD patients, with a total of 32 responses (26% response rate). When families were asked "At the time of discharge, how did you feel about taking your child home the same day following surgery?" the majority (59%) responded "Happy to go home" and an additional 28% responded "Nervous, but OK". Overall, almost 80% replied that they would prefer to be discharged from the recovery room in similar circumstances in the future."
Hussain 10 days	SDD (26) Control group (4)	nr	"At the time of discharge all patients (100%) were highly satisfied."
Yu 30 days	SDD (185) Control group (417)	"All SDD patients were contacted by telephone within 24 hours of discharge to assess their recovery by the surgical team or research staff. A telephone script and a standardized same day discharge appendectomy phone follow-up template were created for documentation within our EMR. Alarming symptoms would prompt the caller to notify the on-call physician and document this within the template."	"Average satisfaction of recent hospitalization reported was 9.4/10 (range 5-10). 88% reported patient satisfaction of 8 or higher and 76% gave a score of 10/10. There was 100% satisfaction with receiving a telephone follow-up."
Non-comparative studies			
Grelpois 30 days	N = 83	"[..] end points [..] were [..] patient satisfaction, and quality of life (according to the 36-Item Short-Form Health Survey administered on discharge)."	"[..] 99% of the patients (n = 82) were satisfied with DCS. The only unsatisfied patient had not wanted to wait for the surgeon before being discharged. The 36-Item Short-Form Health Survey evidenced good quality of life."

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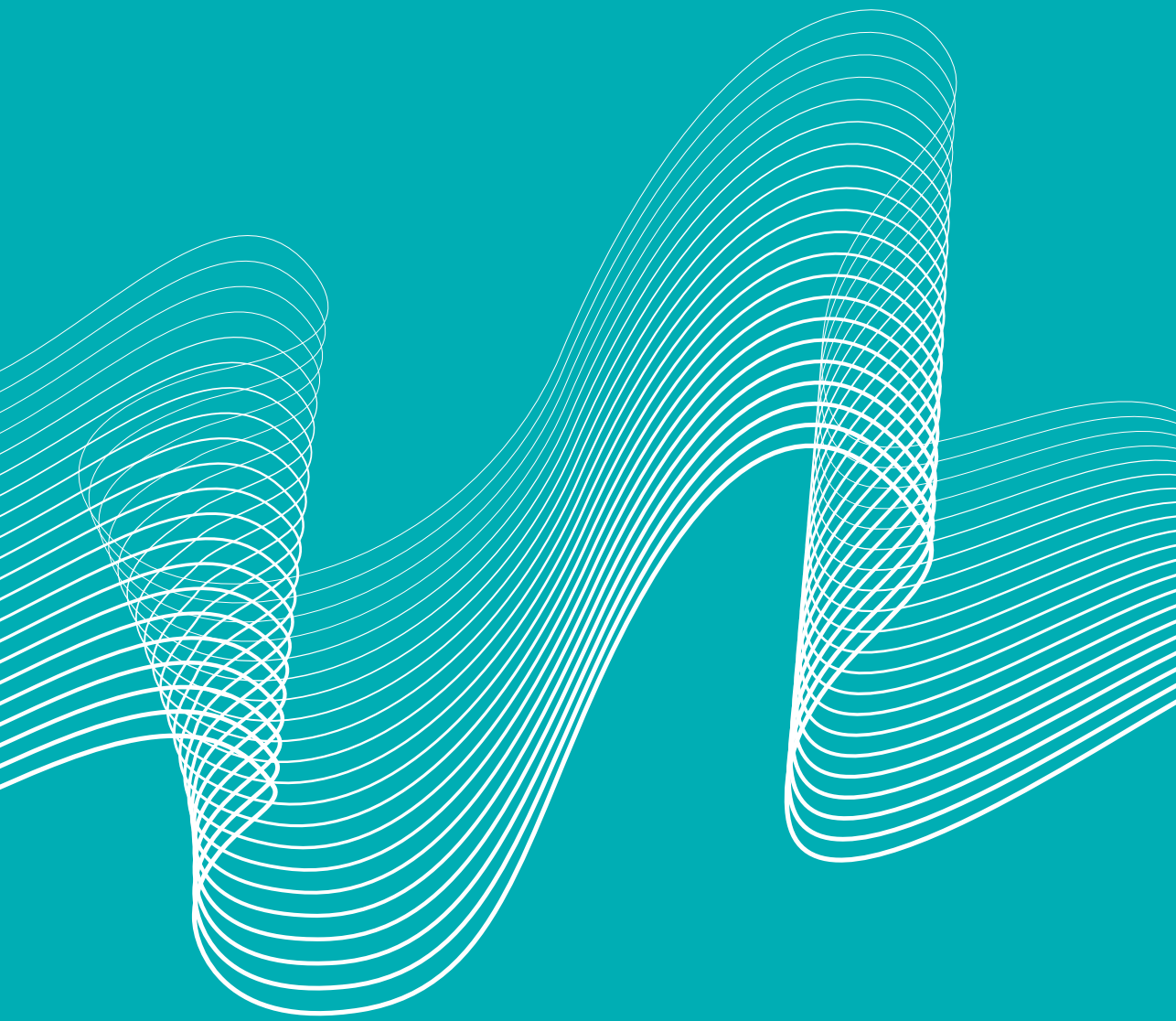

Anne Loes van den Boom, Elisabeth M.L. de Wijkerslooth, Joost van Rosmalen, Frédérique H. Beverdam, Evert-Jan G. Boerma, Marja A. Boermeester, Joanna W.A.M. Bosmans, Thijs A. Burghgraef, Esther C.J. Consten, Imro Dawson, Jan Willem T. Dekker, Marloes Emous, Anna A.W. van Geloven, Peter M.N.Y.H. Go, Luc A. Heijnen, Sander A. Huisman, Dayanara Jean Pierre, Joske de Jonge, Jurian H. Kloeze, Marc A. Koopmanschap, Hester R. Langeveld, Misha D.P. Luyer, Damian C. Melles, Johan W. Mouton, Augustinus P.T. van der Ploeg, Floris B. Poelmann, Jeroen E.H. Ponten, Charles C. van Rossem, Wilhelmina H. Schreurs, Joël Shapiro, Pascal Steenvoorde, Boudewijn R. Toorenvliet, Joost Verhelst, Hendt P. Versteegh, Rene M.H. Wijnen, Bas P.L. Wijnhoven

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7

TWO VERSUS FIVE DAYS OF ANTIBIOTICS AFTER APPENDECTOMY FOR COMPLEX ACUTE APPENDICITIS (APPIC): STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Background:

Acute appendicitis is one of the most common indications for emergency surgery. In patients with a complex appendicitis, prolonged antibiotic prophylaxis is recommended after appendectomy. There is no consensus regarding the optimum duration of antibiotics. Guidelines propose three to seven days of treatment, but shorter courses may be as effective in the prevention of infectious complications. At the same time, the global issue of increasing antimicrobial resistance urges for optimization of antibiotic strategies. The aim of this study is to determine whether a short course (48 hours) of postoperative antibiotics is non-inferior to current standard practice of 5 days.

Methods:

Patients of 8 years and older undergoing appendectomy for acute complex appendicitis – defined as a gangrenous and/or perforated appendicitis or appendicitis in presence of an abscess – are eligible for inclusion. Immunocompromised or pregnant patients are excluded, as well as patients with a contraindication to the study antibiotics. In total, 1066 patients will be randomly allocated in a 1:1 ratio to the experimental treatment arm (48 hours of postoperative intravenous (IV) antibiotics) or the control arm (5 days of postoperative IV antibiotics). After discharge from the hospital, patients participate in a productivity-cost-questionnaire at four weeks and a standardized telephone follow-up at 90 days after appendectomy. The primary outcome is a composite endpoint of infectious complications, including intra-abdominal abscess (IAA) and surgical site infection (SSI), and mortality within 90 days after appendectomy. Secondary outcomes include IAA, SSI, restart of antibiotics, length of hospital stay (LOS), reoperation, percutaneous drainage, readmission rate, and cost-effectiveness. The non-inferiority margin for the difference in the primary endpoint rate is set at 7.5% (one-sided test at α 0.025). Both per-protocol and intention-to-treat analyses will be performed.

Discussion:

This trial will provide evidence on whether 48 hours of postoperative antibiotics is non-inferior to a standard course of five days of antibiotics. If non-inferiority is established, longer intravenous administration following appendectomy for complex appendicitis can be abandoned, and guidelines need to be adjusted accordingly.

Trial registration:

Dutch Trial Register, NTR6128. Registered 20 December 2016, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6128

BACKGROUND & RATIONALE

Acute appendicitis is one of the most common surgical emergencies in children and adults worldwide.[1-3] Although the role of surgery as primary treatment has recently been questioned, appendectomy remains the treatment of choice.[4, 5] In the Netherlands, more than 12,000 patients undergo appendectomy for acute appendicitis each year.[6] In Northern America the estimated number of patients with appendicitis in 2015 was over 378,000.[7] Intraoperatively, acute appendicitis is classified as either simple or complex. A phlegmonous appendix is considered simple. A complex appendicitis includes a gangrenous and/or perforated appendix as well as any appendicitis with an intra-abdominal or pelvic abscess.[8] Previously it was thought that a simple appendicitis could progress towards a complex appendicitis over time, but more recent data suggest that both entities represent distinct types of inflammation.[8, 9] Some 25% – 30% of all patients with appendicitis have a complex appendicitis, which is associated with increased risk of postoperative infectious complications.[10-14] Therefore, following perioperative antibiotic prophylaxis, guidelines recommend postoperative antibiotics for complex appendicitis.[15-18]

Currently, there is no consensus on the duration of postoperative antibiotic treatment and different antibiotic regimes are used.[8, 19-21] A nationwide cohort study from the Netherlands showed that most patients receive 5 days of postoperative antimicrobial therapy.[22] However, it may be safe to stop intravenous antibiotic treatment earlier than 5 days, when a patient meets defined discharge criteria (patient is afebrile, has a normal leukocyte count, has resumed oral intake).[10, 14, 23-29]. Cohort studies show that 3 days of postoperative antibiotic treatment is feasible and safe.[12, 30-32] At least 48 hours of intravenous antibiotics is recommended in the Dutch surgical guideline.[15] Small retrospective studies show that even postoperative prophylaxis less than three days is feasible.[33-36] However, the methodological quality of these studies is poor. Therefore, no definite recommendations can be made regarding the optimum duration of postoperative prophylaxis after appendectomy for complex appendicitis. To date, no randomized clinical trial has been published to address this topic in an adequately powered study population.

Furthermore, there is a growing global health issue of bacterial resistance. Antimicrobial resistance is a natural biological outcome of antibiotic use and antibiotic overtreatment speeds up this process.[37] Hence, restricting antibiotic therapy is warranted, as pointed out in a report by the World Health Organization.[38]. This study aims to evaluate efficacy of a restrictive postoperative antibiotic course as compared to standard regimen for complex appendicitis, in a non-inferiority design. This manuscript is prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[39]

Trial objective and hypothesis

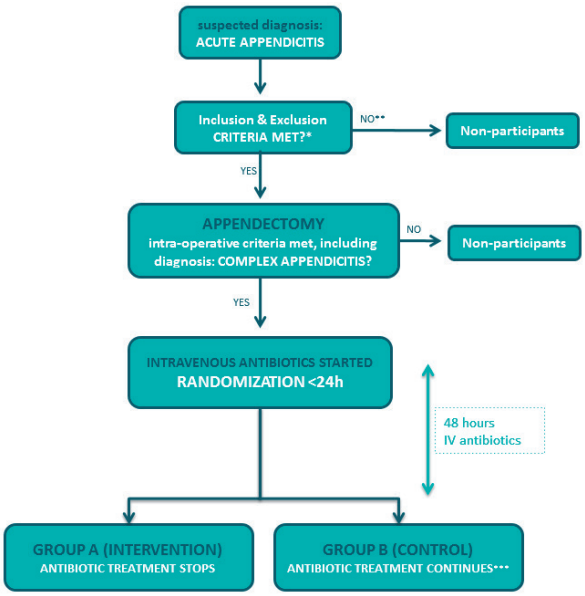
The primary objective of this study is to evaluate the efficacy and safety of discontinuing antibiotic treatment after 48 hours compared to completing a standard course of 5 days, after appendectomy for complex acute appendicitis. It is hypothesized that a 48-hour course is non-inferior to 5 days and will not result in an increase of infectious complications and mortality. Secondary aims are to evaluate length of hospital stay and cost-effectiveness.

METHODS

Trial design

The **A**ntibiotics following a**PP**endectomy **I**n **C**omplex appendicitis (APPIC) trial is a phase IV, prospective, multicenter, non-blinded, randomized controlled trial powered for non-inferiority. Patients are randomly allocated to a short course of 48 hours (intervention arm), or the standard course of 5 days (control arm) of intravenous antibiotics following appendectomy for complex appendicitis. An overview of enrollment, interventions and follow-up of participants in the APPIC trial is shown in figure 1. Figure 2 shows the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) figure. The SPIRIT checklist is shown in Supplementary file S1.

Figure 1. APPIC flowchart of inclusion and randomization



Legend: * All except intra-operative criteria regarding type of appendicitis; ** If the patient hasn't been able to give informed consent prior to appendectomy, this may still be acquired postoperatively, as long as inclusion and randomization takes place within 24 hours; *** Intravenous antibiotic treatment continues for three more days to complete five days in total.

Figure 2. APPIC schedule of enrolment, interventions, and assessments

		STUDY PERIOD						
	APPROACH	DAY OF SURGERY	POST-APPENDECTOMY					Close-out
TIMEPOINT	Arrival ER	0	24hrs	48hrs	5dys	4wks	90dys	90 dys
ENROLMENT:		←	→					
Eligibility screen	←		→					
Informed consent	←		→					
Allocation		←	→					
INTERVENTIONS:								
Short Course Antibiotic Treatment		←		→				
Standard Course Antibiotic Treatment		←			→			
ASSESSMENTS:								
Serious Adverse Events (SAEs)		←						→
Registration of all endpoints		←						→
Productivity-cost-questionnaire						X		
Telephone follow-up with researcher							X	

Trial setting

The trial will run in at least fourteen hospitals in the Netherlands. This includes one academic hospital and thirteen teaching hospitals. The participating hospitals are listed on the trial webpage (www.appictrial.nl). In all participating hospitals appendectomy is mostly performed laparoscopically.

Eligibility criteria

Patients at least 8 years of age scheduled to undergo surgery for suspected acute appendicitis will be approached for participation in the study. If a complex appendicitis is diagnosed intraoperatively, patients are eligible for inclusion. A complex appendicitis is defined as a gangrenous and/or perforated appendicitis or any appendicitis in presence of an intraabdominal or pelvic abscess (8). Written informed consent is preferably obtained before surgery, but may be obtained postoperatively as long as inclusion and randomization is performed within 24 hours after surgery. Exclusion criteria are:

- Unable to give informed consent (language barrier, legally incapable)
- Interval appendectomy
- Clinical suspicion of severe sepsis*
- Conservative treatment of acute appendicitis

- American Society of Anesthesiologists (ASA) score IV or not able to undergo surgery
- Known allergy or other contraindication to study medication*
- Immunocompromised patients*
- Pregnancy
- Concurrent use of antibiotics for other indication*
- Simple acute appendicitis*
- Appendicular infiltrate not amendable for appendectomy
- Inadequate source control in opinion of the surgeon*

** more elaborate definitions are given in the full study protocol.*

Interventions

Postoperative antibiotic treatment

Participants will be randomized (1:1) to receive either: A) a short course of 48 hours, or B) a standard 5-day course of postoperative antibiotic treatment. All patients receive intravenous (IV) antibiotics during the first 48 hours after appendectomy: cefuroxime/metronidazole (3dd 1500/500mg), or alternatively ceftriaxone/metronidazole (1dd 2000mg/3dd 500mg) according to local antibiotic policy. In the control group the IV antibiotics are continued for three more days (a switch to oral formula is not allowed). A daily dose of gentamicin as co-intervention is optional. No other antibiotics are permitted.

Criteria for modifying the allocated treatment

Antibiotic treatment may be prolonged or restarted only in case of a proven source of infection (a decision algorithm is provided in the full protocol). A switch to a different antibiotic regimen is allowed only if necessary due to an adverse reaction to the antibiotics or if indicated by culture results (if a micro-organism resistant to cefuroxime (or ceftriaxone) is cultured a switch should be made to ensure effective antibiotic treatment).

Discharge and follow-up

Laboratory tests, imaging studies and blood cultures will be performed only when clinically indicated. The following clinical parameters will be registered on a daily basis: body temperature <38° Celsius, able to tolerate oral intake, able to mobilize independently; VAS <4 requiring only oral analgesia. However, these criteria are not mandatory for discharge and ultimately the responsible physician decides when a patient is able to go home. After discharge a standard outpatient visit is planned at 2 to 4 weeks according to local hospital policy. Four weeks after appendectomy, patients are asked to complete a productivity-cost questionnaire. At 90 days after appendectomy a standardized follow-up by telephone will be conducted.

Outcome measures

All outcome measures will be registered directly from the electronic patient files. Outcome assessors will not be blinded for the treatment allocation. The telephone follow-up is introduced to check missing data on the primary endpoint, e.g. visits to hospitals or medical facilities other than the center where the patient was treated and included into the trial.

Primary outcome measure

The primary endpoint of this trial is a composite endpoint of infectious complications related to appendectomy, including intra-abdominal abscess (IAA) and surgical site infection (SSI), and mortality within 90 days after appendectomy. An IAA is defined as an infection that involves the abdominal part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure. IAA can be diagnosed through imaging or during reintervention, through purulent drainage from a drain placed into the IAA, or isolation of organisms from a culture of the IAA (40). An SSI can be either deep or superficial, involving the skin, subcutaneous tissue and/or deep soft tissues of the incision. IAA and SSI are defined in more detail according to the Center for Disease Control (CDC) criteria in the full study protocol.[40]

Secondary outcome measures

Secondary endpoints are separate rates of IAA, SSI and mortality; duration of antibiotic treatment; the antibiotic regimen; proportion of patients that restarted antibiotics; length of hospital stay (LOS); time to fulfill discharge criteria; postoperative complications; reoperation; percutaneous drainage; number of visits to the general practitioner (GP), emergency room (ER) and outpatient clinic; readmission rate; adverse events on antibiotics; and cost-effectiveness. Complications will be classified according to the Clavien-Dindo classification of surgical complications as well as the Comprehensive Complication Index (CCI). To analyze cost-effectiveness, the validated iMTA PCQ-questionnaire (version October 2012) will be used, enhanced with a section concerning school absence.

Sample size calculation

A power analysis was performed based on a one-sided 97.5% confidence interval for the effect of study arm (intervention or control), an expected 15% primary endpoint rate and a 7.5% non-inferiority margin. To obtain a power of 90%, 960 patients are needed (480 per treatment arm). To account for possible effects of dropout and missing data (10%) we will recruit 1066 patients. This sample size should also yield sufficient power for the analysis of secondary endpoints.

Recruitment

Recruitment of participants started on April 12th 2017 and is ongoing. Additional participating hospitals may be recruited to ensure feasibility of the trial. The target of 1066 patients is expected to be completed in early 2020.

Allocation

Computerized block randomization (stratified for center) will take place within 24 hours after surgery through ALEA, a web-based application managed by the Clinical Trial Center (CTC) of the Erasmus MC. Random blocks of different lengths are used. Eligible patients will be randomized in a 1:1 ratio to arm A (short course) or arm B (standard course). Each patient will be given a unique study number. An independent data manager from the CTC who is not involved with the clinical practice or patient recruiting created the randomization sequence. The result of the randomization and the patient study number will immediately be provided through ALEA per email to all parties predefined in the system that should receive such notifications.

Implementation

Before the start of the trial, each center is visited by the research team to inform and instruct the involved personnel on study-specific procedures. Surgeons and residents are trained how to assess the type of appendicitis to decide whether patients are eligible for study participation by means of recorded examples of all types of appendicitis.

Blinding

Blinding for treatment allocation in this study would not only be difficult to achieve, but is also undesirable because good clinical decision-making during the postoperative course requires specific knowledge of antibiotics that have or have not been given to the patient. Therefore, this is an non-blinded trial.

Data collection and management

A data manager from each participating hospital will carry out the data collection in collaboration with the trial coordinator. Baseline demographics as well as preoperative, intraoperative and postoperative variables will be collected from the electronic medical records. The validated Productivity Cost Questionnaire (PCQ-iMTA) will be used for cost analysis. A list of all variables is provided in the full study protocol. All data will be entered into the secure online ALEA database, a system validated and supported by the Erasmus University Medical Centre. Data will be handled confidentially and anonymously. A short intraoperative video or static picture(s) should be recorded for quality assurance of the diagnosis complex appendicitis. Quality control will involve collecting data on adherence to the intervention, patient inclusion and follow-up, as well as monitoring the quality of the data entry. Qualified data managers of the Clinical Trial Center of the Erasmus MC will

perform quality control and assurance. Checks and queries will be performed to ensure quality, consistency and completeness. Missing data and inconsistencies will be reported back to the centers to be clarified by the local responsible investigator.

Statistical analysis

We anticipate a 15% rate of infectious complications and mortality in this study population. A 7.5% difference (non-inferiority margin) in the primary endpoint rate is deemed acceptable between the intervention group and control group. This margin is considered acceptable since mortality is expected to account for a negligible proportion within the primary endpoint and infectious complications after appendectomy can be well treated with minimum morbidity and long-term consequences.

Primary endpoint

The study hypothesis will be tested by a one-sided 97.5% confidence interval for the effect of study group (absolute risk difference). This confidence interval will be adjusted for effects of type of appendicitis and age (as a single categorical covariate: <16 years old/non-perforated, <16 years old/perforated, ≥16 years old/non-perforated, ≥16 years old/perforated) using the method proposed by Klingenberg.[41, 42] Non-inferiority will be established if the upper limit of the confidence interval is lower than 7.5%. Both per-protocol and intention-to-treat analyses will be performed. In a secondary analysis, logistic regression analysis will be performed to identify predictors of the composite primary endpoint. Independent variables in this model will include treatment group and also age, sex, surgical approach, type of appendicitis, ASA score and center, as well as significant interaction effects of these independent variables with treatment group.

Secondary endpoints

General patient characteristics and other clinically relevant parameters will be compared between the intervention group and the control group with the independent samples Student's t-test or the Mann-Whitney test in case of continuous outcome variables and the chi-square or Fisher's exact test in case of categorical outcome variables where appropriate. All secondary endpoints will be compared between the trial arms using linear regression for continuous outcomes and logistic regression for dichotomous outcomes, with adjustment for age, sex, surgical approach (open versus laparoscopic), type of appendicitis, ASA score and center. In case of non-normally distributed continuous outcomes, appropriate transformation of these outcomes will be applied. A two-sided significance level of 0.05 will be used for all secondary analyses. Uncertainty with respect to cost-effectiveness will be analyzed by bootstrapping results for incremental costs and health effects. The results will be shown in an acceptability curve that indicates the probability that the intervention meets several cost-effectiveness thresholds.

Data monitoring and Safety

An independent safety committee (DSMB) is assembled to monitor trial safety and progress, with special focus on imbalance between the two trial arms in 90-day mortality and serious postoperative complications. The DSMB is composed of a statistician, two surgeons and a microbiologist, all of whom are unrelated to the study and have no conflict of interest with the coordinating investigator of the study. There will be two planned formal safety analyses: after the first 266 included patients have completed follow-up and after 666 patients have completed follow-up. Safety stopping rules will be applied using the alpha spending approach of O'Brien and Fleming, described into more detail in the full study protocol. The DSMB will notify the coordinating and principal investigators if conditions of the stopping rules have been reached. The steering committee will decide on continuation of the trial. The DSMB roles, responsibilities, meetings and logistics are outlined in the APPIC trial DSMB Charter.

Independent monitors of the Clinical Trial Center of Erasmus MC will visit participating centers intervals at regular intervals to verify adherence to the protocol and legal requirements and perform source data verification. A first site monitoring visit will take place at each participating hospital after the first 3 randomized patients have completed follow-up. Subsequent monitoring visits will be planned according to the predefined monitoring plan.

Rationale for the chosen study design

A non-inferiority design is chosen as the objective of this trial is to show that a short course of antibiotics is *no less effective* than a standard course, in terms of preventing infectious complications. This is relevant in light of several potential advantages of reduced use of antibiotics, such as fewer adverse reactions to antibiotics, shorter length of hospital stay, medical care costs and antimicrobial resistance. In the literature, postoperative infectious complications are reported in 15-20% of patients.[43-45] Furthermore, a similar study by Sawyer *et al.* was aimed at detecting a 10% difference in complication rates after a shorter course of postoperative antibiotic treatment in complicated intra-abdominal infections.[28] Based on these findings and the fact that a reduction in antibiotic consumption will lead to a significant reduction in costs and antimicrobial resistance we accept a 7.5% difference (non-inferiority margin) in the primary endpoint rate. A non-inferiority trial with this margin is acceptable based on the assumption that infectious complications after an appendectomy for a complex appendicitis are in general not associated with severe morbidity and/or mortality. Since it is known that treatment with intravenous antibiotics for 48 hours ensures adequate tissue concentrations (to eliminate the relevant micro-organisms such as E. Coli),[46-48] we have chosen 48 hours of intravenous antibiotics as our intervention. For the individual patient advancing from the regular (3 to) 5 days of antibiotics towards 48 hours may not seem an enormous step forward.

However, extrapolating this to all patients with complex appendicitis could have a major impact on healthcare. From a methodological perspective, we choose to administrate antibiotics completely intravenously for the intervention and control group. Some studies found no support for use of oral antibiotics after the initial postoperative intravenous administration,[26, 49] In addition, it is questioned if adequate tissue concentrations can be met by oral antibiotics for bacteria commonly isolated in complex appendicitis (50). Complete intravenous courses will ensure homogenous treatment in both study arms, without patients' compliance or effectiveness of oral antibiotics as uncertainties.

DISCUSSION

The present study is designed to answer the question whether 48 hours of postoperative antibiotics is non-inferior to the standard treatment of 5 days in patients with a complex appendicitis. If non-inferiority is established, this may lead to a reduction in the use of antibiotics in the future. This in turn may shorten length of hospital stay and may result in lower hospital costs. In the longer term, less use of antibiotics may slow down emergence of antimicrobial resistance.

One of the five main objectives in the global action plan on antimicrobial resistance by the World Health Organization (WHO) is "to optimize the use of antimicrobial medicines".[51] The global threat of antimicrobial resistance urges for action against overuse. More research is needed to determine the minimum effective courses for many diseases. For several infections (e.g. pneumonia, pyelonephritis, cellulitis) shorter courses have proven just as effective as extended courses.[52] Yet, for many diseases, including appendicitis, proper studies have not been performed.[53] With a lifetime risk of about 7 to 8 per cent and a pooled incidence of 100 to 151 per 100,000 person-years in the Western World, acute appendicitis is one of the most common surgical emergencies worldwide.[1, 7, 8] The 25 to 30 per cent of complex appendicitis represents a substantial number of patients that receives prolonged antibiotic prophylaxis, as recommended by the guidelines.[15, 16, 18] To date, no randomized study has evaluated a reduced course of postoperative antibiotics in an adequately powered study. Some studies - all including pediatric patients - have compared a course with a predefined minimum duration (mostly 4 days) with a variable duration based on clinical and laboratory parameters (body temperature <38, resumed oral intake, white blood cell count).[23-25, 32, 54] However, these clinical parameters may still cause overtreatment with antibiotics, as an increased body temperature or delayed clinical improvement may well reflect a prolonged sterile SIRS response rather than an infectious focus.[55] Median antibiotic treatment duration was still 5 days in most studies. Evidence for restricting postoperative antibiotics to less than 3 days after appendectomy is limited. Two retrospective studies demonstrated that antibiotics for more than 24 hours after

surgery for complex appendicitis does not reduce the rate of infectious complications. Kimbrell *et al*. (2014) included 8 patients that received antibiotics for 24 hours at most and 44 patients that received antibiotics for more than 24 hours. Reported IAA rates were 25% and 20.5%, respectively (p = 1.00).[33] In a larger study (n = 410) by Kim *et al*. (2015) multivariable regression analysis revealed no difference in SSI rate between patients with complex appendicitis that received postoperative prophylaxis (for a median of 7 days (range 2 – 21)) and patients that did not.[35] Unfortunately, IAA rate was not reported in this study. Two more studies reported interesting results of antibiotic treatment restricted to less than three postoperative days: no intra-abdominal abscesses occurred in 55 and 11 patients that received antibiotics for 24 – 48 hours and 0 – 24 hours, respectively.[34, 36] The small sample sizes and retrospective nature of these studies must be recognized when interpreting the results. Surgeons may be less inclined to prolong prophylaxis in healthier patients and more so in patients who are at increased risk of complications.

Whereas evidence about the duration of postoperative antibiotics for complex appendicitis is missing, this has been evaluated in patients with intra-abdominal infections. The STOP-IT trial investigated a restricted antibiotic course after adequate source control procedures for complicated intra-abdominal infections.[28] Some 14% of included patients had a complex appendicitis. After a median duration of 4 days of antibiotics in the intervention arm and 7 days in the control arm, infectious complications occurred in 21.8% and 22.3% of the groups, respectively (p = 0.92). Some critical notes can be made. Premature closure of the study, due to concerns of futility led to an underpowered study to demonstrate equivalence of both regimes. Also, in a large proportion of patients (23%) the protocol-specified treatment duration was not adhered to.[56] On the other hand, both intention-to-treat and per-protocol analyses were performed and the rate of complications above 20% in both groups confirms that antibiotics may not have a significant role in prevention of infectious complications at all.[57]

More recently the PEANUTS-trial was published: a multicenter randomized controlled trial of extended (3 days) versus single-dose antibiotic prophylaxis for (mild) acute calculous cholecystitis.[58] Similar rates of postoperative infectious complications were seen in both groups (4%). As for complex appendicitis, the recommended duration of antimicrobial therapy varies in guidelines and there is a lack of randomized trials. In line with results from the STOP-IT trial, no benefit was found for extending postoperative prophylaxis, in a randomized setting. Subsequently, the PEANUTS-II trial started (Dutch Trial Register no. NTR5802), in which patients with (mild) acute calculous cholecystitis are randomized to single-dose perioperative prophylaxis or no antibiotic prophylaxis at all.

A nationwide prospective cohort study from the Netherlands in 2014 showed that in most patients (78%) antibiotics were given for 5 days or more after surgery for complex

appendicitis. The authors concluded that three days of antibiotics led to a similar rate of infectious complications. Surgical site infections and intra-abdominal abscesses were seen in 1.3% and 1.6% (p=0.89) and 8.0% and 8.9% of patients (p=0.81), respectively.[30] In Denmark, postoperative prophylaxis of three days has become standard care already.[59] Moreover, in several hospitals in the UK 24 hours (3 doses) of antibiotics has been introduced.

Two limitations of this study should be mentioned. Firstly, the present study is non-blinded. Blinding for treatment allocation would require patients in arm A (48h) to remain admitted to the hospital and receive a placebo drug intravenously for three days. This would put a significant strain on length of hospital stay and costs for the participating hospitals. More importantly, in terms of good clinical decision-making it is important for the treating physician to know whether or not the patient is still receiving actual antibiotics. It is important to reduce risk of bias wherever possible, yet blinding in this trial would not be feasible or desirable. Another limitation is the diagnosis of complex appendicitis which can be rather subjective and dependent on individual surgeons' opinions.[60] As we strived for this trial to follow clinical practice, we chose to keep the definition of complex appendicitis simple (*a gangrenous and/or perforated appendicitis or appendicitis in presence of intra-abdominal abscess*) and to rely on the surgeon's intraoperative judgement. For quality assurance, a static image or video of the appendicitis is taken for patients included in the APPIC trial. This way, we'll be able to assess the reliability and reproducibility of the diagnosis afterwards.

TRIAL STATUS

Trial registries: EudraCT 2016-003428-21, issued on 16-08-2016. Dutch trial register (NTR) no. 6128, registered on 20-12-2016. The first investigators' meeting took place on 03-04-2017. Twelve centers have been initiated and are actively recruiting. The first patient was included on 09- 06 – 2017. In total, 165 patients were randomized, while this manuscript was being completed. Recruitment is expected to end in early 2020.

DECLARATIONS

Funding

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Availability of data and material

The full study protocol is available online at www.appictrial.nl; Access to the data set will be limited to the research team members.

Authors' contributions

AB and BW acquired a grant from ZonMW for this trial. MB, PG, MK, DM, JM, BT and RW were project advisors for the grant application. AB, BW and EW designed the trial and manage it now. AB and EW wrote this manuscript. BW revised the manuscript. AB, EW, FB, EB, JB, TB, EC, ID, JD, ME, AG, LH, SH, DJ, JJ, JK, HL, ML, AP, FP, JP, CR, WS, JS, PS, BT, JV and HV are involved in participant recruitment and acquisition of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study will be carried out in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study protocol was approved on March 14 2017 by the ethics committee of the Erasmus MC Rotterdam in the Netherlands (MEC2016-719). Secondary approval from local boards is obtained before initiation in each participating center. Any substantial amendments to the original study dossier will be submitted for approval to the ethics committee in line with regulatory requirements. So far, five substantial amendments have been submitted and approved. In the first amendment generalized peritonitis was discarded as exclusion criterion (in the original protocol) and the definition of adverse events was narrowed to events related to the experimental treatment. In the second amendment, ceftriaxone-metronidazole was incorporated in the protocol as alternative to cefuroxime-metronidazole and gentamicin was approved as co-intervention. Moreover, in all five amendments participating centers were added, to add up to fourteen participating centers in total.

Eligible patients will receive detailed information regarding the trial, both orally and in writing. Written informed consent will be obtained from all participants by surgeons and surgical residents from the participating centers. All participants are protected by the liability insurance of the Erasmus MC that is in accordance with the legal requirements in The Netherlands. Data will be handled confidentially and anonymously. Upon inclusion into this study, each patient will be assigned a study number. The key to the code, a subject identification code list, will be stored separately safeguarded by the local investigator. The code will not be based on the patient's initials or birth-date. Only involved investigators will have access to the data. The handling of personal data is in compliance with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). The results of the present study will be disseminated through publication in a general medical or surgical journal and presentation at international conferences.

Competing interests

The authors declare that they have no competing interests.

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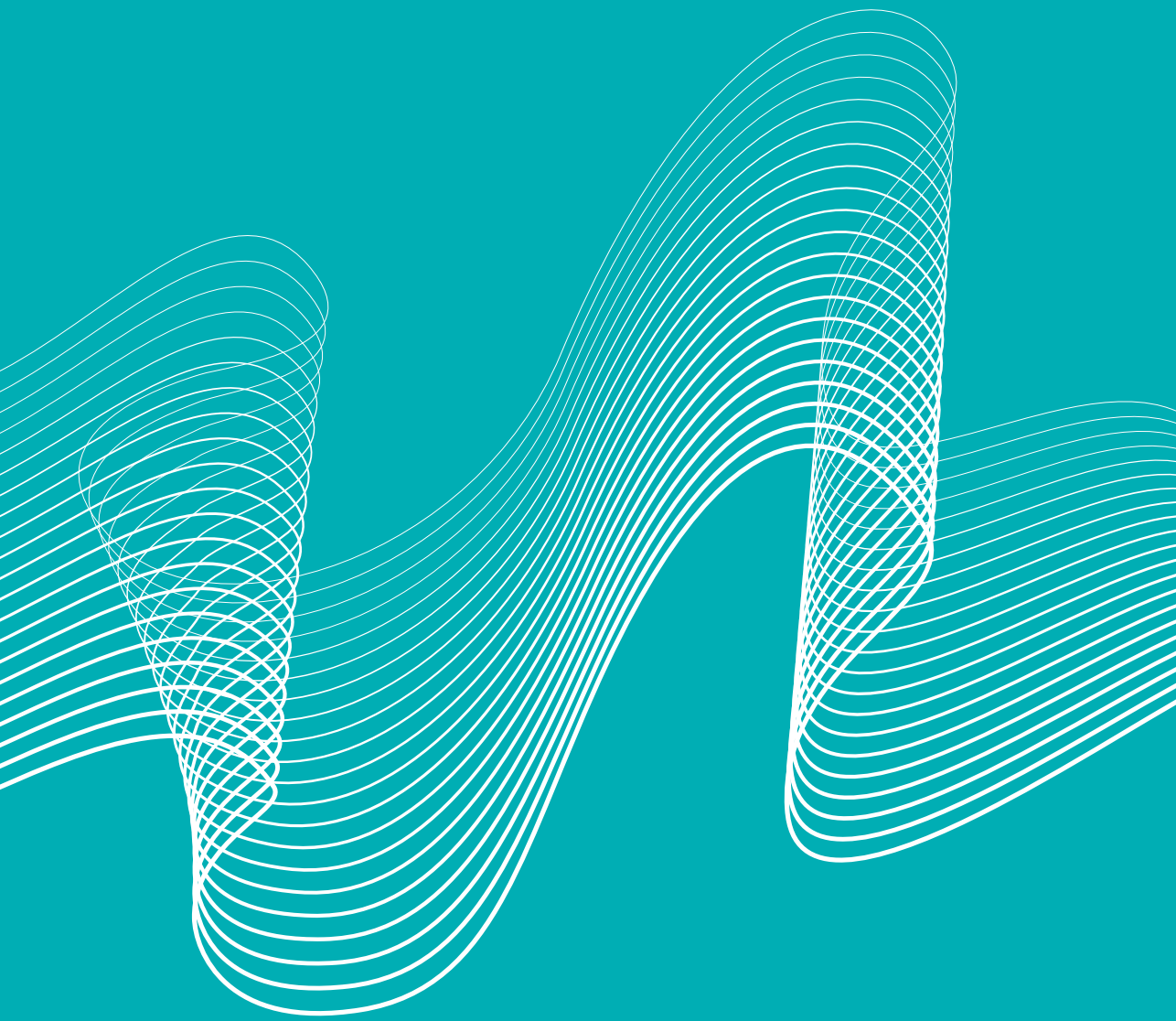

E.M.L. de Wijkerslooth, E.G. Boerma, C.C. van Rossem, J. van Rosmalen, C.I.M. Baeten, F.H. Beverdam; J.W.A.M. Bosmans, E.C.J. Consten, J.W.T. Dekker, M. Emous, A.A.W. van Geloven, A.F. Gijsen, L.A. Heijnen, A.P. Jairam, D.C. Melles, A.P.T. van der Ploeg, P. Steenvoorde, B.R. Toorenvliet, M. Vermaas, B. Wiering, B.P.L. Wijnhoven[†], A.L. van den Boom[†], for the APPIC Study Group [‡]

[†] Shared senior authorship
[‡] Members of the APPIC Study Group are listed at the end of this manuscript

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8

2 DAYS VERSUS 5 DAYS OF POSTOPERATIVE ANTIBIOTICS FOR COMPLEX APPENDICITIS: A PRAGMATIC, OPEN-LABEL, MULTICENTRE, NON-INFERIORITY RANDOMISED TRIAL

ABSTRACT

Background:

The appropriate duration of postoperative antibiotics for complex appendicitis is unclear. The increasing global threat of antimicrobial resistance warrants restrictive antibiotic use, which could also reduce side–effects, length of hospital stay, and costs.

Methods:

In this pragmatic, open-label, non-inferiority trial in 15 hospitals in the Netherlands, patients with complex appendicitis (aged ≥ 8 years) were randomly assigned (1:1) to receive 2 or 5 days of intravenous antibiotics after appendicectomy. The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days. The main outcome was the absolute risk difference (95% CI) in the primary endpoint, adjusted for age and severity of appendicitis, with a non-inferiority margin of 7·5%. Outcome assessment was based on the electronic patient records, and a telephone consultation 90 days after appendicectomy. This trial was registered with the Netherlands Trial Register, NL5946.

Findings:

Between April 12, 2017, and June 3, 2021, 13 267 patients were screened and 1066 were randomly assigned, 533 to each group. 31 were excluded from intention-to-treat analysis of the 2-day group and 30 from the 5-day group owing to errors in recruitment or consent. Appendicectomy was done laparoscopically in 955 (95%) of 1005 patients. The telephone follow-up was completed in 664 (66%) of 1005 patients. The primary endpoint occurred in 51 (10%) of 502 patients analyzed in the 2-day group and 41 (8·2%) of 503 patients analyzed in the 5-day group (adjusted absolute risk difference 2·0%, 95% CI -1·6 to 5·6). Rates of complications and re-interventions were similar between trial groups. Fewer patients had adverse effects of antibiotics in the 2-day group, (45 [9%] of 502 patients) than in the 5-day group (112 [22%] of 503 patients; odds ratio [OR] 0·344, 95% CI 0·237 to 0·498). Re-admission to hospital was more frequent in the 2-day group (58 [12%] of 502 patients) than in the 5-day group (29 [6%] of 503 patients; OR 2·135, 95% CI 1·342 to 3·396). There were no treatment-related deaths.

Interpretation:

2 days of postoperative intravenous antibiotics for complex appendicitis is non-inferior to 5 days in terms of infectious complications and mortality within 90 days, based on a non-inferiority margin of 7·5%. These findings apply to laparoscopic appendicectomy performed in a well-resourced health-care setting. Adopting this strategy will reduce adverse effects of antibiotics and length of hospital stay.

INTRODUCTION

With an incidence of 100 to 151 per 100,000 person years in Western countries, acute appendicitis is the most prevalent surgical emergency in both children and adults.[1] Approximately 30% of patients present with complex appendicitis, which is defined as appendicitis with necrosis, perforation, abscess, or purulent peritonitis.[2-5] The standard treatment for complex appendicitis is appendicectomy followed by antibiotics. The aim of postoperative antibiotics is to reduce infectious complications, which occur in up to 20% of patients.[6-10]

Antibiotics can have side-effects including diarrhea, nausea, allergies, thrombo-phlebitis and *Clostridioides difficile* infection. Restrictive use of antibiotics could reduce length of hospital stay and health-care costs, whereas overuse is one of the main causes of antimicrobial resistance.[11] Antibiotic stewardship and standardization of care is therefore warranted.[12] The STOPIT trial[10] showed that, after an adequate source control procedure for a complicated intraabdominal infection, 4 days of intravenous antibiotics is non-inferior to a longer regimen. The duration and route of administration of postoperative antibiotics for complex appendicitis are highly variable.[13-15] Common practice is to administer intravenous antibiotics for 3–5 days, often followed by oral antibiotics at discharge.[6, 10, 16] One randomised trial (N=80)[17] and several observational studies[13, 14, 18] suggested that antibiotics could be restricted to 24–72 h after appendicectomy without increasing the risk of infectious complications.

The Antibiotics following aPPendicectomy In Complex appendicitis (APPIC) trial was designed to compare a 2-day regimen of intravenous postoperative antibiotics with a 5-day regimen. At the time of drafting the study protocol, 5 days of antibiotics was standard practice and this group was therefore defined as the control group of the study.[15, 16, 19, 20] Cohort studies have suggested that 3 days or fewer might be sufficient.[7, 21-26] Dutch guidelines advise a minimum of 3 days, which should be administered intravenously for at least 2 days. In addition, a 2-day antibiotic regimen was chosen for the experimental group because 2 days of antibiotics ensure sufficient tissue concentration and penetration to act against bacteria that are commonly isolated in patients with appendicitis (e.g., *Escheria coli*).[27, 28] The hypothesis was that a 2-day regimen is non-inferior to a 5-day regimen in terms of infectious complications and mortality within 90 days after appendectomy.

METHODS

Trial design and oversight

The APPIC trial was a pragmatic, open-label, randomised controlled trial powered for non-inferiority. The trial design was published in May 2018,[29] and the full protocol, including the statistical analysis plan, is available in the appendix online (p 27). The trial was approved by the institutional review board of the Erasmus MC (reference number MEC2016-719) and the ethics committee at each trial site. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. An independent Data Safety and Monitoring Board (DSMB) oversaw patient recruitment and patient safety at two prespecified intervals. The authors vouch for the completeness and accuracy of the data, as well as fidelity of the trial to the protocol. This article was prepared in concordance with the Consolidated Standards Of Reporting Trials (CONSORT) checklist and its extensions applicable to the trial design. [30]

Patients

Patients with acute appendicitis were eligible for inclusion if they were aged 8 years or older, had American Society of Anesthesiologists (ASA) class I-III, and had a diagnosis of complex appendicitis (defined as the presence of gangrene/necrosis, perforation, or abscess, as assessed intraoperatively).[2-5] Patients were excluded if they were pregnant, immunocompromised, or had a contraindication to the trial drugs (e.g., allergy) or if adequate source control could not be reached during surgery. Other exclusion criteria are provided in the full protocol (online appendix p 48). Eligible patients were approached for participation in the study before or after surgery in one academic center and 14 teaching hospitals in the Netherlands, a well-resourced health-care setting. All participants gave written informed consent. In June, 2019, an informational video was developed to support the informed consent process.

Randomization and masking

Surgeons and surgical residents recruited and randomly assigned eligible patients online to one of two groups within 24 h after appendicectomy. Computerized block randomization (random sized blocks, size range 4 to 8), stratified for center, was used to allocate patients in a 1:1 ratio to receive 2 days or 5 days of intravenous antibiotics after appendicectomy. Treating physicians and patients were not blinded to treatment allocation because of feasibility concerns.

Procedures

Participants were randomised to 2 days or 5 days of postoperative antibiotics. The antibiotics administered were either intravenous cefuroxime (1500mg three times daily) or ceftriaxone (2000mg once daily), plus metronidazole (500mg three times daily). The first

dose was to be administered within 8 h after appendicectomy. In children (aged 8–17), the dosage was adjusted according to weight. A daily single dose of intravenous gentamycin was allowed as co-intervention, according to local hospital protocol (i.e., in case of sepsis). After 2 days or 5 days, antibiotics were stopped. A deviation in trial regimen was allowed only in one of three situations: intraoperative culture results necessitated a change to a different antibiotic agent, an extension of antibiotic treatment, or both; adverse effects to antibiotics (e.g., allergic reaction or thrombophlebitis) or repeated failure of intravenous administration required early discontinuation; or a postoperative infectious complication (supported by laboratory and imaging studies) warranted a restart or extension of antibiotic treatment, or a change a different antibiotic agent. A change to oral formula was not allowed owing to concerns regarding compliance with the study protocol and possible inferior tissue penetration of oral antibiotics (amoxicillin-clavulanate) that are most used in Dutch practice.[27]

Diagnostic tests, preoperative antibiotic prophylaxis, and surgical approach followed local hospital standards. In each center, the surgical staff was trained in trial procedures (i.e., knowledge of inclusion and exclusion criteria, diagnosis of complex appendicitis, informed consent procedure, and study medication regimen).

Postoperative laboratory tests, imaging studies, and blood cultures were done upon clinical indication, according to local protocol. Discharge criteria were absence of fever for 24 h, ability to tolerate oral intake, ability to mobilize, and adequate pain control with oral analgesics. Final discharge and the type (visit or telephone consult) and timing of follow-up were at the discretion of the treating physician. 4 weeks after appendicectomy, patients received a Productivity Cost Questionnaire by mail. Follow-up ended 90 days after appendicectomy, at which time the central trial coordinator attempted to contact patients for a telephone consultation.

Outcomes

The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days after appendicectomy. Infectious complications were intra-abdominal abscess and surgical site infection, according to the US Centers for Disease Control and Prevention definitions of these conditions.[31] Secondary endpoints were the duration of postoperative antibiotics; the rates of intra-abdominal abscess, surgical site infection, all postoperative complications (classified according to Clavien-Dindo[32]), adverse effects to antibiotics, restart of antibiotics, re-admission to hospital, and surgical or radiological re-interventions; the length of hospital stay (initial admission and any subsequent stay); the type and number of postoperative imaging studies; and costs. Data on costs will be made available in a separate cost-effectiveness analysis. The trial protocol also listed time to reach discharge criteria as a secondary endpoint; however, for most patients, data

on discharge criteria were unavailable or incomplete, so this endpoint is not reported. Primary and secondary outcomes were obtained from the electronic patient files. No routine laboratory or imaging tests were done to detect complications. A structured telephone interview at 90 day follow-up was conducted to complement the information in the electronic patient records regarding complications, including signs of surgical site infection, and unplanned medical facilities.

All data were registered in a secure online ALEA database in a pseudonymized manner by a member of the research team who was unmasked to patient allocation. The ALEA database system was tested and validated by the International Society for Pharmaceutical Engineering GAMP 5 Good Practice Guide.

We conducted two interim safety analyses, after complete follow-up of the 266th patient and the 666th patient, which were reviewed by the data safety and monitoring board. Safety endpoints were mortality and complications classified as Clavien-Dindo class 3 or higher.[32]

Statistical analysis

Cohort studies in the Netherlands have reported infectious complications in 14–19% of patients with complex appendicitis.[21, 33, 34] In other studies, infectious complications were reported in 14–24% of patients.[2, 35-37] On the basis of these data, the primary endpoint for the control arm was estimated to be 15%. Sawyer and colleagues[10] defined a margin of 10% to assess non-inferiority for infectious complications after source control for complicated intra-abdominal infections. We set the non-inferiority margin at 7·5%, assuming that infectious complications after appendicectomy for complex appendicitis would lead to minor morbidity and the anticipated advantageous effects of a 2-day antibiotic regimen would prevail.

We did a power analysis using simulation, based on a one-sided 97.5% confidence interval for the effect (absolute risk difference in primary endpoint, adjusted for severity of disease and age) of the trial group. To obtain a power of 90% to establish non-inferiority under the assumptions listed above, 960 patients were needed (480 per trial arm). To account for possible effects of dropout and missing data in 10% of patients, 1066 patients needed to be included.

We conducted intention-to-treat and per-protocol analyses. In the 2-day group, adherence to the protocol was defined as six doses (within one dose) after appendicectomy. In the 5-day group, adherence to the protocol was defined as 15 doses (within two doses) after appendicectomy. Non-adherence excluded patients from the per-protocol analysis,

although exceptions were made for patients who deviated from the regimen because of intraoperative culture results, adverse events to antibiotics, or postoperative complications.

For the primary endpoint, non-inferiority of the 2-day course using a one-sided 97.5% CI for the effect of the study group (absolute risk difference). This CI was adjusted for the effects of severity of disease (absence vs. presence of perforation or abscess) and age (age below vs. above the median age of the trial population) as one categorical covariate, with the method proposed by Klingenberg for the Mantel-Haenszel common risk difference.[38, 39] A forest plot was created to show the absolute risk difference and adjusted CIs broken down by age, severity of appendicitis and surgical approach.[21] In addition, we did logistic regression analysis to identify predictors of the primary endpoint. We used a generalized estimating equations model with an exchangeable working correlation matrix to account for center effects.[40] The following (prespecified) independent variables were included: treatment allocation, sex, age, ASA classification, surgical approach (laparoscopy vs. open procedure), and severity of appendicitis (absence vs. presence of perforation or abscess). Interaction effects between treatment allocation and other predictors were tested and included in the final regression model if significant ($P < 0{\cdot}05$).

Secondary endpoints were compared between trial arms in univariable analysis. We used the $\chi 2$ test for categorical variables and the Mann-Whitney test for continuous variables. A two-sided $P < 0{\cdot}05$ was considered statistically significant. Secondary endpoints were also compared between trial groups in an exploratory subgroup analysis of patients who had open appendicectomy, given the results of the regression analysis on the primary endpoint.

For interim safety analyses, we compared safety endpoints (90-day mortality and overall complications classified as Clavien-Dindo class 3) among the intention-to-treat population using a $\chi 2$ test, with a significance level based on the alpha spending approach of O'Brien and Fleming.[41] Prespecified trial stopping rules were $p < 0{\cdot}000014$ at the first interim analysis and $p < 0{\cdot}009130$ at the second interim analysis. The safety analyses were conducted by the trial statistician (JvR). The results were included in interim reports prepared by the central trial coordinator for review by the data safety and monitoring board; the board was unmasked to treatment allocation. Local collaborators did not have access to interim data. No interim analysis of efficacy (the primary endpoint) was conducted, therefore we did not adjust for bias in the primary endpoint analysis.

In absence of missing data in the primary outcome and predictors in multivariable analyses, imputation of missing data was not necessary. No allowance was made for multiplicity. Data were analyzed with SPSS (version 25) and R statistical software (version 3·5·0).

This trial was registered with the Netherlands Trial Register, NL5946

Role of the funding source

The funder of the study had no role in trial design, the collection, data analysis, data interpretation, or writing of the report.

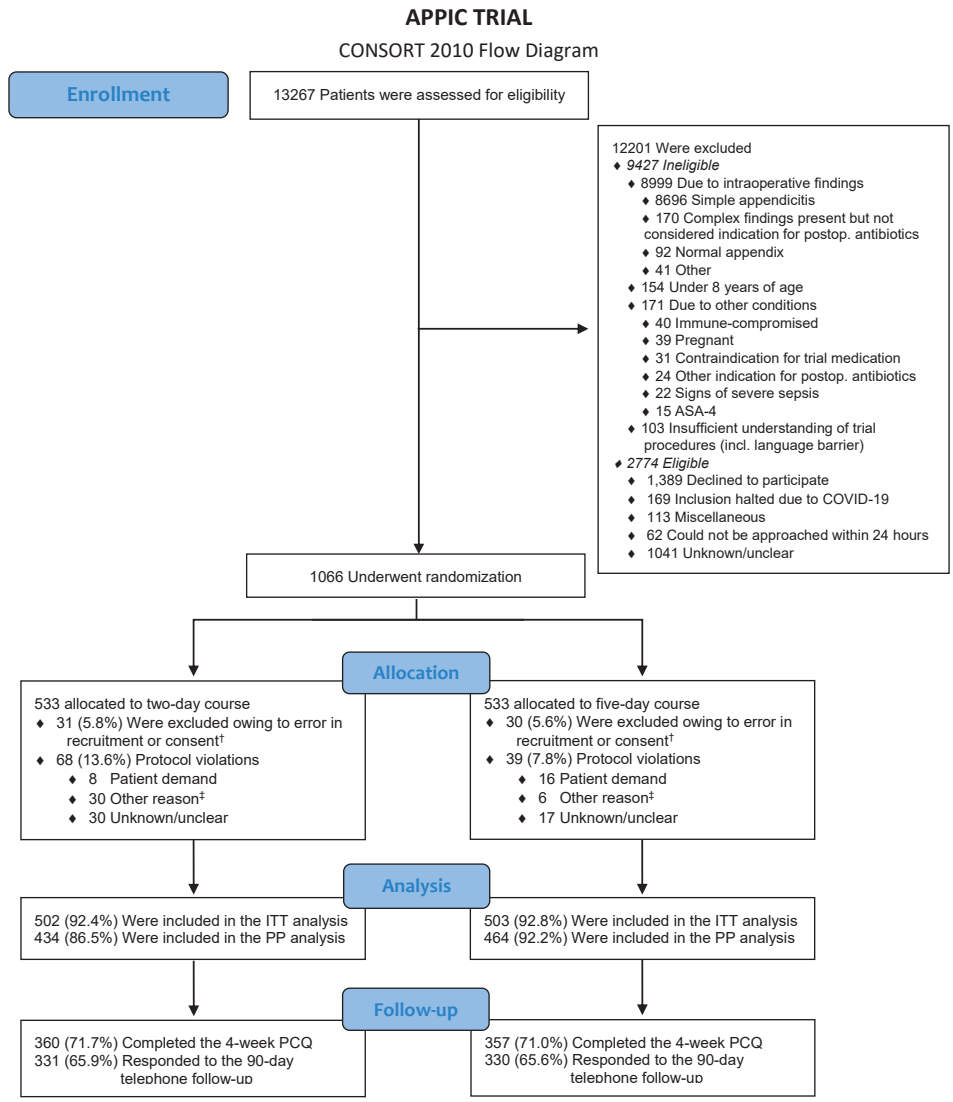
RESULTS

Between April 12, 2017, and June 3, 2021, 13267 patients were screened for participation, of whom 9427 (71%) were ineligible for inclusion (Figure 1). 1066 patients were randomly assigned: 533 were allocated to the 2-day group and 533 were allocated to the 5-day group. After exclusions due to errors in recruitment or consent, 502 patients in the 2-day group and 503 patients in the 5-day group were included in the intention-to-treat analysis. Follow-up ended on September 1, 2021. No important changes in design or methods were made after start of the trial. Because of the COVID-19 pandemic, trial inclusion was temporarily halted in 10 centers for periods ranging from 23 days to 105 days. Evaluation of interim safety reports at the prespecified intervals led the data safety and monitoring board to recommend continuation of the trial (online appendix pp 17-18, 25-26). Demographic and clinical characteristics of the intention to treat population (N=1005) are shown in Table 1. Protocol adherence was 87% in the 2-day group and 92% in the 5-day group (Table 2). Baseline characteristics of the per-protocol population (N=898) are shown in supplementary Table S1.

In 84 (19%) of 434 patients in the 2-day group and 66 (14%) of 464 patients in the 5-day group who adhered to the protocol, a deviation in antibiotic regimen was recorded. The duration of antibiotics was reduced in 12 patients because of adverse reactions to antibiotics and extended in 47 patients because of perioperative culture results or postoperative complications (details available in supplementary Table S2). In 88 patients (58 [13%] of 434 patients in the 2-day group and 30 [6%] of 464 patients in the 5-day group), antibiotics were restarted because of postoperative complications.

The primary endpoint occurred in 51 (10%) of 502 patients in the 2-day group and 41 (8%) of 503 patients in the 5-day group (Table 2). No data were missing for the primary endpoint or for covariates used in multivariable analyses. The absolute risk difference, adjusted for age and severity of appendicitis, was 2·0% (95% CI – 1·56 to 5·57%). By not exceeding the prespecified non-inferiority margin of 7·5%, this finding was consistent with non-inferiority of the 2-day course to the 5-day course. In the logistic regression analysis, an interaction effect was found between treatment allocation and surgical approach (p = 0·046). This interaction effect was included in the final regression model. Estimates of the effect of treatment allocation are stratified by the type of surgery. Treatment allocation was not an independent predictor of the primary endpoint (adjusted odds ratio [OR] 1·128 [95% CI 0·719 1·769]; p = 0·599) in patients who had laparoscopic appendicectomy. For patients

Figure 1. Screening, randomization and follow up.



*Sixty one patients were excluded from analysis owing to an error in recruitment or consent: 14 due to a missed exclusion criterion (11 immunocompromised patients, two ASA IV patients and one with a concurrent other indication for postoperative antibiotics), 39 due to incomplete/unsaved written consent and eight due to patient withdrawal shortly after randomization. ‡Three patients (two in the two-day arm) were given an off-protocol antibiotic agent and seven patients (six in the two-day arm) were prescribed an insufficient dosage of cefuroxime. In 26 patients (22 in the two-day arm) antibiotic use was prolonged in response to clinical signs such as elevated body temperature or a once-measure elevated serum CRP without additional laboratory or imaging studies that detected an infectious focus.

Table 1. Baseline Characteristics of the IntentiontoTreat Population

	TWO DAYS (N = 502)	FIVE DAYS (N = 503)
Age – year	51 [31; 62]	52 [30; 64]
Age distribution		
8 to 17	49 (10)	62 (12)
18 to 64	346 (69)	320 (64)
65 and older	107 (21)	121 (24)
Male sex	285 (57)	286 (57)
American Society of Anaesthesiologists (ASA) score †		
ASA I	235 (47)	235 (47)
ASA II	216 (43)	217 (43)
ASA III	51 (10)	51 (10)
Bodymass index‡	26 [23; 29]	25 [23; 29]
Missing	97	109
Duration of symptoms – days	2·0 [1·0; 3·0]	2·0 [1·0; 2·8]
Missing	9	11
Body temperature – °C	37·5 [37·0; 38·2]	37·6 [37·0; 38·2]
Missing	6	6
Pulse – bpm	90 [78; 102]	90 [79; 104]
Missing	30	21
White blood cell count – x 109/L	15·1 [12·0; 18·1]	15·0 [12·2; 18·7]
Missing	-	2
Creactive protein – mg/L	100 [44; 175]	99 [48; 167]
Missing	-	1
Imaging test		
Ultrasonography	397 (79)	389 (77)
Computed tomography	238 (47)	228 (45)
Multiple imaging tests	153 (31)	139 (28)
Faecolith on imaging	170 (34)	151 (30)
Intravenous antibiotics in the ER/ward	150 (30)	151 (30)
Antibiotic prophylaxis in the OR	418 (83)	405 (81)
Missing	-	3
Laparoscopic procedure	480 (96)	475 (94)
Operating time – minutes	47 [36; 59]	46 [36; 58]
Missing	3	11
Classification of appendicitis§		
Gangrenous	264 (53)	283 (56)
Perforated	365 (73)	365 (73)
Periappendiceal abscess	75 (15)	61 (12)
Pus or peritonitis present	421 (84)	440 (88)
Diffuse peritonitis	51 (10)	45 (9)
Drain placement	8 (2)	13 (3)
Histopathological examination¶		
Appendicitis	485 (97)	491 (98)
Malignant or premalignant lesion	12 (2·4)	8 (1·6)
Missing	4	5

ER, Emergency Room; OR, Operating Room; Data are n (%) or median [interquartile range], unless otherwise stated

† For 57 patients in the two day arm and 51 in the five day arm ASA classification was not registered in the electronic patient files, but was retrospectively assigned by the researchers based on information present in the patient files.

‡ Body mass index is the weight in kilograms divided by the square of the height in meters.

§ For 23 patients in the two day arm and 17 in the five day arm the type of appendicitis was judged as complex, without explicit description of necrosis, perforation or abscess in the surgical report. For another 3 patients the surgical report was missing or incomplete, but notes in the electronic patient dossier confirmed complex findings.

¶ For 7 patients in the two day arm and 13 patients in the five day arm the histopathology report reflected findings of appendicitis alongside findings of benign or (pre)malignant lesion. For one patient in the two-day arm and three in the five-day arm benign pathology was found in absence of signs of appendicitis.

Percentages may not total 100 because of rounding.

Distribution of patient allocation stratified by centre is depicted in supplementary table S7.

who had open appendicectomy, the adjusted OR of treatment allocation was 10·825 (1·231 to 95·201; p = 0·032) to the disadvantage of the 2-day group. A forest plot of the adjusted absolute risk difference in primary endpoint between the 2-day group and the 5-day group, broken down by age, severity of appendicitis and surgical approach, is shown in Figure 2 for the intention-to-treat population. Per-protocol analyses of the primary endpoint showed similar results (Table 2).

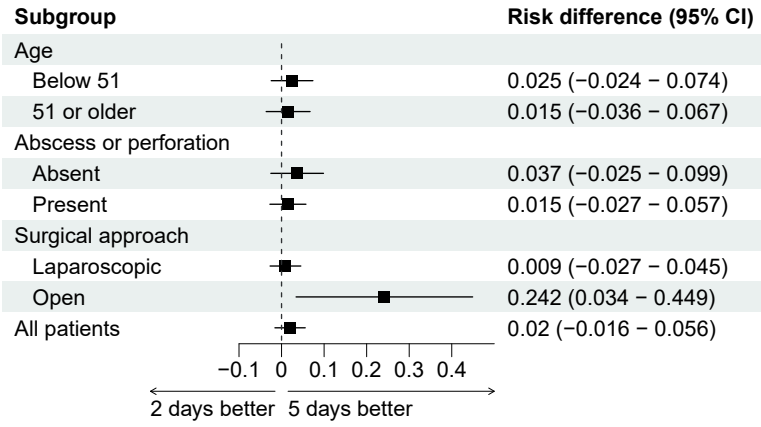
Table 2. Primary endpoint analysis

	TWO DAYS	FIVE DAYS	Risk difference (95% CI)		Odds ratio (95% CI)	
Intention-to-treat	**N = 502**	**N = 503**	**Univariable**	**Multivariable†**	**Univariable**	**Multivariable‡**
IAA, SSI and/or mortality	51 (10·2)	41 (8·2)	2·0% (–1·6 to 5·6)	2·0 (-1·56 to 5·57)	1·274 (0·828 to 1·961)	1·128 (0·719 to 1·769)
IAA	43 (8·6)	36 (7·2)	1·4% (–1.9 to 4·8)		1·215 (0·766 to 1·927)	
SSI	10 (2·0)	5 (1·0)	1·0% (–0.6 to 2·6)		2·024 (0·687 to 5·965)	
Mortality	1 (0·2)	0	0·2% (–0.5 to 0·9)		-	
Per-Protocol	**N = 434**	**N = 464**				
IAA, SSI and/or mortality	45 (10·4)	39 (8·4)	2·0% (–1·9 to 5·8)	2·1 (-1·76 to 5·89)	1·261 (0·804 to 1·978)	1·132 (0·710 to 1·805)†
IAA	38 (8·8)	34 (7·3)	1·4% (–2.2 to 5·0)		1·214 (0·749 to 1·966)	
SSI	8 (1·8)	5 (1·1)	0·8% (–0.9 to 2·5)		1·724 (0·560 to 5·311)	
Mortality	1 (0·2)	-	0·2% (–0.5 to 1·0)		-	

† Adjusted for age (below vs. above median age) and severity of appendicitis (absence vs. presence of perforation or abscess).

‡ Adjusted for the following independent variables: treatment allocation, centre, sex, age, ASA classification, surgical approach (laparoscopy vs. open procedure) and severity of appendicitis (absence vs. presence of perforation or abscess) and interaction effect between treatment allocation and surgical approach. Given values apply to patients undergoing laparoscopic appendectomy. For open appendectomy patients the adjusted OR of treatment allocation was 10·825 (95% CI 1·231 to 95·201; P = 0·032) in the ITT population and 11·038 (95% CI 1·115 to 109·242; P = 0·040) in the PP population.

Figure 2. Forest plot of primary endpoint broken down by age, severity of appendicitis and surgical approach.



Risk differences and 95% confidence intervals are based on the Klingenberg method for the 'Mantel-Haenszel common risk difference'.[48,49]

Intra-abdominal abscess was observed in 43 (9%) of 502 patients in the 2-day group and in 36 (75) of 503 patients in the 5-day group (Table 2); of these patients, 22 (4%) in the 2-day group and 14 (3%) in the 5-day group required invasive treatment (percutaneous drainage or re-operation. Surgical site infection occurred in ten (2%) of 502 patients in the 2-day group and in five (1%) of 503 patients in the 5-day group (Table 2), requiring invasive treatment in only two (<1%) patients in the 2-day group. One patient (in the 2-day group) died on postoperative day 84 of metastasized esophageal cancer. No significant difference was observed in rates of re-interventions (Table 3).

Table 3. Univariable Comparison of Secondary Outcomes in the IntentiontoTreat Population

	TWO DAYS (N = 502)	FIVE DAYS (N = 503)	Effect size† (95% CI)
Protocol adherence	434 (87)	464 (92)	0·536 (0·354 to 0·812)
Administered study medication ‡			
No. of days	2·0 [2·0; 2·3]	5·0 [4·7; 5·0]	-2·7 (-3·0 to -2·7)
No. of doses	6 [6; 7]	15 [14; 15]	-8·0 (-9·0 to -8·0)
Missing	20	13	
Any complication	125 (24·9)	104 (20·7)	1·272 (0·946 to 1·710)
ClavienDindo class 1	36 (7·2)	53 (10·5)	0·656 (0·421 to 1·021)
ClavienDindo class 2	72 (14·3)	51 (10·1)	1·484 (1·013 to 2·175)
ClavienDindo class 3a	19 (3·8)	11 (2·2)	1·759 (0·829 to 3·736)
ClavienDindo class 3b	14 (2·8)	12 (2·4)	1·174 (0·537 to 2·564)
ClavienDindo class 4a	1 (0·2)	0	-
Comprehensive Complication Index §	20·9 [20·9; 26·2]	20·9 [8·6; 29·4]	0·0 (0·0 to 3·2)
Reintervention	32 (6·4)	21 (4·2)	1·563 (0·888 to 2·749)
Percutaneous drainage	18 (3·6)	13 (2·6)	1·402 (0·679 to 2·892)
Reoperation	15 (3·0)	10 (2·0)	1·518 (0·676 to 3·413)
Adverse effects of antibiotics¶	45 (9·0)	112 (22·3)	0·344 (0·237 to 0·498)
Postoperative length of stay – hours	69 [61; 94]	126 [118; 139]	-56 (-58 to -53)
Missing	1	2	
Postoperative length of stay – days	3·0 [2·0; 4·0]	5·0 [5·0; 6·0]	-2·0 (-2·0 to 2·0)
Missing	-	1	
Unplanned medical visits	76 (15·1)	39 (7·8)	2·118 (1·409 to 3·185)
Emergency room visits	59 (11·8)	49 (9·8)	1·231 (0·825 to 1·838)
Outpatient clinic visits	56 (17·0)	47 (14·1)	1·248 (0·819 to 1·902)
General practitioner visits	172	169	
Missing			
Hospital readmission	58 (11·6)	29 (5·8)	2·135 (1·342 to 3·396)
Total length of stay – days ¶¶	3·0 (3·0; 5·0)	5·0 (5·0; 6·0)	-2·0 (-2·0 to -2·0)
Missing	-	1	

Data are n (%) or median [interquartile range], unless otherwise stated.†Effect size is depicted as OR (95% CI) for categorical outcomes and absolute difference in median (95% CI) for continuous outcomes.

‡ Postoperative administration of cefuroxime 3dd1500mg or ceftriaxone 1dd2000mg combined with metronidazole 3dd500mg. In the twoday arm 16 patients (3·2%) were prescribed followup oral antibiotics, 5 (1·0%) of which were protocol violations. In the fiveday arm 28 patients (5·6%) were prescribed followup oral antibiotics, 13 of which were¶¶ protocol violations. Two patients (0.3%) in the two-day arm and six patients (1.2%) in the five-day arm received gentamycin as cointervention.

§ Comprehensive Complication Index (CCI) result is a median of CCI scores of 125 patients in the twoday arm and 104 patients in the fiveday arm that had a postoperative complication.

¶ Reported adverse effects were nausea/vomiting (N=96), diarrhoea (N=83), allergic reaction (N=4), Clostridium difficile (N=3) and thrombophlebitis (N=2). In 31 patients two adverse effects were reported.

¶¶ Total length of stay is the sum of hospital stay of the original hospital admission and possible readmission(s).

The difference in median postoperative length of stay was – 2·0 days (95% CI – 2·0 to 2·0) in favor of the 2-day group (Table 3). Adverse effects of antibiotics (mostly nausea or vomiting and diarrhea) were observed in more patients in the 5-day group than in the 2-day group (Table 3). Visits to the emergency department and hospital re-admission were more frequent in the 2-day group than in the 5-day group (Table 3). 94 hospital re-admissions were recorded for 87 (9%) of 1005 patients. Infectious complications were the cause of 49 (52%) of the 94 re-admissions; other reasons are listed in supplementary Table S4. Median time between discharge and re-admission was 5·2 days (IQR 1·3; 8·8) in the 2-day group and 8·8 days (4·6; 11·2) in the 5-day group (Hodges-Lehmann estimate of the median difference – 3·2, 95% CI -5·3 to -1·0). 20 (35%) of 58 re-admissions in the 2-day group occurred within 5 days after appendicectomy.

Results for secondary endpoints were similar in the per-protocol analysis, as shown in supplementary Table S3.

Appendicitis with a perforation or periappendiceal abscess was reported in 775 (77%) of 1005 trial patients; 388 allocated to the 2-day group and 387 to the 5-day group. Outcomes for these patients were similar to outcomes for the total study population. The primary endpoint occurred in 42 (11%) of 388 patients in the 2-day group and 36 (9%) of 387 patients in the 5-day group (adjusted risk difference of 1·5% [95% CI -2·7 to 5·7]; Figure 2). Complications required re-admission in 50 (13%) of 388 in the 2-day group and 26 (7%) of 387 patients in the 5-day group (unadjusted OR 2·054 [95% CI 1·250 to 3·375]). 27 (7%) of 388 patients in the 2-day group and 17 (4%) of 387 patients in the 5-day group had a radiological or surgical reintervention (unadjusted OR 1·628 [0·872 to 3·038]).

50 (5%) of 1005 patients had an open appendicectomy, including 28 patients for whom laparoscopy was converted to an open procedure during surgery. In the 2-day group, six (27%) of 22 patients had an infectious complication (four intra-abdominal abscesses and two surgical site infections). In the 5-day group, one (4%) of 28 patients had an infectious complication. Details of patients who had an open appendicectomy are shown in supplementary Tables S5 and S6.

DISCUSSION

This pragmatic, randomised controlled trial on the duration of postoperative antibiotics in patients with complex appendicitis showed that 2 days of intravenous antibiotics was non-inferior to 5 days. The absolute risk difference in infectious complications and mortality – corrected for age and severity of appendicitis – was 2·0%, in favor of the 5-day group (95% CI –1·6 to 5·6). Patients in the 5-day group had fewer Clavien-Dindo class 2

complications, visits to the emergency department, and re-admissions than patients in the 2-day group. Patients in the 2-day group had fewer adverse effects to antibiotics than those in the 5-day group, and their overall hospital stay was shorter, even when including re-admissions.

This study supports the idea that extended antibiotic prophylaxis for intra-abdominal infections is not indicated after adequate source control.[10, 18, 42] 2 days of antibiotics did not result in a statistically significant increase of postoperative complications or re-interventions. However, the higher rate of Clavien-Dindo class 2 complications in the 2-day group than in the 5-day group deserves attention. In approximately half of these patients in the 2-day group, an infectious focus (intra-abdominal abscess, surgical site infection, pneumonia, urinary tract infection, or other) was diagnosed and treated with antibiotics. In about a quarter of the patients, antibiotics were restarted due to fever, abdominal pain, elevated inflammation parameters, or ileus, without confirmation of an infection in imaging studies or cultures. These symptoms could be considered as a manifestation of ongoing postoperative systemic inflammatory response, and restart of antibiotics might have been avoided.

The higher rate of hospital re-admissions in the 2-day group than in the -5day group could be attributed to infectious complications in 53% of these patients. Other indications for re-admission were mostly postoperative ileus and pain or fever without an infectious focus. A third of hospital re-admissions in the 2-day group occurred within 5 days after appendicectomy. Patients in the 5-day group could have had similar symptoms while in hospital. Despite the higher rate of re-admission, the total length of hospital stay within 90 days (including re-admission) was still significantly shorter in the 2-day group than in the 5-day group. One may conclude that the benefit of reduced antibiotic use and shorter hospital stay outweighs an increased risk of re-admission or complications that do not need surgical or radiological interventions. Physicians may have had a low threshold for re-admitting patients and restarting antibiotics for patients in the 2-day group, as this was experimental when the study started. Implementation of a 2-day course of postoperative antibiotics in clinical practice might increase familiarity with this regimen and result in fewer re-admissions to hospital and a reduction in restarting of antibiotics in the absence of an infectious focus.

The findings of this study are valid for laparoscopic appendicectomy. In a small subgroup of patients who had an open appendectomy (N=50), allocation to the 2-day group was an independent predictor of infectious complications. Approximately half of the open procedures were laparoscopies converted to open procedures during surgery. Patients in this group possibly had more severe intra-abdominal contamination, which could therefore represent suboptimal source control with an increased risk of infectious

complications. 5 days of antibiotics could be indicated after open appendicectomy for complex appendicitis, but this needs further investigation.

Overuse of antibiotics is a risk factor for antimicrobial resistance.[11, 43] This increasing worldwide threat calls for critical review of standard antibiotic courses. As approximately 15% of prescribed antibiotics are related to perioperative care, this setting can be a major driver of emerging infections (e.g., *Clostridium difficile*) and antimicrobial resistance.[12] Traditional courses of antibiotics have been reduced in length after studies showed no benefit of extended courses.[42] The STOPIT trial showed similar rates (22%) of infectious complications and mortality after a fixed 4-day course of antibiotics to those after a longer, variable course (median 8 days), in patients with complicated intra-abdominal infections and adequate source control.[10] 73 of 518 patients in that trial had complex appendicitis. Hence, no definite conclusion on the safety and efficacy of a short course of antibiotics after complex appendicectomy could be made.

Two randomised studies on postoperative antibiotics for complex appendicitis have been published within the last 4 years. Liu and colleagues[6] found similar rates of infectious complications in children with a fixed 72 h intravenous course (N=350) and with a prolonged intravenous course of antibiotics (minimum 5 days intravenous antibiotics followed by oral antibiotics to complete 10 days; N=336). 9% of patients in the 72 h group still received additional oral antibiotics at discharge. Saar and colleagues[17] compared 24 h of intravenous antibiotics to an extended course based on clinical signs. Approximately 20% of patients had infectious complications in both groups. The small sample size (N=80) and short follow-up of 1 month limit the internal validity of this study. The rate of infectious complications in our trial was lower than expected. We anticipated a rate of 15%, based on pre-existing cohort studies, [2, 23, 33-37] including a large Dutch cohort of 1901 patients with appendicitis.[21] A potential explanation is that the rate of open surgery (or surgery converted to open from laparoscopic) in the present population was lower compared to the latter study (5% vs. 8%) and the median age in our study was higher (51 vs. 44 years). Few pediatric patients (111 patients, aged 8–17 years) were included in our trial. Younger age is associated with an increased risk of intra-abdominal abscess after appendicectomy.[33, 44, 45] The rate of surgical site infection in the study by Liu and colleagues[6] (7%) was almost five times that in our study (1·5%). Their follow-up was longer (6 months); however, all infectious complications in the present study were diagnosed within 34 postoperative days. To minimize the risk of bias in data collection by an unmasked research team, an independent trial agency monitored trial conduct at regular intervals. The monitors also reviewed primary endpoint assessment in a random selection of trial patients. Another measure taken to prevent underreported complications was the telephone consultation at 90 days follow-up. 664 (66%) of 1005 patients responded to the follow-up call. None of these patients reported a complication that was not already

present in the electronic patient files. However, surgical site infection could still be under-reported. A study showed high risk of under-reported surgical site infection when no physical examination was conducted.[46]

The 7·5% non-inferiority margin might seem large given the low rate of infectious complications, but the risk difference observed between groups was small. Logistic regression analysis also showed no significant association between treatment allocation and infectious complications for laparoscopic appendicectomy. The risk difference of 2·0% translates to a number needed to treat of 50; that is, for each 50 patients that would be treated with the experimental 2-day course, one additional patient will have an infectious complication. The upper limit of the 95% CI for the risk difference, 5·6%, would translate to a number needed to treat of 18. Given the mild to moderate morbidity associated with infectious complications, and the shorter hospital stay and reduced adverse events related to antibiotics that are associated with a shorter course, the 7·5% non-inferiority margin is still adequate.

This study has limitations. Only 28% of eligible patients agreed to participate in our study. Our screening log revealed that for 27% of eligible patients the reason for non-participation was unclear. This could have introduced some level of selection bias. Upon completion of data collection for the cohort of eligible non-participants, comparison with the trial population will address this concern. As few children participated in the trial and patients who were pregnant or immunocompromised were excluded from participation, whether a 2-day course of antibiotics is safe in these patients remains unclear. Non-adherence to the study protocol was 14% in the 2-day group and 8% in the 5 day group. Incomplete adherence potentially creates bias in the intention-to-treat analysis towards the hypothesis of non-inferiority of the experimental intervention. The per-protocol analysis produced nearly identical results, which alleviates this concern. This was a pragmatic trial, in which clinicians and researchers were not masked to treatment allocation. Masking could have reduced the risk of outcome assessment bias; however, the choice for non-masked design was made because of feasibility concerns. Having the experimental group remain in hospital for additional days of intravenous saline fluid administration would have increased the pressure on hospital bed capacity compared with general practice. We anticipated that this would discourage hospitals from participating, which in turn would have jeopardized completion of the trial within an acceptable timeframe. Unnecessary hospital stay would also put patients at risk of nosocomial infections. We were unable to reach 34% of patients for the telephone follow-up after 90 days. However, the response rate was similar in both arms, which limits the concern of bias due to potentially under-reported outcomes. As it is nearly impossible to conceal shorter and longer intravenous treatment (and hospital stay) from the electronic patient dossier, outcome assessment was not masked. Of interest is the ongoing ABAP study, which will clarify whether 24 h of

intravenous antibiotics can be considered non-inferior to 3 days in a placebo controlled design.[3] The Danish PIPA trial, a cluster-randomised study of 3 days of postoperative oral versus intravenous antibiotics may also support reduced intravenous antibiotics for complex appendicitis in the future.[47]

In conclusion, after laparoscopic appendicectomy for complex appendicitis, 2 days of intravenous antibiotics is non-inferior to 5 days in prevention of infectious complications, as measured against our prespecified non-inferiority margin of 7·5%. Restricting postoperative antibiotics to 2 days is expected to lead to a clinically relevant reduction in antibiotic use and hospital stay. Special consideration should be given to patients who have open surgery, who could benefit from an extended regimen of postoperative antibiotics. Further analysis, considering direct hospital costs and societal costs, will show whether the restrictive 2-day course was also cost-effective.

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Group information

The complete list of collaborators in the APPIC Study Group: CIM Baeten, MD PhD (Groene Hart Hospital, Gouda); FH Beverdam, MD (Franciscus Gasthuis, Rotterdam); EG Boerma, MD PhD (Zuyderland Medical Centre, Heerlen/Sittard); AL van den Boom, MD (Erasmus Medical Centre, Rotterdam); JWAM Bosmans, MD PhD (Zuyderland Medical Centre, Heerlen/Sittard); TA Burghgraef, MD (Meander Medical Centre, Amersfoort); ECJ Consten, MD PhD (Meander Medical Centre, Amersfoort, and University Medical Centre Groningen); JWT Dekker, MD PhD (Reinier de Graaf Gasthuis, Delft); M Emous, MD PhD (Medical Centre Leeuwarden, Leeuwarden); AAW van Geloven, MD PhD (Tergooi Medical Centre, Hilversum/Blaricum); AF Gijsen, MD (Medisch Spectrum Twente, Enschede); LA Heijnen, MD PhD (Northwest Clinics, Alkmaar); F Heinink, MSc (Zuyderland Medical Centre, Heerlen/Sittard); SA Huisman, MD PhD (Franciscus Gasthuis, Rotterdam); AP Jairam, MD PhD (Catharina Hospital, Eindhoven); PTJHM Janssen, MD PhD (Ikazia Hospital, Rotterdam); J de Jonge, MD (Tergooi Medical Centre, Hilversum/Blaricum); D Jou Valencia, MD (Medical Centre Leeuwarden, Leeuwarden); S Klaphake, MD (Maasstad Hospital, Rotterdam); J Kloeze, MD (Medisch Spectrum Twente, Enschede); LF Kroese, MD PhD (Reinier de Graaf Gasthuis, Delft); HR Langeveld, MD PhD (Erasmus Medical Centre, Rotterdam); MDP Luyer,

MD PhD (Catharina Hospital, Eindhoven); DC Melles, MD PhD (Meander Medical Centre, Amersfoort); BJ Noordman, MD PhD (Franciscus Gasthuis, Rotterdam); APT van der Ploeg, MD PhD (Maasstad Hospital, Rotterdam); FB Poelmann, MD (Medical Centre Leeuwarden, Leeuwarden); CC van Rossem, MD PhD (Maasstad Hospital, Rotterdam); J van Rosmalen, PhD (Erasmus Medical Centre, Rotterdam); WH Schreurs, MD PhD (Northwest Clinics, Alkmaar); P Steenvoorde, MD PhD (Medisch Spectrum Twente, Enschede); BR Toorenvliet, MD PhD (Ikazia Hospital, Rotterdam); M Vermaas, MD PhD (IJsselland Hospital, Capelle a/d IJssel); J Shapiro, MD PhD (IJsselland Hospital, Capelle a/d IJssel); FPR Verbeek, MD PhD (Groene Hart Hospital, Gouda); J Verhelst, MD PhD (Ikazia Hospital, Rotterdam); HP Versteegh, MD PhD (Reinier de Graaf Gasthuis, Delft); JLA van Vugt, MD PhD (IJsselland Hospital, Capelle a/d IJssel); B Wiering, MD PhD (Slingeland Hospital, Doetinchem); BJ van Wijk, MD (Slingeland Hospital, Doetinchem); EML de Wijkerslooth, MD (Erasmus Medical Centre, Rotterdam); BPL Wijnhoven, MD PhD (Erasmus Medical Centre, Rotterdam).

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APPENDIX I. Per-protocol analyses

Table S1. Baseline Characteristics of the Per-Protocol Population

	TWO DAYS (N =434)	FIVE DAYS (N = 464)
Age – year	51 [30; 62]	52 [29; 64]
Age distribution – n (%)		
8 to 17	43 (10)	58 (13)
18 to 64	310 (71)	300 (65)
65 and older	90 (21)	113 (24)
Male sex	247 (57)	262 (57)
American Society of Anaesthesiologists (ASA) score		
ASA I	209 (48)	214 (46)
ASA II	180 (42)	202 (44)
ASA III	45 (10)	48 (10)
Body-mass index†	25·8 [23·2; 28·4]	25·5 [22·5; 28·7]
Missing	81	101
Duration of symptoms – days	2·0 [1·0; 3·0]	2·0 [1·0; 3·0]
Missing	7	11
Body temperature - °C	37·6 [37·0; 38·2]	37·6 [37·0; 38·2]
Missing	5	6
Pulse – bpm	90 [78; 102]	90 [78; 104]
Missing	25	21
White blood cell count – x 10^9/L	15·0 [12·0; 18·0]	15·2 [12·2; 18·7]
Missing	-	2
C-reactive protein – mg/L	98 [44; 170]	99 [48; 169]
Missing	-	1
Imaging test		
Ultrasonography	352 (81)	363 (78)
Computed tomography	200 (46)	207 (45)
Multiple imaging tests	136 (31)	128 (28)
Faecolith on imaging	145 (33)	136 (29)
Intravenous antibiotics in the ER/ward	127 (29)	139 (30)
Antibiotic prophylaxis in the OR	369 (85)	372 (81)
Missing	-	2
Laparoscopic procedure	416 (96)	439 (95)
Operating time – minutes	47 [37; 59]	45 [35; 58]
Missing	3	9
Classification of appendicitis		
Gangrenous	232 (54)	261 (56)
Perforated	311 (72)	335 (72)
Periappendiceal abscess	68 (16)	57 (12)
Pus or peritonitis present	359 (83)	402 (87)
Diffuse peritonitis	43 (10)	38 (8)
Drain placement	8 (2)	11 (2)
Histopathological examination‡		
Appendicitis	418 (97)	453 (99)
Malignant or premalignant lesion	10 (2)	7 (2)
Missing	4	4

ER, Emergency Room; OR, Operating Room; Data are n (%) or median [interquartile range], unless otherwise stated.

† Body-mass index is the weight in kilograms divided by the square of the height in meters. Data was missing for 81 patients in the 2-day arm and for 101 patients in the 5-day arm

‡ For 5 patients in the 2-day arm and 10 patients in the 5-day arm the histopathology report reflected findings of appendicitis alongside findings of benign or (pre)malignant lesion. For one patient in the two-day arm and three in the five-day arm benign pathology was found in absence of signs of appendicitis.

Percentages may not total 100 because of rounding.

Table S2. Deviations in the postoperative antibiotic regimen within the Per-Protocol population

	TWO DAYS (N =434)	FIVE DAYS (N = 464)
Reduced regimen, n (%)	0	12 (3)
Due to repeated iv failure	-	6
Due to thrombophlebitis	-	1
Due to severe nausea/vomiting/diarrhoea	-	5
Prolonged regimen, n (%)*	26 (6)	21 (5)
Due to culture results†	9	3
Due to complication	17	18
Switch in antibiotic agent, n (%)*	2 (0.5)	11 (2)
Due to culture results†	2	5
Due to complication	-	6
Restart due to complication, n (%)	58 (13)	30 (7)

Data are n (%) or median [interquartile range], unless otherwise stated.

* The deviation consisted of a switch in antibiotic agent and prolongation in 2 patients in the two-day arm and 8 patients in the five-day arm.

† Culture results were derived from intraoperative pus cultures in 4 patients in the two-day arm and 5 patients in the five-day arm, culture results of the remaining patients were preoperative blood cultures.

Table S3. Univariable Comparison of Secondary Outcomes in the Per-Protocol Population

	TWO DAYS (N =434)	FIVE DAYS (N = 464)	Effect size† (95% CI)	p value
Administered study medication‡				
No. of days	2·0 [2·0; 2·0]	5·0 [4·7; 5·0]	-3·0 (-3·0 to -3·0)	< 0·0001
No. of doses	6·0 [6·0; 6·0]	15 [14; 15]	-9·0 (-9·0 to -9·0)	< 0·0001
Missing	14	11		
Any complication	105 (24)	97 (21)	1·208 (0·882 to 1·652)	0·238
Clavien-Dindo class 1	28 (7)	50 (11)	0·571 (0·352 to 0·925)	0·021
Clavien-Dindo class 2	60 (14)	46 (10)	1·458 (0·969 to 2·194)	0·069
Clavien-Dindo class 3a	16 (4)	10 (2)	1·738 (0·780 to 3·872)	0·171
Clavien-Dindo class 3b	14 (3)	11 (2)	1·373 (0·616 to 3·057)	0·436
Clavien-Dindo class 4a	1 (0·2)	0	-	0·301
Comprehensive Complication Index§	20·9 [20·9; 26·2]	20·9 [8·7; 28·9]	0·0 (0·0 to 5·3)	0·251
Reintervention	29 (7)	19 (4)	1·677 (0·926 to 3·037)	0·085
Percutaneous drainage	16 (4)	12 (3)	1·442 (0·674 to 3·084)	0·343
Reoperation	15 (4)	9 (2)	1·810 (0·784 to 4·180)	0·159
Adverse effects of antibiotics¶	32 (7)	106 (23)	0·269 (0·177 to 0·409)	< 0·001
Postoperative length of stay – hours	68 [59; 90]	126 [120; 140]	-59·0 (-62·0 to -57·0)	< 0·0001
Missing	1	1		
Postoperative length of stay – days	3·0 [2·0; 3·0]	5·0 [5·0; 6·0]	-2·0 (-3·0 to -2·0)	< 0·0001
Unplanned medical visits				
Emergency room visits	68 (16)	35 (8)	2·277 (1·480 to 3·504)	< 0·001
Outpatient clinic visits	50 (12)	44 (10)	1·243 (0·810 to 1·907)	0·319
General practitioner visits	45 (16)	43 (14)	1·161 (0·738 to 1·827)	0·518
Missing	152	158		
Hospital readmission	52 (12)	28 (6)	2·120 (1·312 to 3·424)	0·002
Total length of stay – days∏	3·0 [3·0; 5·0]	5·0 [5·0; 6·0]	-2·0 (-2·0 to -2·0)	< 0·0001
Missing	2	1		

Data are n (%) or median [interquartile range], unless otherwise stated.

† Effect size is depicted as OR (95% CI) for categorical outcomes and absolute difference in median (95% CI) for continuous outcomes.

‡ Postoperative administration of cefuroxime 3dd1500mg or ceftriaxone 1dd2000mg combined with metronidazole 3dd500mg. One patient (0.2%) in the two-day arm and six patients (1.3%) in the five-day arm received gentamycin as cointervention.

§ Comprehensive Complication Index (CCI) result is a median of CCI scores of 105 patients in the two-day arm and 97 patients in the five-day arm that had a postoperative complication.

¶ Reported adverse effects were nausea/vomiting (N = 86), diarrhoea (N = 71), allergic reaction (N = 4), Clostridium difficile (N = 3) and thrombophlebitis (N = 2). In 27 patients two adverse effects were reported.

∏ Total length of stay is the sum of hospital stay of the original hospital admission and possible readmission(s).

APPENDIX II. Readmissions

Table S4. Hospital readmission the Intention-to-Treat Population

	TWO DAYS	FIVE DAYS
No. of patients with one or more readmission(s)*	58/502 (11.6)	29/503 (5.8)
Total no. of readmissions*	64	30
Causes for readmission:		
IAA	31 (48)	16 (53)
SSI	2 (3)	-
Intraabdominal free fluid or infiltrate†	3 (5)	1 (3)
Infected hematoma	1 (2)	-
Pneumonia	-	1 (3)
Fever e.c.i.	7 (11)	-
Abdominal pain e.c.i.	5 (8)	1 (3)
Thoracal pain e.c.i.	2 (3)	1 (3)
Closed loop bowel obstruction	-	1 (3)
Ileus/gastroparesis	8 (13)	5 (17)
Gastroenteritis	1 (2)	-
Clostridium	-	2 (7)
Wound dehiscence	1 (2)	-
Pulmonary embolism	1 (2)	-
Urinary retention	1 (2)	-
Delirium	-	1 (3)

* One patient was readmitted three times (two-day arm); five were readmitted twice (one in the five-day arm, four in the two-day arm); the remaining 81 were readmitted once.
† Suspected ongoing peritonitis, but no diagnosis of intraabdominal infection.
Percentages may not total 100 because of rounding.
Abbreviation: e.c.i. = e causa ignota (of unknown origin).

APPENDIX III. Subgroup Analyses

Table S5. Baseline Characteristics of the Open Surgery Population (ITT)

	TWO DAYS (N=22)	FIVE DAYS (N = 28)
Age – year	49 [16; 65]	51 [27; 71]
Age distribution – n (%)		
8 to 17	7 (32)	6 (21)
18 to 64	10 (46)	12 (43)
65 and older	6 (27)	10 (36)
Male sex	17 (77)	16 (57)
American Society of Anaesthesiologists (ASA) score		
ASA I	10 (46)	11 (39)
ASA II	10 (46)	13 (47)
ASA III	2 (9)	4 (14)
Body-mass index‡	25·7 [21·4; 27·8]	26·2 [21·2; 28·6]
Missing	2	7
Duration of symptoms – days	2·0 [1·0; 2·5]	2·0 [1·0; 3·0]
Missing	1	2
Body temperature - °C	37·7 [37·0; 38·5]	37·4 [37·1; 38·0]
Missing	1	-
Pulse – bpm	95 [80; 106]	100 [82; 111]
Missing	5	1
White blood cell count – x 10^9/L	16·1 [11·9; 18·7]	16·3 [12·1; 20·9]
C-reactive protein – mg/L	107 [49; 269]	103 [56; 144]
Imaging test		
Ultrasonography	16 (73)	21 (75)
Computed tomography	12 (55)	10 (36)
Multiple imaging tests	7 (32)	6 (21)
Faecolith on imaging	9 (41)	8 (29)
Intravenous antibiotics in the ER/ward	6 (27)	8 (29)
Converted procedure	12 (55)	16 (57)
Antibiotic prophylaxis in the OR	18 (82)	23 (82)
Operating time – minutes	47 [43; 88]	53 [40; 71]
Classification of appendicitis		
Gangrenous	11 (50)	15 (54)
Perforated	18 (82)	24 (86)
Periappendiceal abscess	3 (14)	4 (15)
Pus or peritonitis present	17 (77)	22 (82)
Diffuse peritonitis	3 (14)	4 (15)
Drain placement	1 (5)	2 (7)
Histopathological examination		
Appendicitis	22 (100)	28 (100)
Malignant or premalignant lesion	0	1 (4)

ER, Emergency Room; OR, Operating Room; Data are n (%) or median [interquartile range], unless otherwise stated.

‡ Bodymass index is the weight in kilograms divided by the square of the height in meters.

Table S6. Univariable Comparison of Clinical Outcomes in the Open Surgery Population (ITT)

	TWO DAYS (N = 22)	FIVE DAYS (N = 28)	Effect size† (95% CI)	p value
Protocol adherence	18 (82)	25 (89)	0·540 (0·107 to 2·715)	0·450
Administered study medication				
No. of days	2·0 [2·0; 2·0]	5·0 [4·7; 5·0]	-3·0 (-3·0 to -2·7)	<0·001
No. of doses	6 [6; 6]	15 [14; 15]	-9·0 (-9·0 to -8·0)	<0·001
IAA, SSI and/or mortality	6 (27)	1 (4)	10·125 (1·116 to 91·879)	0·017
IAA	4 (18)	0	-	0·019
SSI	2 (9)	1 (4)	2·700 (0·229 to 31·892)	0·415
Mortality	0	0	-	-
Reintervention	5 (23)	1 (4)	7·941 (0·853 to 73·936)	0·039
Percutaneous drainage	2 (9)	1 (4)	2·700 (0·229 to 31·892)	0·415
Reoperation	3 (14)	0	-	0·044
Any complication	8 (36)	9 (32)	1·206 (0·372 to 3·911)	0·754
Clavien-Dindo class 1	1 (5)	6 (21)	0·175 (0·019 to 1·576)	0·088
Clavien-Dindo class 2	2 (9)	5 (18)	0·460 (0·080 to 2·636)	0·375
Clavien-Dindo class 3a	2 (9)	1 (4)	2·700 (0·229 to 31·892)	0·415
Clavien-Dindo class 3b	3 (14)	0	-	0·044
Clavien-Dindo class 4a	0	0	-	0·132
Comprehensive Complication Index‡	26·2 [20·9; 33·7]	20·9 [10·5; 26·7]	6·113 (-1·722 to 13·973)	0·132
Adverse effects of antibiotics	2 (9)	3 (11)	0·833 (0·127 to 5·479)	0·849
Postoperative length of stay – hours	84 [66; 127]	133 [121; 153]	-52·0 (-70·0 to -33·0)	<0·001
Postoperative length of stay – days	3·0 [2·8; 5·0]	5·0 [5·0; 6·0]	-2·0 (-3·0 to -1·0)	<0·001
Unplanned medical visits				
Emergency room visits	4 (18)	0	-	0·019
Outpatient clinic visits	2 (9)	3 (11)	0·833 (0·127 to 5·479)	0·849
General practitioner visits	2 (13)	4 (20)	0·571 (0·091 to 3·608)	0·549
Missing	6	8		
Hospital readmission	5 (23)	1 (4)	7·941 (0·853 to 73·936)	0·039
Total length of stay – days¶	5·0 [3·0; 7·3]	6·0 [5·0; 7·5]	-1·0 (-2·0 to -0·0)	0·132

Data are n (%) or median [interquartile range], unless otherwise stated.

† Effect size is depicted as OR (95% CI) for categorical outcomes and absolute difference in median (95% CI) for continuous outcomes.

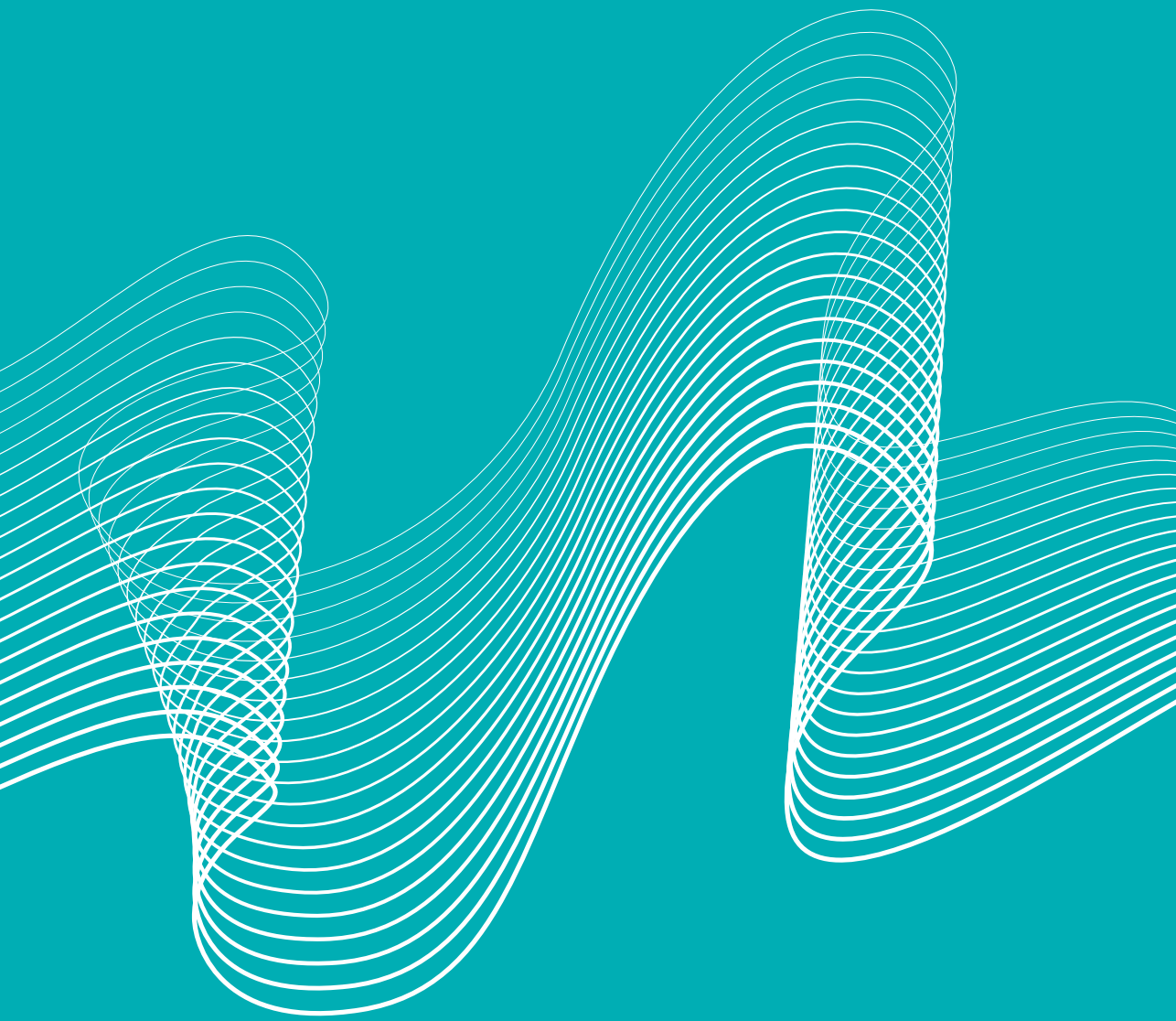
‡ Comprehensive Complication Index (CCI) result is a median of CCI scores of 8 patients in the two-day arm and 9 patients in the five-day arm that had a postoperative complication.

¶ Total length of stay is the sum of hospital stay of the original hospital admission and possible readmission(s).

APPENDIX IV. Overview of patient allocation among centres

Table S7. Number of patients per allocation per centre

Centre	Province	N=502 TWO DAYS	N=503 FIVE DAYS	N=1005 TOTAL
Catharina Hospital	Noord-Brabant	17 (3)	18 (4)	35 (4)
Erasmus Medical Centre	Zuid-Holland	8 (2)	6 (1)	14 (1)
Franciscus Hospital	Zuid-Holland	48 (10)	43 (9)	91 (9)
Groene Hart Hospital	Zuid-Holland	8 (2)	10 (2)	18 (2)
IJsselland Hospital	Zuid-Holland	30 (6)	27 (6)	57 (6)
Ikazia Hospital	Zuid-Holland	44 (9)	44 (9)	88 (9)
Maasstad Hospital	Zuid-Holland	50 (10)	50 (10)	100 (10)
Medical Centre Leeuwarden	Friesland	27 (5)	31 (6)	58 (6)
Meander Medical Centre	Utrecht	25 (5)	24 (5)	49 (5)
Medical Spectrum Twente	Overijssel	54 (11)	53 (11)	107 (11)
Northwest Clinics	Noord-Holland	23 (5)	23 (5)	46 (5)
Reinier de Graaf Hospital	Zuid-Holland	35 (7)	33 (7)	68 (7)
Slingeland Hospital	Gelderland	18 (4)	20 (4)	38 (4)
Tergooi	Utrecht	20 (4)	22 (4)	42 (4)
Zuyderland Medical Centre	Limburg	95 (19)	99 (20)	194 (19)



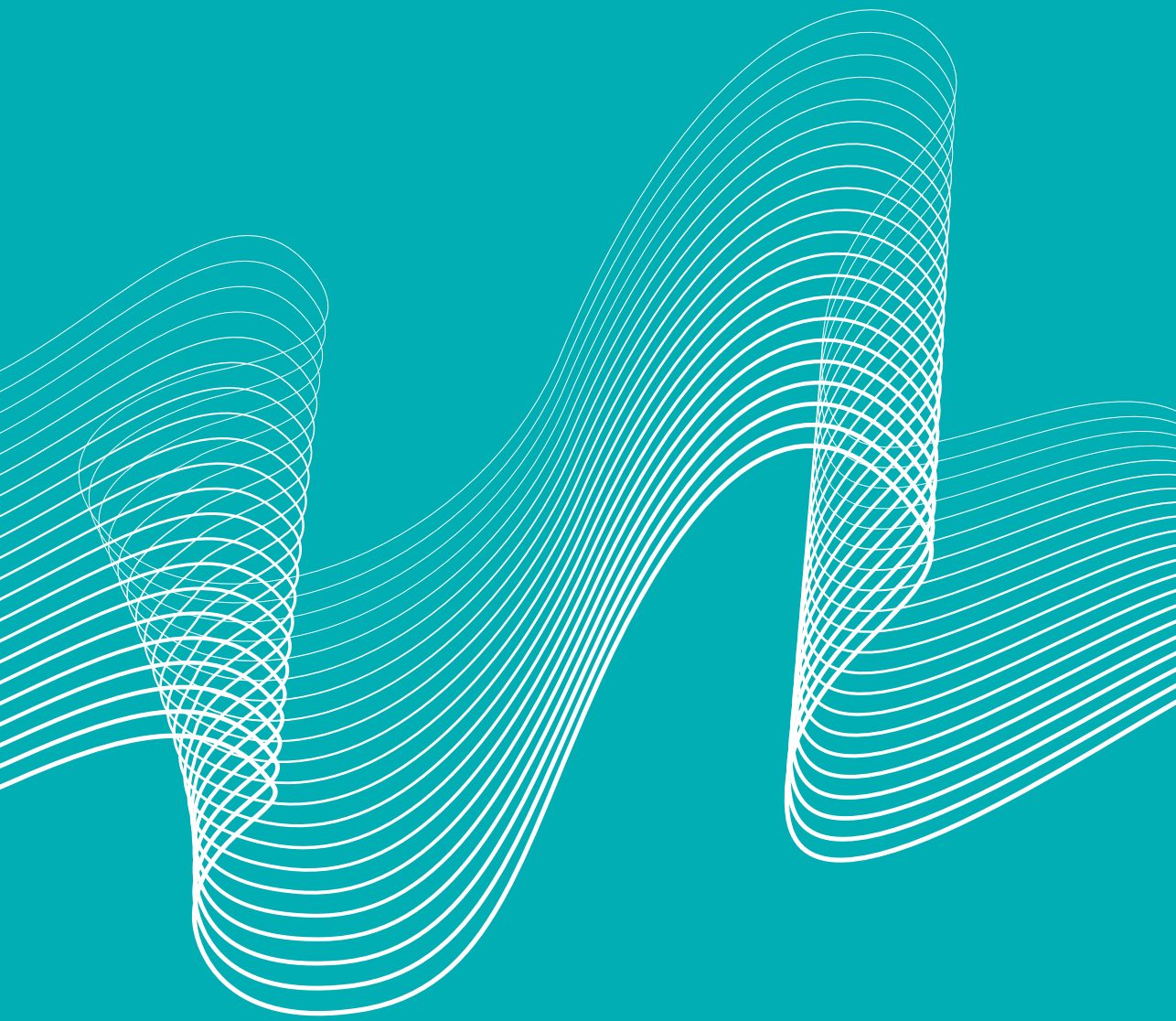
EML de Wijkerslooth, EG Boerma, CC van Rossem, MA Koopmanschap, CIM Baeten, FH Beverdam, JWAM Bosmans, ECJ Consten, JWT Dekker, M Emous, AAW van Geloven, AF Gijsen, LA Heijnen, AP Jairam, APT van der Ploeg, P Steenvoorde, BR Toorenvliet, M Vermaas, BPL Wijnhoven*, AL van den Boom*, for the APPIC Study Group

* Shared senior authorship

Submitted

9

COST ANALYSIS OF 2 DAYS VERSUS 5 DAYS OF POSTOPERATIVE ANTIBIOTICS FOR COMPLEX APPENDICITIS



10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

In the late 1880s John B. Murphey stated 'When in doubt, take it out'. He referred to appendectomy in patients with a clinical suspicion of acute appendicitis. For a long time this strategy remained unquestioned. Over the past decades, the increased use of imaging studies in the evaluation of acute abdominal pain has reduced the number of negative appendectomies.[1, 2] It has also become clear that emergency appendectomy within 24 h after diagnosis in patients with (suspected) simple appendicitis is safe without increased risk of perforation or postoperative complications.[3] Furthermore, non-operative treatment has emerged as an alternative to surgery for patients with simple appendicitis.[4] These developments illustrate that challenging old dogmas of 'standard practice' by performing scientific research is the key to change practice, leading to improved outcomes for the patient.

Between 2006 and 2016, approximately 13,500 patients underwent appendectomy for acute appendicitis on an annual basis in the Netherlands (Chapter 2). This resulted in nearly 50,000 days of hospital admission and nearly 50 million in reimbursed hospital costs per year. Still, this may reflect an underestimation of the total burden of disease for acute appendicitis, given the higher number of extracted appendices (over 16,500 annually) in the Dutch histopathology database PALGA, and the exclusion of non-operative treatment from this study.[5] In view of rising health-care costs and constant overflow of hospital bed capacity, improvement in treatment efficiency is needed. Non-operative treatment as an alternative to surgery for patients with (suspected) simple acute appendicitis may reduce the need for hospitalization. Multiple randomized trials have recently established non-operative treatment as a safe option.[4, 6, 7] It may also be associated with lower costs.[4, 8] After initial non-operative management, some 30 to 40% of patients will undergo delayed appendectomy in the following five years.[4] The risk of perforated appendicitis or postoperative complications is not increased. What remains uncertain, is the effect of omitting appendectomy for appendicitis beyond 5 years.[6, 9] Published studies present conflicting results regarding the association between appendectomy and risk of inflammatory bowel disease, diverticulitis and malignancies.[10] Furthermore, how to reliably distinguish simple from complex appendicitis before surgery is much debated. Whereas simple appendicitis allows for a 24-hour window to surgery or non-operative treatment, complex appendicitis necessitates surgery within 8 h to prevent complications.[11, 12] Imaging (ultrasound followed by CT or MRI if inconclusive) results in a sensitivity of 35% and specificity of 93% for the diagnosis of complex appendicitis.[13] Clinical scoring systems have been developed but are not widely used.[14, 15] For the moment, appendectomy remains the cornerstone of treatment. In the future, the non-operative approach is expected to gain territory.

Controversy in classification of appendicitis

This thesis shows that there is a substantial level of variability in classification and postoperative treatment of acute appendicitis (Chapter 3 and 4). Daily practice may be quite different in hospital A compared to hospital B, or even for patients treated in a single hospital by different surgeons. A recent study among 562 American surgeons and residents using static images showed similar results.[16] Disagreement between surgeons regarding the categorization of intraoperative findings into a simple and a complex appendicitis complicates the interpretation and comparison of studies on diagnosis and treatment of appendicitis. The need for a universal classification system was addressed by several colleagues recently.[3, 17-19] The guideline on acute appendicitis by the Dutch Association of Surgery (NVvH), revised in 2019, defines a complex appendicitis as a more severe, progressive variant with necrosis and/or perforation of the appendix.[20] This definition was used throughout part III and part III and IV of this thesis. A more reliable severity classification is required, to enhance the comparison of studies and improve patient outcomes. Cameron *et al*. proposed that a macroscopic perforation, an extraluminal faecolith and an intraabdominal abscess are the hallmarks of complex appendicitis.[17] These might reflect findings associated with better interobserver agreement. Aside from intraoperative findings, preoperative variables could be included in a clinical decision rule model to support or oppose postoperative antibiotic use. Then again, not many confounders were consistently identified in literature as independent risk factors for infectious complications, other than appendiceal perforation or faecolith.[21-25] Perhaps less is more. From a pragmatic point of view, the future standardized classification of complex appendicitis could simply include (macroscopic) perforation, faecolith, abscess and/or diffuse peritonitis.

Controversy in treatment particularly exists in patients with a gangrenous, nonperforated appendicitis in the presence of intra-abdominal pus or turbid fluid. Gangrenous appendicitis is defined as transmural inflammation of the appendix with necrosis, impending perforation.[26] Though there is no perforation of the hollow organ yet, there may already be bacterial translocation to the intraabdominal cavity, which could explain the increased risk of postoperative infectious complications compared to suppurative/phlegmonous appendicitis. The World Society of Emergency Surgery (WSES) guideline on acute appendicitis, last revised in 2020, acknowledges that complex appendicitis entails several presentations of appendicitis, but is unclear about the postoperative management of gangrenous appendicitis.[3] The Surgical Infection Society (SIS) guideline on management of complicated intra-abdominal infections, last revised in 2017, recommends to restrict postoperative antibiotics to 24 h after appendectomy for gangrenous unperforated appendicitis.[27] For perforated appendicitis, four days of antibiotics is advised. In Chapter 5 it was demonstrated that patients with a gangrenous unperforated appendicitis (11% of the population operated for acute appendicitis) are at higher risk of postoperative

infectious complications than patients with phlegmonous appendicitis. However, the group of patients presenting with gangrenous appendicitis were older, presented with higher serum inflammation markers and a higher degree of intra-abdominal contamination, as compared to patients with a phlegmonous appendicitis. Most patients with gangrenous appendicitis (75%) received postoperative antibiotics based on their intraoperative classification. Similar results were found in a more recent cohort of 4401 patients operated for acute appendicitis in 9 Dutch hospitals in 2019 and 2020.[28] In this cohort, 303 of 417 patients with unperforated gangrenous appendicitis (73%) received postoperative antibiotics. It seems justified to abandon postoperative antibiotics for gangrenous appendicitis because 1) the assessment of gangrene/necrosis during surgery is unreliable, 2) its presence is not an independent risk factor for infectious complications, and 3) there is no evidence showing a benefit of postoperative antibiotics for this group. It is unlikely that more studies will address this since the group of unperforated gangrenous appendicitis is a small subgroup of patients with acute appendicitis and its assessment and treatment are so heterogeneous. A shift towards standardized treatment without postoperative antibiotic use could be initiated and audited, to evaluate its effect.

Efficiency in postoperative management

Given the high prevalence of acute appendicitis and the substantial clinical and economic burden of disease, optimization of treatment is important. In the past decades, advances in the preoperative diagnostic work-up, anesthetics and surgical technique have led to a reduction in appendix sana rates and shorter hospital stay. As shown in Chapter 2, mean total length of stay per patient was three to four days in Dutch practice between 2006 and 2015. This included both simple and complex appendicitis patients. The Dutch Snapshot Appendicitis Collaborative Study Group reported a median postoperative length of stay of 2 days in their 1378 adult patients treated in 2014.[2] Over time the proportion of patient undergoing laparoscopic surgery has steadily increased. Further reducing hospital stay has several advantages: patient comfort/satisfaction (in recovering at home), less demand on hospital bed capacity, less direct hospital costs and less exposure to hospital pathogens. The challenge is to achieve this without compromising patient safety.

Postoperative hospital stay – simple appendicitis

Appendectomy is generally considered a low-risk procedure. Associated morbidity and mortality rates are relatively low.[4] Many other low-risk minimally invasive procedures are now day case surgeries, e.g. cholecystectomy and inguinal and abdominal wall hernia repairs. Given the acute, non-elective aspect of appendicitis, same-day discharge after appendectomy is uncommon. In a multicenter cohort study of 4,401 Dutch patients treated in 2019 and 2020, we found a mean postoperative hospital stay of 2 days as well.[28] Among the 2,655 patients with simple appendicitis, 179 (6.7%) were discharged on the same calendar day as the operation took place. Mean postoperative length of stay was 19

h (87% of patients discharged after one night of hospitalization). A retrospective cohort study of 5266 pediatric patients with simple appendicitis treated in the USA between 2015 and 2020 reported a similar mean postoperative stay of 0.9 days (21.6 hours).[29] Recent studies have suggested that expedited discharge after appendectomy is safe (Chapter 6). However, most studies were observational cohort studies, raising concerns of patient selection and selective reporting bias. A meta-analysis by Zheng *et al*. on same-day discharge in pediatric patients, including two additional observational studies that were published after 2019, showed similar results.[30] Several observational studies and one randomized trial by Trejo-Avila *et al*. reported success rates in over 80% of patients after implementation of a same-day discharge protocol.[31-35] Rates of postoperative complications and readmission to the hospital showed no significant increase after same-day discharge. These results seem to justify enhanced recovery after appendectomy, suggesting to perform appendectomy as an outpatient procedure. This may reduce hospitalization without compromising patient safety. Important to take into account, are the selection criteria in these study populations. The success of such protocols depend on good patient selection and surgical planning. Current guidelines recommend to perform an appendectomy for simple appendicitis within 24 h after diagnosis, leaving some room for surgical planning.[20] Having an operating room available for acute procedures is not a given in many hospitals. Moreover, patient education and instructions should be carefully overseen out when rolling out an outpatient appendectomy protocol. Once the logistic issues are overcome and eligibility criteria are carefully drafted, implementation of a fast-track protocol could boost treatment efficiency in a large patient population.

Postoperative antibiotic use – complex appendicitis

Before the start of the APPIC trial, most complex appendicitis patients were prescribed postoperative antibiotics for 5 days. As described in Chapter 3 and Chapter 4, protocols and expert opinion on the duration of postoperative antibiotics differed considerably. Restriction of antibiotics to 24 or 48 h was already adopted in some UK and Danish centers, whereas this was uncommon in Dutch practice. The APPIC trial was initiated to show non-inferiority of a 2-day regimen (Chapter 7). Whilst drafting the protocol, a further restriction of the duration of postoperative antibiotics to 24 h was also considered. Unfortunately, there were insufficient data in the literature to substantiate this and 48 h would ensure adequate tissue concentrations to be effective against common bacteria (i.e., *E. coli*).[36, 37] We decided to administer a complete intravenous course in both treatment arms. Allowing a switch to oral formula might have raised issues of treatment compliance, questionable tissue penetration of oral augmentin and heterogeneity in treatment in the control arm. Some hospitals that were approached for participation had concerns about safety for the 2-day treatment. On the other hand, there were hospitals that would have preferred a more experimental restriction to 24 h intravenous antibiotics. Since 2016, a 3-day intravenous course has become increasingly popular in the Netherlands.[21] From

data collection of non-participants that we retrieved over the course of the trial, it has become clear that the majority patients are still prescribed postoperative antibiotics for longer than 3 days. Data from 1015 non-participants (treated in 2019-2020) with complex appendicitis showed that 11% received postoperative antibiotics for 48 h at most. Another 20% was treated for 3 days and in the remaining 69% of patients postoperative antibiotics were extended beyond 3 postoperative days. Mean duration was 5.5 postoperative days (intravenous and oral administration together). This supports the choice for our regimen of 5 days as standard treatment in the APPIC trial.

The APPIC trial showed that there were no statistically significant differences between the two arms in rates of intra-abdominal abscess, surgical site infection or death within 90 days after appendectomy. There was also no difference in the rate of postoperative complications that required invasive treatment, such as percutaneous drainage or reoperation. The results are in line with other studies failing to demonstrate a preventive effect of prolonged antibiotic on surgical site infections after appendectomy.[38-42] In the 5-day group, there were some patients who were diagnosed with an abscess on postoperative day 4 or 5, while still receiving intravenous antibiotics.

Some secondary outcomes deserve further evaluation. The rate of hospital readmission in the 2-day group was nearly double the rate in the 5-day group but not related to an increased number of postoperative abscesses or other complications. Overall duration of hospital stay (readmissions included) was still significantly shorter in the 2-day group. Nevertheless, it is important to further explore this high rate (12%). Analysis of these readmissions will shed light on the causes and potential ways for prevention when a 2-day course will be implemented in clinical practice. The same applies to the number of patients that were restarted on antibiotics in the 2-day group (Clavien-Dindo class 2 complications). In several patients, there was no evidence for an infectious complication, but antibiotics were restarted for fever or elevated serum C-reactive protein. We feel that these two less favorable outcomes for the experimental 2-day treatment are not alarming. Surgeons may have had a low threshold for readmitting patients and restarting antibiotics in patients allocated to the experimental treatment. Supported by the trial results, surgeons will hopefully be less liberal to restart antibiotics patients and/or readmit patients, without evidence of an infectious complication in the future. Further experience with the restrictive 2-day treatment may also aid patient education regarding symptoms they may experience at home after discharge, which may reduce the number of hospital visits.

The reduction in antibiotic use, hospital stay and adverse effects related to antibiotics outweigh the increase in readmissions and Clavien-Dindo class 2 complications. The 2-day course of postoperative antibiotics was shown to result in lower direct hospital

costs and comparable productivity losses, as compared to the 5-day course (Chapter 9). Cost-effectiveness was established through cost savings over € 31,117 per additional complication in the 2-day group. As 5 days of intravenous antibiotics is not the standard (anymore) in most Dutch hospitals, it is questionable whether cost savings will match this level upon implementation of the 2-day course in daily practice. Nevertheless, these results are illustrative and encouraging.

It will be of interest to see whether results of the APPIC trial can be confirmed in future studies, in similar patient populations and in patients that were not represented in the APPIC trial (e.g. pregnant, immunocompromised and pediatric patients). One such future study is the ABAP trial in France, which is currently in the phase of patient inclusion.[43] In this placebo-controlled and double-blind trial, one postoperative day of intravenous antibiotics is compared to 3 days. Another trial of interest is the Danish PIPA-trial, a randomized study comparing 3 days of intravenous versus oral antibiotics after appendectomy for complex appendicitis.[44] These trials together with the APPIC trial form a movement against antibiotic overuse for appendicitis and will hopefully result in significant reduction of antibiotic use globally in the future.

FUTURE PERSPECTIVES

Standardization of practice

The variability in classification of intraoperative findings, indications for postoperative antibiotic use and postoperative antibiotic regimens call for standardization in practice. A clinical decision algorithm on the use of imaging was incorporated in the Dutch guideline on acute appendicitis in 2010 and has been widely adopted since. A decision tool for intraoperative assessment and postoperative management of appendicitis could also be helpful. Four intraoperative findings could be used for defining a complex appendicitis: a macroscopic perforation of the appendix, a faecolith or abscess in the intraabdominal cavity and/or diffuse (four-quadrant) peritonitis of the abdomen. Presence of necrosis without macroscopic perforation or extraluminal faecolith would not qualify for complex appendicitis and as such postoperative antibiotics are not indicated. Nor would localized pus or peritonitis be an indication for antibiotics. Standardized postoperative antibiotic regimen would entail 2 days of intravenous antibiotics, cefuroxime/metronidazole or ceftriaxone/metronidazole, depending on hospital preference and resistance patterns. This guideline could also include a decision tool for the restart of antibiotics to prevent its unnecessary use. Patients that are immunocompromised, pregnant or classified ASA 4 may need a different approach.

This definition of complex appendicitis and clinical decision tool could be incorporated in the Dutch guideline on acute appendicitis and once implemented, adherence should be audited. A snapshot study design could well serve this aim.

Outpatient treatment of simple appendicitis

Studies support the idea of day case appendectomy. A challenge is the logistics. Given the acute nature of appendicitis, patients may present to the hospital any hour in the day. Obviously, feasibility of day case surgery for appendicitis depends on the timing of the surgical procedure. Appendectomy in the first half of the day provides the best chance of discharge the same day. This would require that some patients presenting with appendicitis could go home with oral analgesics and return the next morning for appendectomy. Not every patient may qualify for this and an operating room should be made available for the next morning. Eligible patients would be ASA class I-II patients with a simple appendicitis and have a clear ability to understand and act on signs of complication in which to contact the hospital. To support patients at home, a digital app could be designed to guide patients with pain medications, oral intake and possible alarm symptoms that would require them to contact the hospital/surgical team. The app could also be used to disperse patient questionnaires (providing patient consent), as a means to evaluate patient satisfaction for instance. Such a protocol could be implemented and studied in a few hospitals for feasibility and safety.

Non-operative management of (suspected) simple appendicitis is likely to become more common in the future. The non-operative approach – whether it entails antibiotics or solely analgesics and antiemetics – is expected to become more efficient as well. Most studies included a few days of intravenous antibiotics, before allowing discharge with oral antibiotics.[4, 6, 47] Latest studies looked at oral antibiotics or no antibiotics, which could shorten or omit hospital admission.[45, 46, 48] The CODA trial reported an impressive 47% discharge straight from the Emergency Room in their antibiotics only group.[7] Treatment of (suspected) simple appendicitis could become a predominantly ambulatory treatment in the near future being surgery or conservative management. Shared decision-making will deliver the choice between surgical or non-operative treatment and patient characteristics will determine whether or not this treatment requires hospital admission or can be overseen in an outpatient setting.

Further reduction of antibiotics for complex appendicitis

The APPIC trial supports 2 days of intravenous administration of postoperative antibiotics for complex appendicitis. This applies to ASA class I-III patients that undergo a laparoscopic appendectomy and are not pregnant or immunocompromised. In the near future we may move towards a further reduction of postoperative use of antibiotics,[43, 44] as has been established for cholecystectomy.[47]

Future trials comparing a single preoperative prophylactic dose to 24 or 48 h of postoperative intravenous antibiotics should be performed. Such a trial would require a large sample size. Patient recruitment in RCTs is challenging. In a potential future trial, a patient-oriented randomization scheme could be considered. For instance, a cluster-randomized design may allow for more steady progress in recruitment. International collaboratives could overcome the issue of large sample sizes by running large trials in several counties led by dedicated research groups, e.g., in Finland, Denmark, France and the Netherlands. Furthermore, patient-reported outcomes should be included as important outcome measures. Quality of life and treatment satisfaction are important, especially when moving towards reduced hospitalization. Improving treatment efficiency should not come at the cost of patients' (sense of) safety.

Essential to facilitate the interpretation of future trials will be the availability of a complementary cohort of non-participants. Patients' reasons for declining participation might in some way correlate to factors associated with outcomes. Comparison of trial patients to non-participants provides insight into whether or not results can be extrapolated to the general patient population or not (generalizability). Regulations concerning patient consent need to be taken into consideration. Eligible patients that decline participation should directly be requested to participate in a non-interventional cohort study. In this way, the organizational structure for the trial is optimally utilized

to retrieve data from a larger patient sample, which may further aid analysis of adverse outcomes. In the future, the possibility of patient consent through digital signature may ease this process. This will relieve a lot of paperwork at the same time.

Prevention of infectious and other complications after appendectomy remains important. Some risk factors have been identified but not all can be modified to decrease the risk of postoperative complications. Surgical techniques (i.e. use of irrigation), antibiotic prophylactic strategies and the liberal use of microbiology cultures have so far not provided definite answers. Data from the APPIC trial together with data of the nonparticipants (data collection ongoing) may provide new opportunities to gain insights in of the development of infectious complications. Improved understanding of the underlying pathophysiology may be key in coming up with preventive strategies. Subgroup analyses of patients according to age and intraoperative disease characteristics, as well as patients with early postoperative abscess formation, may give rise to new insights and ideas for prospective studies.

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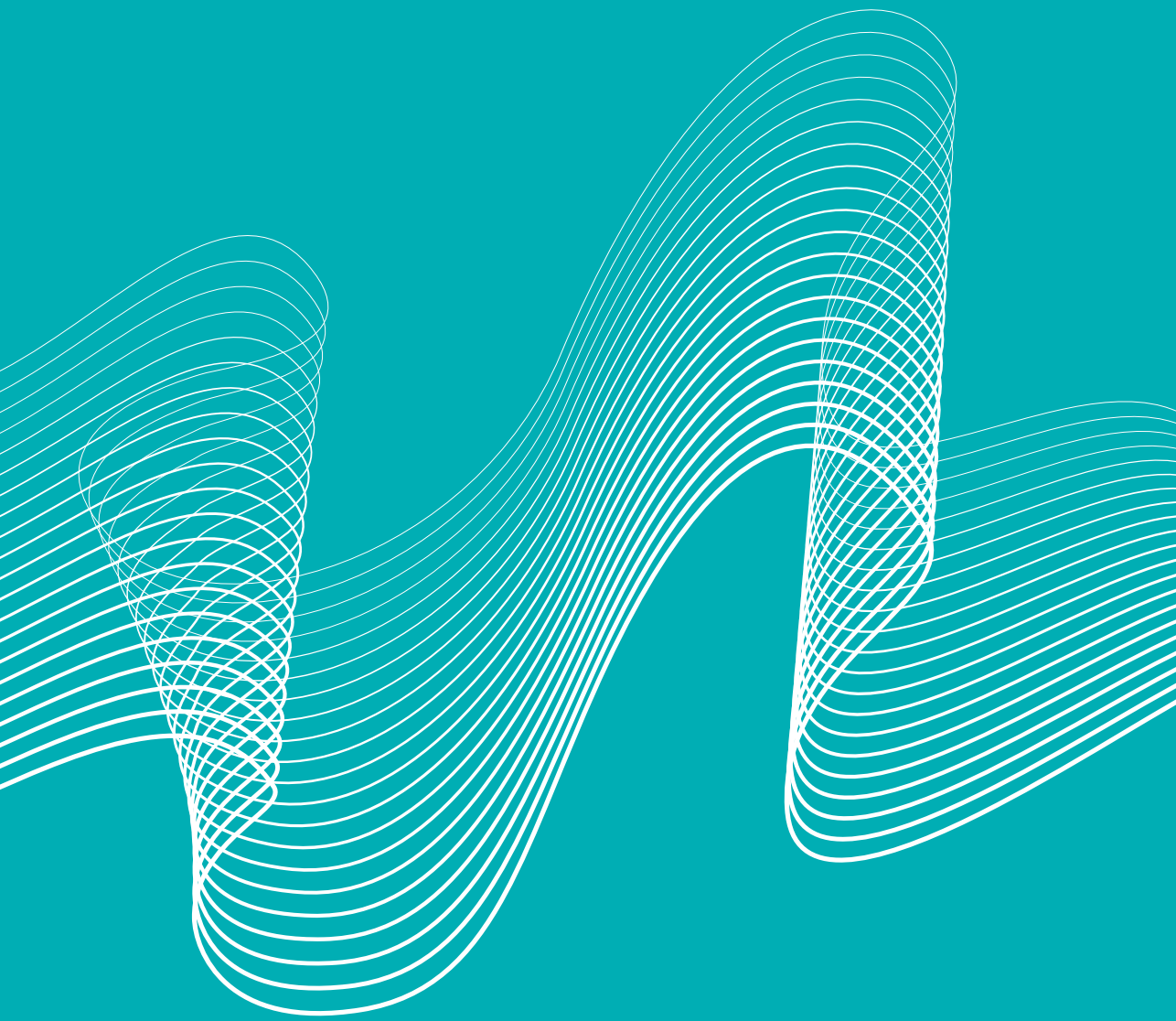

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ENGLISH AND DUTCH SUMMARY

ENGLISH SUMMARY

In this thesis, we focused on the surgical treatment of acute appendicitis, and in particular: the distinction between simple and complex appendicitis, postoperative length of hospital stay and postoperative antibiotic use.

In **chapter 2**, we evaluated the clinical and economic burden of surgically treated acute appendicitis in the Netherlands. We performed a population-based retrospective cohort study of 135,025 patients who underwent appendectomy for acute appendicitis between 2006 and 2016. Overall incidence of appendectomy for appendicitis was 81 per 100,000 inhabitants, which decreased over time and age. Mean length of stay per patient was 3.7 days. Length of stay increased with age and was significantly longer after open surgery compared to laparoscopy. Mean hospital costs per patient were €3,700, similar for open and laparoscopic surgery from 2012 onwards. This national cohort shows that surgically treated appendicitis represents a substantial clinical and economic burden in the Netherlands, and a preference for minimally invasive technique seems justified.

PART II - THE SURGICAL CLASSIFICATION OF ACUTE APPENDICITIS

In **chapter 3** we aimed to assess interobserver variability among surgeons in the intraoperative classification of appendicitis and its postoperative management. We conducted a cross-sectional study by having 80 surgeons and surgical residents watch and classify video fragments taken during laparoscopic appendectomy. Interrater agreement was minimal for the classification of appendicitis into simple or complex, as well as for the decision to prescribe postoperative antibiotics. Agreement would only have been slightly higher, had our proposed definition of complex appendicitis consistently been applied. Opinions varied concerning the need for postoperative antibiotics in case of appendicitis with localized pus or gangrenous unperforated appendicitis. And duration of prescribed antibiotics varied between 3 and 5 days. The results suggest that the current intraoperative classification of appendicitis is unreliable and, by extension, the postoperative management of appendicitis is highly variable.

We further explored the theme of intraoperative classification and postoperative antibiotic use in **chapter 4**. In this online survey study among 137 international surgeons across Europe, we aimed to document current practice in variation in classification, indication for postoperative antibiotics and preferred duration of antibiotic use. Opinions varied substantially regarding the management of appendicitis, in particular for phlegmonous appendicitis with localized pus, gangrenous appendicitis and iatrogenic rupture of appendicitis. The most common duration of postoperative antibiotics was evenly spread

over less than 3, 3, 5 and 7 days. Whereas most respondents indicated a combined intravenous and oral route of administration was common practice, 28% answered a completely intravenous route of administration was standard practice. The findings of this study further highlighted the level of variability in management of complex appendicitis.

In light of findings from chapter 3 and 4, we decided to zoom in on patients with gangrenous nonperforated appendicitis. In a prospective Dutch snapshot study of 1863 patients, presented in **chapter 5**, we assessed the risk of postoperative infectious complications (intraabdominal abscess or surgical site infection) per type of appendicitis. Among the total, 181 of 1863 (9.7%) were classified to have gangrenous, nonperforated disease. In this study, 75% of patients with gangrenous appendicitis was given postoperative antibiotics. The risk of infectious complications after appendectomy for this group was significantly higher compared to patients with phlegmonous appendicitis, but gangrenous disease was not an independent predictor in multivariable analysis.

PART III – POSTOPERATIVE HOSPITAL STAY FOR SIMPLE APPENDICITIS

In the next chapters we addressed treatment efficiency for patients with simple appendicitis (in absence of necrosis, perforation or abscess). **Chapter 6** provides an overview of available literature on same-day discharge after appendectomy for acute simple appendicitis. Results from 17 comparative and 8 non-comparative studies indicate that same-day discharge is not associated with an increased risk of readmission, unplanned hospital visits or postoperative complications. Most only reported on same-day discharge after laparoscopic procedure. Due to clinical and methodological between-study heterogeneity, pooling of data for meta-analysis was limited. We concluded that current literature indicates that same-day discharge is feasible and safe in a large proportion of both pediatric and adult patients.

PART IV – POSTOPERATIVE ANTIBIOTIC USE FOR COMPLEX APPENDICITIS

To address the considerable variation in postoperative management of complex appendicitis – outlined in part II – we designed a randomized study to determine the appropriate duration of postoperative antibiotic use. **Chapter 7** summarizes the study protocol of the APPIC trial, a pragmatic non-inferiority trial to compare 2 days of postoperative intravenous antibiotics to 5 days. Eligible for inclusion were patients aged 8 or older undergoing emergent appendectomy that were diagnosed with complex appendicitis during surgery. Patients that were pregnant or immunocompromised were excluded, as well as patients with a contraindication for the study medication (cefuroxime

or ceftriaxone in combination with metronidazole). Included patients were to be randomized 1:1 to receive either 2 days or 5 days of intravenous antibiotics. The primary endpoint was a composite endpoint of intraabdominal abscess, surgical site infection or death within 90 days after appendectomy. Secondary outcomes included length of hospital stay, reinterventions, readmission, all postoperative complications and cost-effectiveness. The non-inferiority margin for the absolute risk difference in the primary endpoint was 7.5%. And both per-protocol and intention-to-treat analysis were to be performed.

Onwards, in **chapter 8**, the primary results of the APPIC trial are outlined. Non-inferiority of 2 days was demonstrated by the adjusted absolute risk difference in primary endpoint of 2.0%, in favor of the 5-day group (95% confidence interval -1.6 to 5.6%). The primary endpoint occurred in 51/502 (10.2%) patients in the 2-day group and 41/503 (8.2%) patients in the 5-day group. The median duration of antibiotics was 2.0 days (interquartile range (IQR) 2.0 to 2.3) vs. 5.0 (IQR 4.7 to 5.0), $P < 0.001$. Rates of complications and reinterventions were similar between trial arms. In the 2-day group, fewer patients experienced adverse effects to antibiotics (45 (9%) vs. 112 (22%), $P < 0.001$). Readmission was more frequent in the 2-day group (58 (11.6%) vs. 29 (5.8%), $P = 0.001$). Results were similar in per-protocol and intention-to-treat analysis. These findings confirm that a significant reduction in antibiotic use and hospital stay can be achieved. We argue that these benefits outweigh potential disadvantages, since the rate of infectious complications and reinterventions were similar in both trial arms. Restricting postoperative antibiotics to 2 days is expected to lead to a clinically relevant reduction in antibiotic use and hospital stay. Special consideration should be given to patients undergoing open surgery, for whom no definite conclusions can be drawn based on this trial, given the small number of patients.

Further analysis considering direct hospital costs as well as societal costs, in **chapter 9**, demonstrates that the restrictive 2-day course is also cost-effective compared to 5 days. Reducing antibiotics to 2 days offers statistically significant savings in overall societal costs, as compared to 5 days. These savings derive mainly from reduced hospital admission. Developing strategies to further restrict postoperative antibiotic use and minimize length of hospital stay may relieve pressure on hospital bed capacity and health care in the future.

NEDERLANDSE SAMENVATTING

Dit proefschrift is gericht op de chirurgische behandeling van acute appendicitis, met speciale aandacht voor het onderscheid tussen simpele en complexe appendicitis, postoperatieve ligduur en postoperatief antibiotica gebruik.

In **hoofdstuk 2** hebben we de klinische en financiële ziektelast van chirurgisch behandelde appendicitis in Nederland geëvalueerd. Hiertoe hebben we een populatie-breed retrospectief cohort onderzoek uitgevoerd van 135,025 patiënten die tussen 2006 en 2016 een appendectomie vanwege appendicitis ondergingen. Over het geheel genomen, was de incidentie van appendectomie voor appendicitis 81 per 100,000 inwoners, welke een daling vertoonde over tijd en leeftijd. De gemiddelde opnameduur was 3.7 dagen per patiënt. Opnameduur liep op met leeftijd en was significant langer in geval van een open ingreep in vergelijking met laparoscopie. De gemiddelde gedeclareerde zorgkosten per patiënten bedroegen € 3700 per patiënt, vergelijkbaar voor open en laparoscopische chirurgie vanaf registratiejaar 2012. Dit nationale cohort liet zien dat chirurgisch behandelde appendicitis gepaard gaat met een substantiële klinische en financiële ziektelast, en dat een voorkeur voor minimaal invasieve techniek gerechtvaardigd lijkt.

DEEL II – DE CHIRURGISCHE CLASSIFICATIE VAN ACUTE APPENDICITIS

In **hoofdstuk 3** was het doel om interobserver variabiliteit onder chirurgen te evalueren als het gaat om het classificeren van appendicitis tijdens laparoscopie en het al dan niet voorschrijven van antibiotica na de operatie. We voerden een cross-sectionele studie uit waarin 80 chirurgen en chirurgen-in-opleiding laparoscopie fragmenten hebben bekeken en geclassificeerd. De interobserver overeenkomst was minimaal voor zowel de classificatie in simpel en complex, als ook het besluit om wel of niet antibiotica voor te schrijven na de operatie. De overeenkomst was slechts enigszins beter geweest, wanneer een vaste definitie van complexe appendicitis zou zijn toegepast. De meningen verschilden betreffende de indicatie voor postoperatieve antibiotica in het geval van een appendicitis met gelokaliseerde pus en een gangreneuze ongeperforeerde appendicitis. En de duur van voorschrijven varieerde tussen de 3 en 5 dagen. De resultaten suggereren dat de huidige intraoperatieve classificatie onbetrouwbaar is en, in het verlengde daarvan, het voorschrijven van postoperatief antibiotica sterk varieert.

Het thema van variatie in intraoperatieve classificatie en het voorschrijven van postoperatieve antibiotica hebben we verder uitgediept in **hoofdstuk 4.** Via een online survey onderzoek onder 137 internationale chirurgen verspreid door Europa, hebben we in kaart gebracht wat de huidige gebruiken zijn in de classificatie en het postoperatief

antibioticabeleid. De meningen ten aanzien van het beleid voor appendicitis verschilden aanzienlijk, met name voor appendicitis in aanwezigheid van gelokaliseerde pus, gangreneuze appendicitis en appendicitis met een iatrogene ruptuur. De meest gehanteerde duur van postoperatief antibiotica was gelijk verdeeld over minder dan drie, drie, vijf en zeven dagen. De meeste respondenten gave aan dat een combinatie van intraveneus en oraal het meest gebruikelijk was, maar 28% indiceerde dat een compleet intraveneus schema standaard praktijk was. De bevindingen in deze studie benadrukken te meer hoe variabel de behandeling van (complexe) appendicitis momenteel is.

In navolging van hoofdstuk 3 en 4 besloten we om patiënten met gangreneuze ongeperforeerde appendicitis onder de loep te leggen. In een prospectieve Nederlandse snapshot studie van 1863 patiënten, gepresenteerd in **hoofdstuk 5**, hebben we het risico op postoperatieve infectieuze complicaties (intraabdominaal abces of wondinfectie) per type appendicitis. Binnen de totale populatie werden er 181 (9.7%) geclassificeerd als gangreneuze, ongeperforeerde appendicitis. In deze studie werd 75% van hen postoperatieve antibiotica toegediend. Het postoperatieve risico op infectieuze complicaties lag voor deze groep significant hoger in vergelijking tot patiënten met flegmoneuze ontsteking, maar gangreneuze ziekte bleek geen onafhankelijke voorspeller in multivariabele analyse.

DEEL III – POSTOPERATIEVE LIGDUUR VOOR SIMPELE APPENDICITIS

In de volgende hoofdstukken hebben we ons gericht op efficiëntie in de behandeling van patiënten met simpele appendicitis (appendicitis zonder necrose, perforatie of abces). **Hoofdstuk 6** geeft een overzicht van de beschikbare literatuur over appendectomie in dagbehandeling voor simpele acute appendicitis. De resultaten van 17 vergelijkende en 8 niet-vergelijkende studies tonen dat appendectomie in dagbehandeling niet geassocieerd is met een verhoogd risico op heropname, ongepland ziekenhuisbezoek of postoperatieve complicatie. De meeste studies rapporteerden alleen over dagbehandeling na een laparoscopische ingreep. Vanwege klinische en methodologische heterogeniteit tussen de studies, was het bundelen van data in meta-analyse maar beperkt mogelijk. We concludeerden dat de huidige literatuur erop duidt dat appendectomie in dagbehandeling haalbaar en veilig is in een groot deel van de pediatrische en volwassen populatie.

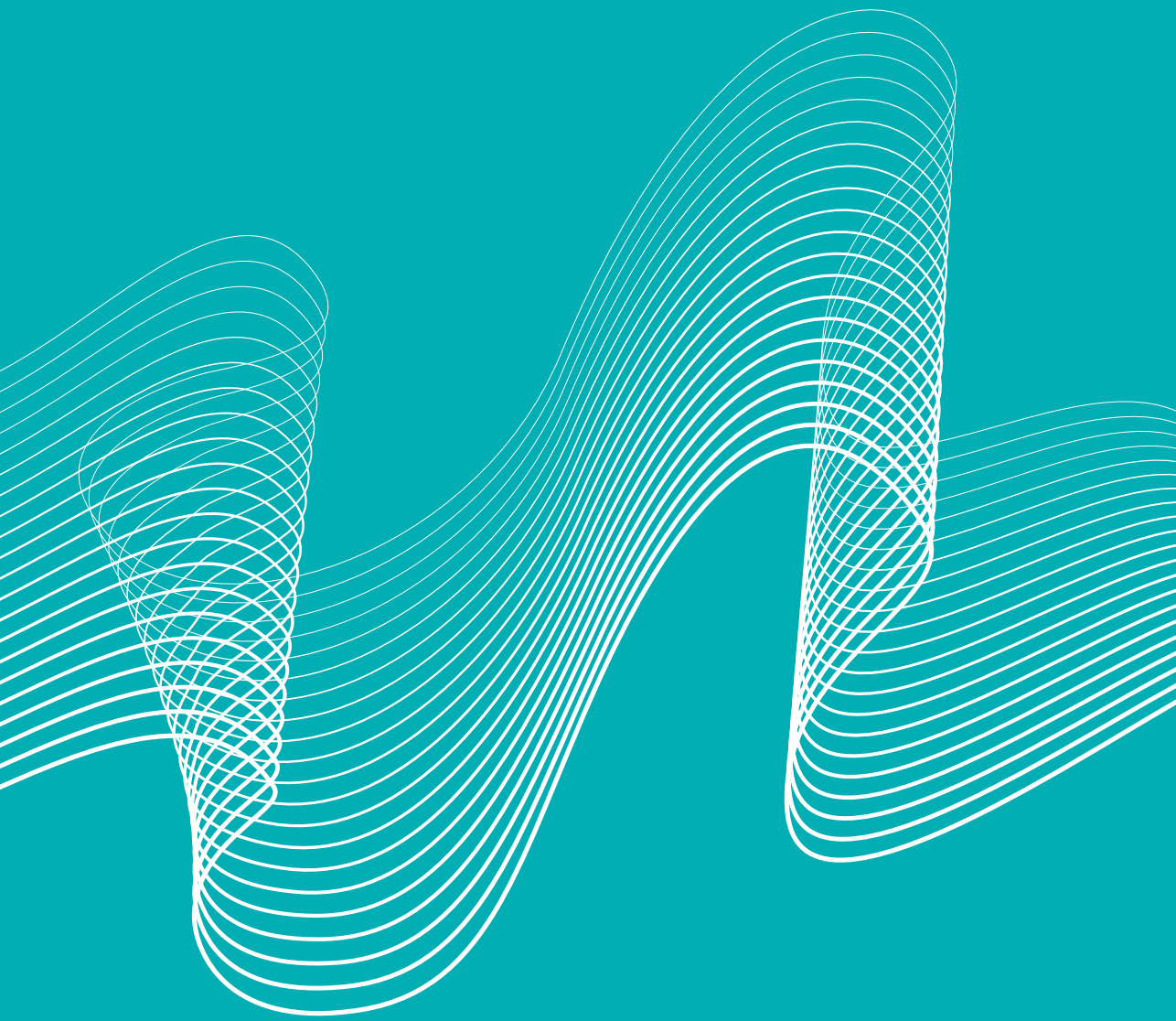
DEEL IV – POSTOPERATIEVE ANTIBIOTICA VOOR COMPLEXE APPENDICITIS

Zoals beschreven in deel II, bestaat er een aanzienlijke variatie wat betreft het postoperatief beleid voor patiënten met complexe appendicitis. Om hier op in te

grijpen hebben we een gerandomiseerde studie ontworpen om de adequate duur van postoperatieve antibiotica te bepalen. **Hoofdstuk 7** vat het studieprotocol van de APPIC trial samen, een pragmatische non-inferioriteitsstudie waarin twee dagen postoperatieve intraveneuze antibiotica wordt vergeleken met vijf dagen. Geschikt voor deelname waren patiënten van 8 jaar of ouder, die een acute appendectomie ondergingen en gedurende de operatie werden gediagnosticeerd met complexe appendicitis. Patiënten die zwanger of immuungecompromitteerd waren, of een contra-indicatie hadden voor de studie medicatie (cefuroxim of ceftriaxon gecombineerd met metronidazol) werden geëxcludeerd. Geïncludeerde patiënten zouden 1:1 gerandomiseerd worden naar twee of vijf dagen intraveneuze antibiotica. Het primair eindpunt was een samengesteld eindpunt van intraabdominaal abces, wondinfectie of overlijden binnen 90 dagen na appendectomie. Secundaire eindpunten waren opnameduur, reïnterventies, heropnames, alle postoperatieve complicaties en kosteneffectiviteit. De non-inferioriteitsmarge voor het absolute risicoverschil in primair eindpunt was 7.5%. En zowel per-protocol als intention-to-treat analyses zouden worden uitgevoerd.

Vervolgens worden in **hoofdstuk 8** de primaire resultaten van de APPIC trial beschreven. Non-inferioriteit van twee dagen werd aangetoond door het gecorrigeerde absolute risicoverschil in primair eindpunt van 2.0%, ten faveure van de vijf-dagen arm (95% betrouwbaarheidsinterval -1.6% tot 5.6%). Het primair eindpunt werd geobserveerd in 51/502 (10.2%) patiënten in de twee-dagen arm en 41/503 (8.2%) patiënten in de vijf-dagen arm. De mediane duur van antibiotica was 2.0 dagen (interquartile range (IQR) 2.0 tot 2.3) *vs.* 5.0 dagen (IQR 4.7 tot 5.0), $P < 0.001$. Het voorkomen van postoperatieve complicaties en reïnterventies was vergelijkbaar tussen beide studie armen. In de twee-dagen arm, ervaarden minder patiënten bijwerkingen van antibiotica (45 (9%) *vs.* 112 (22%), $P < 0.001$). Heropname kwam frequenter voor in de twee-dagen arm (58 (11.6%) vs. 29 (5.8%), $P = 0.001$). De resultaten in de per-protocol en de intention-to-treat analyses waren vergelijkbaar. Deze bevindingen bevestigen dat een significante reductie in antibiotica gebruik en opnameduur kan worden bereikt. De conclusies kunnen niet direct worden geëxtrapoleerd naar patiënten die een open ingreep ondergaan, gezien het geringe aantal patiënten met een open ingreep in de trial.

Nadere analyse van directe ziekenhuiskosten evenals maatschappelijke kosten, in **hoofdstuk 9**, liet zien dat 2 dagen antibiotica ook kosteneffectief is ten opzichte van 5 dagen. Het staken van antibioticagebruik na 2 postoperatieve dagen biedt statistisch significante besparing in de totale maatschappelijke kosten. Deze besparing komt met name voort uit kortere opnameduur. Het verder terugbrengen van postoperatief antibioticagebruik en ligduur in het ziekenhuis kan in de toekomst de druk op ziekenhuisbedden en kosten in de gezondheidszorg verminderen.



APPENDICES

LIST OF PUBLICATIONS

CONTRIBUTING AUTHORS

ACKNOWLEDGMENTS

PHD PORTFOLIO

ABOUT THE AUTHOR

LIST OF PUBLICATIONS

This thesis

2023. **EML de Wijkerslooth**, EG Boerma, CC van Rossem, J van Rosmalen, CIM Baeten *et al*. Cost analysis of 2 days versus 5 days of postoperative antibiotics for complex appendicitis. Submitted.

2023. **EML de Wijkerslooth**, EG Boerma, CC van Rossem, J van Rosmalen, CIM Baeten *et al*. 2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicenter, noninferiority randomised trial. The Lancet. doi: 10.1016/S0140-6736(22)02588-0

2021. **EML de Wijkerslooth**, JM Bakas, J van Rosmalen, AL van den Boom, BPL Wijnhoven. Same-day discharge after appendectomy for acute appendicitis: a systematic review and meta-analysis. Int J Colorectal Dis. doi: 10.1007/s00384-021-03872-3

2019. **EML de Wijkerslooth**, J de Jonge, AL van den Boom, AAW van Geloven, WA Bemelman, BPL Wijnhoven, CC van Rossem. Postoperative outcomes of patients with nonperforated gangrenous appendicitis: a national multicenter prospective cohort analysis. Dis Colon Rectum. doi: 10.1097/DCR.0000000000001466

2019. **EML de Wijkerslooth**, AL van den Boom, BPL Wijnhoven. Disease burden of appendicitis and surgery: a population-based retrospective cohort study. Surg End. doi: 10.1007/s00464-019-06738-6

2018. **EML de Wijkerslooth**, AL van den Boom, BPL Wijnhoven. Variation in classification and postoperative management of complex appendicitis: a European survey. World J Surg. doi: 10.1007/s00268-018-4806-4

2018. AL van den Boom, **EML de Wijkerslooth**, J van Rosmalen, FH Beverdam, EG Boerma *et al*. Two versus five days of antibiotics after appendectomy for complex acute appendicitis (APPIC): study protocol for a randomized controlled trial. Trials. doi: 10.1186/s13063-018-2629-0

2018. AL van den Boom, **EML de Wijkerslooth**, KAL Mauff, I Dawson, CC van Rossem, BR Toorenvliet, BPL Wijnhoven. Interobserver variability in the classification of appendicitis during laparoscopy. Br J Surg. doi: 10.1002/bjs.10837

Other publications

2022. AL van den Boom, **EML de Wijkerslooth**, LJX Giesen, CC van Rossem, BR Toorenvliet, BPL Wijnhoven. Postoperative antibiotics and time to reach discharge criteria after appendectomy for complex appendicitis. Dig Surg. doi: 10.1159/000526790

2022. D Huijgen, **EML de Wijkerslooth**, JC Janssen, FH Beverdam, EG Boerma *et al*. Multicenter cohort study on the presentation and treatment of acute appendicitis during the COVID-19 pandemic. Int J Colorectal Dis. doi: 10.1007/s00384-022-04137-3

2022. VP Bastiaenen, JLP van Vliet, EA de Savornin Lohman, BJGA Corten, J de Jonge *et al*. for the **Dutch Snapshot Research Group**. Safety and economic analysis of selective histopathology following cholecystectomy: multicenter, prospective, cross-sectional FANCY study. Br J Surg. doi: 10.1093/bjs/znab469

2021. VP Bastiaenen, J de Jonge, BJGA Corten, EA de Savornin Lohman, AC Kraima *et al*. for the **Dutch Snapshot Research Group**. Oncological Safety and Potential Cost Savings of Routine Versus Selective Histopathological Examination Following Appendectomy: Results of the Multicenter, Prospective, Cross-Sectional FANCY Study. Ann Surg. doi: 10.1097/SLA.0000000000005228

2019. AL van den Boom, **EML de Wijkerslooth**, BPL Wijnhoven. Systematic review and meta-analysis of postoperative antibiotics for patients with a complex appendicitis. Dig Surg. doi: 10.1159/000497482

2017. AL van den Boom, **EML de Wijkerslooth**, BPL Wijnhoven. Minder lang antibiotica voor complexe appendicitis? Ned Tijdschr Geneeskd.

2016. J Straatman, **E de Wijkerslooth de Weerdesteijn**, JB Tuynman, MA Cuesta, DL van der Peet. C-reactive protein as a marker for postoperative complications. Are there differences in emergency and elective colorectal surgery? Dis Colon Rectum. doi: 10.1097/DCR.0000000000000506

CONTRIBUTING AUTHORS

J.M. (Jay) Bakas
C.I.M. (Coen) Baeten
W.H. (Willem) Bemelman
F.H. (Frédérique) Beverdam
E.G. (Evert-Jan) Boerma
M.A. (Marja) Boermeester
A.L. (Anne Loes) van den Boom
J.W.A.M. (Anne-Claire) Bosmans
T.A. (Thijs) Burghgraef
E.C.J. (Esther) Consten
I. (Imro) Dawson
J.W.T. (Jan Willem) Dekker
M. (Marloes) Emous
A.A.W. (Nanette) van Geloven
A.F. (Anton) Gijsen
P.M.Y.H. (Peter) Go
L.A. (Luc) Heijnen
S.A. (Sander) Huisman
A.P. (An) Jairam
D. (Dayanara) Jean Pierre
J. (Joske) de Jonge
J.H. (Jurian) Kloeze
M.A. (Marc) Koopmanschap
H.R. (Hester) Langeveld
M.D.P. (Misha) Luyer
K.A.L. (Katya) Mauff
D.C. (Damian) Melles
J.W. (Johan) Mouton
A.P.T. (Stijn) van der Ploeg
F.B. (Floris) Poelmann
J.E.H. (Jeroen) Ponten
J. (Joost) van Rosmalen
C.C. (Charles) van Rossem
W.H. (Hermien) Schreurs
J. (Joël) Shapiro
P. (Pascal) Steenvoorde
B.R. (Boudewijn) Toorenvliet
J. (Joost) Verhelst
M. (Maarten) Vermaas
H.P. (Hendt) Versteegh
R.M.H. (Rene) Wijnen
B.P.L. (Bas) Wijnhoven

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PHD PORTFOLIO

Name PhD student	Elisabeth M. L. de Wijkerslooth
Erasmus MC department	Surgery
PhD period	October 2016 – October 2022
Promotor	Prof. dr. B.P.L. Wijnhoven

Courses

		ECTS
2016	Research integrity, Erasmus MC	0.3
2016	BROK, NFU Academy	1.5
2017	CPO (Course Patient Oriented research), Molmed	0.3
2017	Basic Introduction Course on SPSS, Molmed	1.0
2017	Survival Analysis Course, Molmed	0.5
2017	Biostatistical Methods I, NIHES	5.7
2017	Biomedical English Writing Course, Molmed	2.0
2018	Workshop 'Coachen van toekomstige Erasmusartsen Basis'	0.3
2018	Course on GraphPad Prism, Molmed	0.3
2018	Workshop 'How to Write a Clinical Paper', BJS	1.0
2018	Course on R, Molmed	1.8
2019	Workshop on Microsoft Excel 2010: Advanced, Molmed	0.3

Oral presentations

2018,2019	Erasmus MC Wetenschapsdag Heelkunde, R'dam, NL	4.0
2018, 2019	NVGE Digestive Disease Days, Veldhoven, NL	4.0
2018	NVvH Najaarsdag, Ede, NL	2.0
2019	NVvH Chirurgendagen, Veldhoven, NL	2.0
2019	ACS Clinical Congress, San Francisco, USA (2x)	2.0
2022	ZonMw 'Goed Gebruik Geneesmiddelen', Den Bosch, NL	2.0
2022	NVvH Chirurgendagen, Den Haag, NL	2.0
2022	Digestive Disease Days, Veldhoven, NL	2.0

Poster presentations

2018	SIS-E Congress, Athens, Greece	0.5
2018	European Colorectal Congress, St. Gallen, Switzerland	0.5

Conferences and seminars

2016,2018	NVvH Najaarsdag, Ede, NL	1.0
2017-2019	Erasmus MC Wetenschapsdag Heelkunde, R'dam, NL	1.5
2017	ZonMw Goed Gebruik Geneesmiddelen, A'dam, NL	0.5
2017-2019	NVvH Chirurgendagen, Veldhoven, NL	3.0
2018	Appendix Symposium, Delft, NL	0.5
2018,2019	NVGE Digestive Disease Days, Veldhoven, NL	1.0
2018	SIS-E Congress, Athens, Greece	1.5
2018	European Colorectal Congress, St. Gallen, Switzerland	1.5
2019	ACS Clinical Congress, San Francisco, USA	1.5
2022	ZonMw 'Goed Gebruik Geneesmiddelen', Den Bosch, NL	0.5
2022	NVvH Chirurgendagen, Den Haag, NL	1.0
2022	Digestive Disease Days, Veldhoven, NL	0.5

Teaching

2016-2018	Examination Basic Life Support	1.0
2018-2021	Coaching bachelor students	1.0
2018-2019	Supervision master thesis student J.M. Bakas	2.0
2020-2021	Supervision master thesis student D. Huijgen	2.0
2020-2021	Supervision elective research student J. Janssen	1.0

Awards

2022	Best Abstract Award, NVvH Chirurgendagen, Veldhoven, NL	-
2022	Best Abstract Award, Digestive Disease Days, Veldhoven, NL	-

Other

2018-2022	Peer reviewer for scientific journals British Journal of Surgery BMC Surgery International Journal of General Medicine Chronic Wound Care Management and Research Frontiers in Pediatrics	4.0

ABOUT THE AUTHOR

Elisabeth M. L. de Wijkerslooth de Weerdesteijn was born on April 22, 1991, in Utrecht. After graduation from secondary school in 2009 (Christelijk Gymnasium Utrecht), she moved to Maastricht to commence medical school. Between the second and third year of her bachelor studies she took a year to apply herself as a fulltime boardmember of her student association (SV Circumflex). During her clinical rotations she developed an interest in scientific research. For her master thesis she conducted research in the field of colorectal surgery at the VU medical center. Subsequently, during her senior internship at the surgical department of the Zuyderland MC, she participated in a research project concerning palliative esophageal surgery. She decided to go to Rotterdam to fulfill her final internship at the surgical department of the Maasstad Ziekenhuis, at the time unaware that she would be bound to this city for many years to come. After obtaining her medical degree in September 2016, Elisabeth started in the PhD programme that ultimately resulted in this thesis. During her PhD period, she gained clinical experience as a surgical resident not-in-training at the IJsselland Ziekenhuis (2019-2020), the Ikazia Ziekenhuis (2021) and the Spaarne Gasthuis (2022). After a quick dip in cosmetic medicine, Elisabeth continues her medical career as a radiologist-in-training at the Maasstad Ziekenhuis in Rotterdam from April 2023 onwards.