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Perioperative Antibiotic Therapy and Postoperative Infectious Complications in Appendicitis

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List of Abbreviations

ACTUAA	Appendectomy versus conservative treatment with antibiotics for patients with uncomplicated acute appendicitis
AKI	Acute kidney injury
APPAC	Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis
ASA	American Society of Anesthesiologists
AUC	Area under the curve
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (German Association of Scientific Medical Societies)
BMI	Body mass index
CA	Complicated appendicitis
CODA	Comparing Outcomes of Drugs & Appendectomy
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
EHR	Electronic healthcare record
ER	Emergency room
GI	Gastrointestinal
ID	Identifier
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
MNAR	Missing not at random
MDRGN	Multidrug resistant Gram-negative bacteria
MRR	Medical record review
MRI	Magnetic resonance imaging
NA	Negative appendectomy
NC	No category regarding the severity of appendicitis
OECD	Organisation for Economic Co-operation and Development
OPS	Operation and Procedure Classification System
PBP5	Penicillin-binding protein 5
POSAW	Prospective Observational Study on Acute Appendicitis Worldwide
RCR	Retrospective chart review
ROC	Receiver operator characteristic
SD	Standard deviation
spp.	species pluralis (multiple species)
UA	Uncomplicated appendicitis
WSES	World Society for Emergency Surgery
VRE	Vancomycin-resistant Enterococci

1 Introduction

The aim of this retrospective study was to provide an overview of perioperative antibiotic therapy in appendicitis and examine the frequency and severity of postoperative complications following appendectomies. To achieve this objective, an analysis of electronic healthcare records (EHRs) from patients who underwent surgery at a German university hospital (Tübingen University Hospital) between April 2015 and March 2021 was performed. The findings offer insights into the complications that may occur after appendectomies. By establishing associations with microbiological and laboratory analyses, these results can improve informed decision-making to prevent infectious complications. Additionally, this study presents updated information on the loco-regional bacterial spectrum, enabling updated recommendations for empirical antibiotic therapy in accordance with antibiotic stewardship guidelines.

Acute appendicitis is a common condition with a lifetime prevalence of 8.6% in men and 6.7% in women (considering data from a large epidemiological study conducted in 1979-1984 in the USA) (Addiss et al., 1990). The disease is most common in the second and third decades of life but affects all age groups and is the most frequent cause of surgical interventions for cases of acute abdominal pain (Andersen et al., 2001). In Germany, the average incidence of appendectomies between 2005 and 2013 was 177/100,000 persons per year, according to data from the Organisation for Economic Co-operation and Development (OECD) (Ferris et al., 2017). A notable reduction in incidence of 1.21% per year was observed during this period. This finding aligns with a systematic review of international epidemiological studies, indicating a consistent decline in the number of appendectomies performed in Western countries since 1990 (Ferris et al., 2017). A large German epidemiological study by Stöß et al. (2021) showed that the incidence of appendectomies, which were coded as appendicitis, decreased from 139 to 123/100,000 persons per year between 2010 and 2017.

As early as 1886, Fitz published the first scientific paper using the term appendicitis. His work demonstrated the interrelation between this condition's clinical manifestations and pathological indicators for the first time. Furthermore, he advocated for adopting early surgical intervention as the gold standard treatment (Fitz, 1886; Sifri & Madoff, 2015). Since then, surgical therapy has undergone significant advancements fueled by technological progress, so today, the predominant surgical approach is minimally invasive. In recent years, there has been increasing research into conservative therapy for appendicitis, focusing on antibiotic therapy (Flum et al., 2020; Salminen et al., 2015; Salminen et al., 2018). Most of these studies refer to cases of so-called uncomplicated appendicitis, i.e., non-perforated cases of appendicitis without abscess or gangrene (for further details, see section 2.5).

Antibiotics also play a crucial role in surgical therapy, particularly in the prevention of postoperative complications. Selection of appropriate active agents for the prevention of antimicrobial resistance and enhancement of precision medicine is emphasized in guidelines for antibiotic stewardship. The following sections cover the clinical presentation of appendicitis and provide an overview of various hypotheses regarding its pathophysiology. Later, treatment options and associated prognoses will be presented.

1.1 Definition of Appendicitis

The appendix, formally known as the vermiform appendix, is a tubular extension of the coecum, ranging from 0.5 to 1 cm in thickness and approximately 10 cm in length. Similar to the coecum, the appendix is located within the peritoneal cavity and possesses its own mesentery, referred to as the mesoappendix (Lüllmann-Rauch & Asan, 2019). The appendix is typically located in retrocoecal or retrocolic positions. However, pelvic, paracoecal, parailealand postileal locations have also been described in the literature (Humes & Simpson, 2006).

The purpose, function, and role of the appendix still remain a matter of controversial scientific debate. In the literature, many authors consider the numerous occurrence of lymphoid follicles, which often present with large germinal centers (Lüllmann-Rauch & Asan, 2019) in the wall of the appendix, as suggestive of an immunological function of the appendix.

The term acute appendicitis describes the acute inflammation of the appendix. It is often associated with luminal obstruction and poly-microbial infection. Common complications include perforation, peritonitis and intraabdominal abscesses (Sifri & Madoff, 2015).

1.2 Pathophysiology of Acute Appendicitis

The pathophysiology of acute appendicitis has not yet been clearly investigated. Various theories, such as the pathophysiological cascade presented in Figure 1 (Sifri & Madoff, 2015), have been proposed as parts of the pathophysiology.

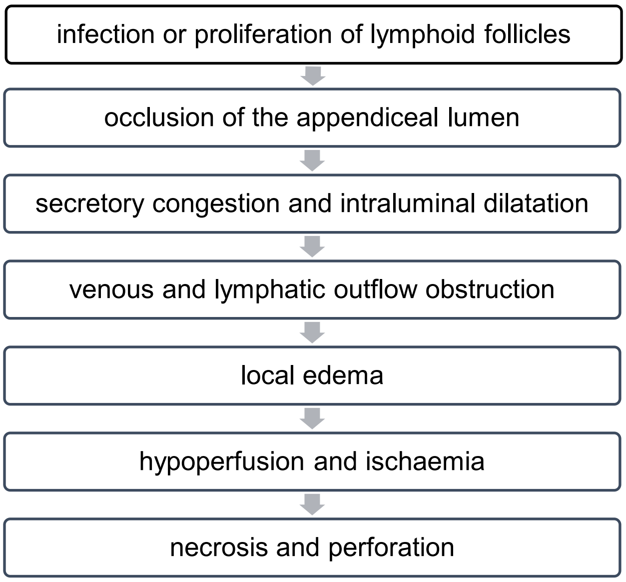

Figure 1. Pathophysiological Cascade Leading to Appendicitis (according to Sifri & Madoff, 2015).

Other authors have argued that obstruction may not be a cause but rather a consequence of inflammation (Arnbjornsson & Bengmark, 1983). The role of other mechanical obstructions to the outflow of the appendix, such as intraluminal fecaliths (also known as appendicoliths when located in the appendix), is also controversially discussed (Ramdass et al., 2015; Tran et al., 2021), as the presence of fecaliths has also been described in clinically and pathologically unremarkable appendices (Chang, 1981). Some authors assume that there are various pathomechanisms all leading to the invasion of the mucosa of the appendix by intraluminal bacteria (Carr, 2000).

In 1938 Altemeier demonstrated that polymicrobial infections from characteristic gastrointestinal pathogens can be considered the norm. Figure 2 presents the most common pathogens isolated from peritoneal fluid during appendectomies in a large international observational study by Sartelli et al. (2018).

aerobic gram negative bacteria	aerobic gram positive bacteria	anaerobic bacteria
•E. coli •Klebsiella pneumoniae •Klebsiella oxycota •Enterobacter spp. •Pseudomonas aeruginosa •Proteus spp.	•Enterococcus faecalis •Streptococcus spp. •Enterococcus faecium •Staphylococcus aureus	•Bacteroides spp. •Clostridium spp.

Figure 2. Commonly Isolated Pathogens from Peritoneal Fluid During Appendectomies (Sartelli et al., 2018).

In the aforementioned observational study by Sartelli et al. (2018), intraabdominal samples or swabs for microbiological diagnostics were taken in about 20% of appendectomies. Pathogens could be detected in approximately one-third of the cases with intraoperative sampling. Advanced appendicitis is usually accompanied by polymicrobial culture results with the most commonly isolated pathogens being Bacteroides fragilis and E. coli (Bennion et al., 1990).

1.3 Diagnosing Appendicitis

Symptoms of acute appendicitis include abdominal pain, fever, nausea, vomiting, loss of appetite, and constipation. Initially, there is typically diffuse, periumbilical, or epigastric visceral pain, which gradually shifts to right-sided somatic pain within 24 hours (Humes & Simpson, 2006). This somatic pain may be exacerbated by compression of the right lower quadrant. In some cases, such as an abnormally elongated appendix or during advanced pregnancy, the appendix can be positioned in diverse locations, leading to potential variations in clinical pain symptoms (Humes & Simpson, 2006).

The diagnosis of acute appendicitis is usually established through a detailed patient history and a physical examination (Humes & Simpson, 2006), including the examination of painful pressure points (known as appendicitis signs such as McBurney's point, Lanz's point) and performance of maneuvers that elicit pain (e.g. psoas sign, Blumberg's sign). Additionally, laboratory tests, urine analysis, and diagnostic imaging techniques such as sonography, magnetic resonance imaging, or computer tomography are employed to further assess the suspected diagnosis (Humes & Simpson, 2006).

The differential diagnosis for acute appendicitis encompasses a broad range of potential causes for acute abdominal pain, falling into different categories, including surgical, urological, gynecological, and medical diagnoses (Humes & Simpson, 2006). Moreover, it is imperative to consider and assess the possibility of regular pregnancy in women of reproductive age.

1.4 Classifying the Severity of Appendicitis

Complicated Appendicitis (CA) is a term widely applied in clinical practice to differentiate severe instances of appendicitis from less severe or uncomplicated appendicitis (UA) and negative appendectomies (NA). However, diverse definitions of UA and CA can be found in the existing literature. On the other hand, the term NA is consistently used to describe the surgical removal of a non-inflamed appendix. However, the methods used to assess the presence of inflammation (i.e., surgical or histopathological evaluation) vary among studies.

In the 2020 update of the World Society for Emergency Surgery (WSES) Jerusalem Guidelines, it is described that CA is not solely defined by the commonly used criterion of perforation. According to the guideline update, CA is also defined, depending on the study, by the severity of inflammation (non-perforated gangrenous appendicitis), as well as the presence of pus, purulent peritonitis, abscesses or appendicoliths (Di Saverio et al., 2020).

In the guideline for the therapy of acute appendicitis in adults published by the German Association of Scientific Medical Societies (AWMF), CA is defined as "any type of gangrenous appendicitis with or without perforation, with periappendicular phlegmon, free fluid, or perityphlitic abscess" (Andric et al., 2021). Table 1 provides an overview of the differences regarding the definition of CA and illustrates which factors are considered in the various definitions.

Table 1. Comparison of Definitions of Complicated Appendicitis.

Factors relevant for classification	Classification System	
	WSES*	AWMF**
Visible acute inflammation of the appendix	x	x
Phlegmon of the appendix		x
Gangrene of the appendix	x	x
Perforation of the appendix	x	x
Peritonitis	x	
Intraabdominal fluid		x
Abscess at the appendix	x	x
Intraabdominal pus	x	
Fecalith of the appendix (appendicolith)	x	

*WSES = World Society of Emergency Surgery; **AWMF = German Association of Scientific Medical Societies.
Note that crosses indicate whether a factor can potentially play a role in the definition of Complicated Appendicitis.

1.5 Therapeutic Strategies for Acute Appendicitis

Acute appendicitis represents a surgical emergency and, if left untreated, can lead to severe complications, including the spread of infection through the abdominal cavity, leading to peritonitis and potentially terminating in sepsis and death (Berry & Malt, 1984). Treatment can be divided into surgical and non-operative (mainly antibiotic) strategies.

1.5.1 Overview of Therapeutic Strategies

Surgical therapy has remained unchanged as the gold standard for the treatment of acute appendicitis since Fitz described the appendectomy in 1886. Surgical techniques have continuously evolved over the past decades, with the minimally invasive laparoscopic technique progressively replacing the traditional open approaches to appendectomy in industrial nations. Sahm et al. (2012) have reported several advantages of the laparoscopic approach compared to the open approach, including a lower rate of wound healing complications, shorter hospitalization and operation duration, and a lower mortality rate.

In addition to surgical intervention, adjunctive antibiotic therapy is typically given to patients. The optimal duration of antibiotic therapy and the selection of specific agents remain a topic of ongoing debate. However, the selection process is generally influenced by factors such as the severity of appendicitis (CA vs. UA), the local and regional microbial spectrum, and, if available, the individual's antibiotic susceptibility profile.

In recent years, the status of appendectomy as the therapeutic gold standard for appendicitis has been increasingly questioned and investigated to determine the cases in which non-operative management can be successful. These investigations have primarily focused on cases with mild disease manifestations rather than CA cases. Overall, the findings suggest that primary non-operative management in UA cases without the presence of appendicoliths represents a medically justifiable treatment option that should be discussed with patients despite relatively high recurrence rates (Doleman et al., 2024).

Given the availability of appropriate medical intervention, the outlook for appendicitis today demonstrates considerable improvement compared to the era preceding the widespread implementation of surgical or non-operative treatment modalities (Baum et al., 2019). The advantages, disadvantages, and prognoses for conservatively managed and surgically treated appendicitis will now be presented.

1.5.2 Non-Operative Management of Appendicitis

A conservative approach to the management of acute appendicitis primarily includes symptomatic and antibiotic therapy. The key advantage of conservative therapy lies in the avoidance of surgical risks. Additionally, it offers the benefit of cost reduction.

Notable among the large, randomized, controlled studies evaluating the effectiveness of conservative treatment with long-term follow-up results are the Finnish APPAC I Trial (Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis) conducted by Salminen et al. (2015), as well as the CODA Trial (Comparing Outcomes of Drugs & Appendectomy) carried out by the US-based CODA Collaborative (Davidson et al., 2021; Flum et al., 2020). Additionally, the Italian ACTUAA Trial (Appendectomy versus conservative treatment with antibiotics for patients with uncomplicated acute appendicitis) by Podda et al. (2021) is also noteworthy.

These studies have shown that primary antibiotic therapy for UA is a medically viable alternative to primary appendectomy for the majority of cases, implying that patients who undergo antibiotic therapy did not experience a recurrence of appendicitis during the follow-up period, or in cases where recurrence and subsequent appendectomy occurred, no more complications were observed compared to what would have been expected with primary appendectomy (Podda et al., 2021; Salminen et al., 2015). Delayed appendectomy rates were up to 49% at four years in the CODA Trial (Davidson et al., 2021) and 39.0% at seven years in the APPAC I Trial (Sippola et al., 2020).

Overall, complication rates are observed to be lower in conservative therapy compared to surgical therapy, as indicated by meta-analyses of randomized controlled trials that explore UA. The rates of complications stand at 12.6% versus 18.4% (Yang et al., 2019) and 11.6% versus 19.0% (Varadhan et al., 2012) for conservative therapy and surgical therapy, respectively. However, these meta-analyses do not provide a definitive consensus regarding the superior efficacy of conservative therapy. This is due to a lack of conclusive findings on whether the perceived benefits derived from selecting a conservative therapeutic approach, which aims to minimize the risks associated with surgery, outweigh the potential downsides associated with its reduced effectiveness in specific groups of patients or specific presentations of appendicitis. For example, increased complication rates were described for the non-operative management of patients with appendicoliths (Flum et al., 2020).

1.5.3 Surgical Therapy of Appendicitis

The central advantage of the surgical approach lies in its ability to provide a causal treatment for appendicitis. In cases of perforated appendicitis, source control through surgical debridement is particularly important, as non-operative measures show limited effectiveness in these instances. Another advantage of surgical therapy is the opportunity for histological examination of the appendix, which can contribute to the diagnosis of neoplasms or other rare conditions of the appendix. With the laparoscopic access technique, the diagnostic spectrum extends to large parts of the peritoneum, allowing for the detection of macroscopic abnormalities in other organs (e.g., cholecystitis, Meckel's diverticulum, adnexitis), of which some can potentially be treated during the procedure (Téoule et al., 2020).

The risk of postoperative complications following an appendectomy is relatively low compared to other visceral surgical procedures. In Germany, the rates of severe complications and mortality associated with appendectomies during the period from 2009 to 2015 were reported to be 2.1% and 0.2%, respectively, out of approximately 700,000 performed procedures (Baum et al., 2019). According to Téoule et al. (2020), early postoperative complications include wound infections, bleeding, abdominal wall abscesses, insufficient closure of the appendiceal stump, and intraabdominal abscesses. Late complications may include incisional hernias, stump appendicitis, or intraabdominal adhesions, leading to symptoms ranging from mild impairment of bowel movement to bowel obstruction (Téoule et al., 2020).

To mitigate the risk of infectious complications, it is common practice worldwide to administer additional antibiotic therapy to patients. Nonetheless, there is currently a lack of standardization regarding the specific type and duration of antibiotic treatment. The duration of antibiotic therapy and the selection of agents are based on disease-related and patient-related factors, such as patient age, clinical presentation and severity of disease, allergies, organ function status, the localization of a suspected infection, and the common pathogens associated with that localization. Additionally, the loco-regional spectrum of pathogens and, if available, an individual antibiogram are considered in treatment planning. For patients with uncomplicated appendicitis, only perioperative antimicrobial prophylaxis is recommended (Daskalakis et al., 2014). For patients with CA, a minimum period of 3-5 days of IV antibiotic therapy is typically recommended (Daskalakis et al., 2014). To provide an overview of frequently used agents, the results from the Prospective Observational Study on Acute Appendicitis Worldwide (POSAW) (Sartelli et al., 2018) are presented in Figure 3:

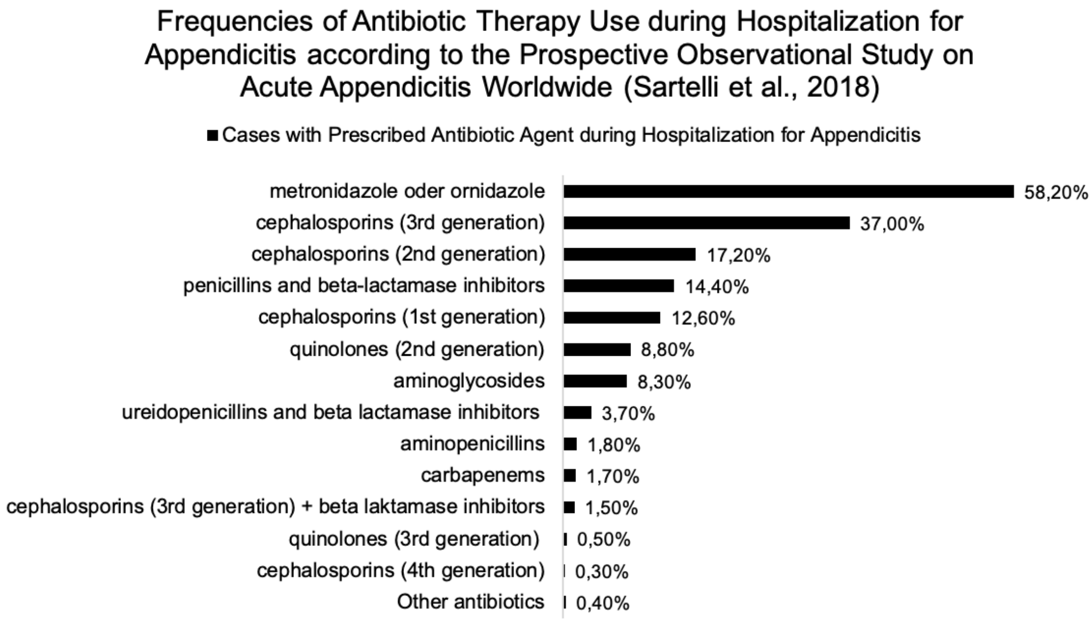

Figure 3. Frequencies of Antibiotic Therapy Use During Hospitalization for Appendicitis (Sartelli et al., 2018).

When making an informed decision regarding the choice between surgical and conservative therapies, it is essential to thoroughly evaluate the respective benefits and drawbacks of each approach. Ultimately, the treatment decision should be made through a shared decision-making process considering the patient's individual preferences.

1.6 Classification of Postoperative Complications

In the field of visceral surgery, accurate coding of complication severity is facilitated by the Dindo-Clavien classification, developed by Dindo, Demartines, and Clavien (Dindo et al., 2004). The system classifies complications into five grades, ranging from Grade I to Grade V. Table 2 corresponds to the original publication by Dindo et al. (2004).

Table 2. Dindo-Clavien Classification of Postoperative Complications.

Grade I	Any deviation from the typical postoperative course that does not necessitate surgical, endoscopic, or radiological intervention is considered in this category. Pharmacological treatments should be limited to antiemetics, antipyretics, analgesics, diuretics, and electrolytes. Physiotherapy and bedside wound management are permissible within this category.
Grade II	Complications requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and complete parenteral nutrition are also considered part of this category.
Grade III	Complications requiring surgical, endoscopic, or radiological intervention.
Grade IV	Life-threatening complication requiring intensive care unit management.
Grade V	Death of the patient.

This classification system established standards for communication regarding complications and serves as a reference point to help surgeons in assessing the safety and efficacy of surgical procedures.

1.7 Research Objective for this Dissertation

Acute appendicitis is a prevalent and potentially life-threatening condition that occurs worldwide and can be cured through appropriate therapy. Due to the high incidence of this condition, appendectomies are frequently performed on a global scale. At the Tübingen University Hospital, appendectomies represent the most commonly performed general surgical procedure.

The therapy for acute appendicitis, however, lacks sufficient standardization. It is hypothesized that the prescription of antibiotics in some cases is unnecessarily prolonged and not specific enough. By utilizing an assessment that considers the course of the disease and considers the local and regional spectrum of pathogens, antibiotics could potentially be prescribed more specifically, leading to a reduction in their usage. This aligns with the global objective of preventing antibiotic resistance (worldwide level), serves the national economic interests of the German healthcare system (national level), and can mitigate the adverse effects of antibiotics on individual patients (individual level).

The objective of this dissertation can be divided into three parts:

1. Assessment of the current status quo of infectious complications following appendectomy at the Tübingen University Hospital in order to identify risk factors associated with such complications.
2. Evaluation of microbial profiles from intraabdominal bacterial cultures obtained during appendectomies to develop a recommendation for empiric antibiotic therapy based on locoregional microbial patterns.
3. Exploratory analysis of parameters obtained from patient demographics, patient history, and routine clinical and laboratory tests to evaluate their association with complicated appendicitis.

2 Material and Methods

This section outlines the manual data collection process from electronic healthcare records (EHRs), followed by case selection, as well as the subsequent data transformation. It also discusses the reasons for the chosen dual classification procedure for appendicitis severity, particularly in identifying CA, and addresses the strategies used for handling ambiguous data. Additionally, it describes the procedures selected for exploratory statistical analysis and the criteria for excluding cases from specific analyses. Ethics approval (Internal Ethics Approval Procedure Code: PV11644) was given by the university hospital's ethics committee before the patient data collection process was started.

2.1 Collection of Data

In order to address the research question, a retrospective analysis was conducted using patients' EHRs. The dataset consisted of all cases of patients aged 16 and above who underwent appendectomy, resection of the coecum, or ileocoecal resection at Tübingen University Hospital between April 2015 and March 2021 due to suspected acute appendicitis or another related condition.

The cases were identified using the corresponding Operation and Procedure Classification System (OPS) codes for appendectomy (5-470.0, 5-470.10, 5-470.11, 5-470.1x, 5-470.2), coecum resection (5-455.31, 5-455.35, 5-455.37), and ileocoecal resection (5-455.21, 5-455.25, 5-455.27, 5-455.2x).

The OPS codes, along with the case number and information regarding the patient's name, gender, date of birth, and date of surgery, were provided by a medical documentation specialist at the Tübingen University Hospital. The data was subsequently transformed into a table format and imported into the IBM SPSS Statistics program (Version: 28.0.0.0). An identification number (ID) was assigned to each case.

A manual query of the corresponding EHR was performed for each case number using the i.s.h. med software (SAP program of the Tübingen University Hospital). The following documents from the EHRs were utilized to construct the dataset that serves as the foundation for the analyses conducted in this study: patient's demographic data, admission reports, surgical operation reports, anesthesia protocols, medication charts, documentation of daily ward rounds including notes created by nurses and doctors, microbiology reports, histology reports, laboratory findings, discharge summaries, reports on pre-existing conditions, emergency re-visits, elective follow-up visits, and treatments in surgical departments at the University Hospital Tübingen before and after appendectomy, as well as reports on pre-existing conditions and treatments in non-surgical departments at the Tübingen University Hospital before and after appendectomy.

After creating the dataset, all duplicates and cases where the appendectomy took place outside the data collection period were excluded. For instance, some patients underwent primary appendectomy and were later subjected to ileocoecal resection due to complications, resulting in these individuals being listed twice with two different case numbers in the OPS code list. In such instances, the appendectomy was considered the primary operation, while the subsequent ileocoecal resection was classified as a complication, provided that it was performed as an emergency procedure and was related to appendicitis or appendectomy. Additionally, further cases that did not meet the inclusion criteria stated in section 2.2 were excluded.

Due to the retrospective design of this study, all utilized data correspond to regular EHRs that were collected for documentation purposes rather than specifically for use in this study. As the documentation in regular clinical practice is not entirely standardized, the data relevant to this study is not complete in all cases. The study protocol did not include contacting patients or surgeons by the author of this work to obtain missing data.

2.2 Inclusion Criteria for Patient Cases

The following inclusion criteria were utilized for the present study:

1. Surgical removal of the appendix as part of:
    a. Appendectomy (5-470.0, 5-470.10, 5-470.11, 5-470.1x, 5-470.2),
    b. Coecal resection (5-455.31, 5-455.35, 5-455.37), or
    c. Ileocoecal resection (5-455.21, 5-455.25, 5-455.27, 5-455.2x).
2. The procedure occurs within the timeframe of April 2015 and March 2021.
3. The procedure is performed by involving surgeons from the Department of General, Visceral- and Transplantation Surgery at Tübingen University Hospital.
4. The patients' age at the time of the procedure is at least 16 years.
5. The primary objective of the surgery is the non-elective management of a suspected intraabdominal inflammation.

Cases that did not meet the inclusion criteria for the study were excluded from all subsequent analyses. For a study cohort flow diagram, see Figure 4.

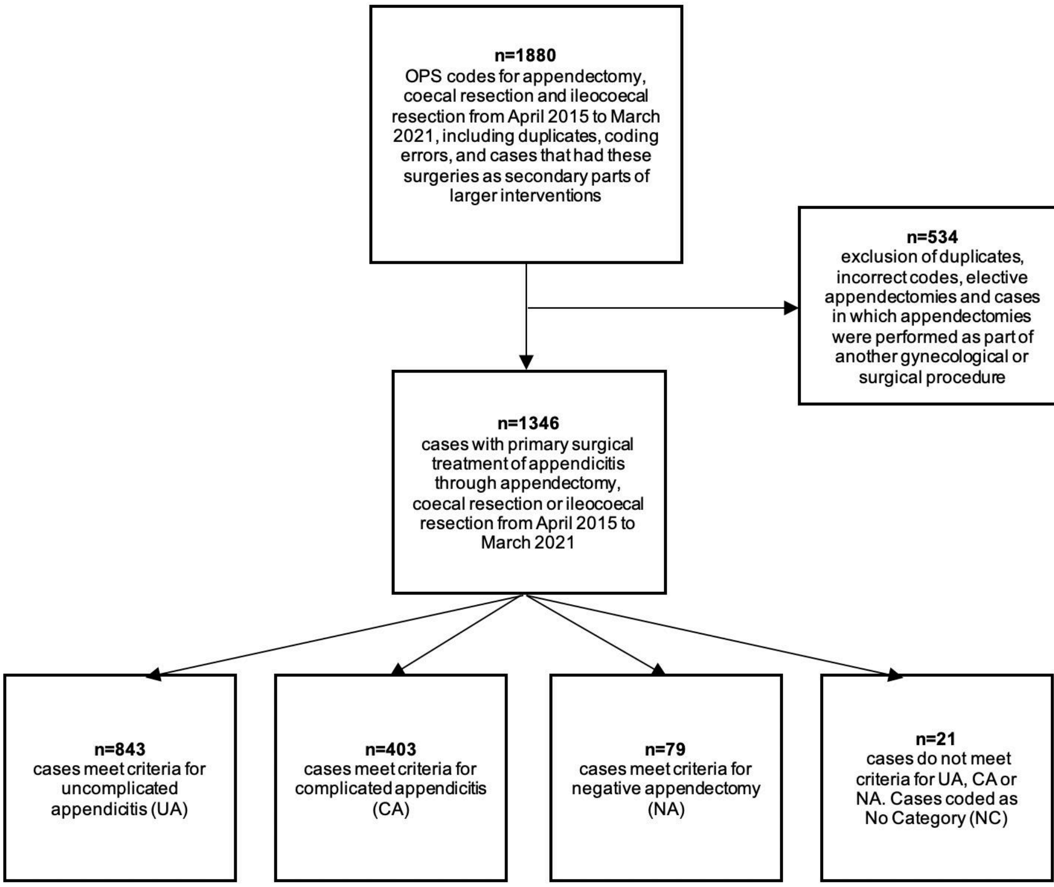

Figure 4. Study Cohort Flow Diagram.

2.3 Data Transformation

After transferring the relevant information from the EHRs into the table, additional variables such as length of hospital stay in days or Body Mass Index (BMI) obesity grades were derived from the raw data.

2.4 Missing Data and Ambiguous Information

As previously described, the relevant information for this study is partially incomplete across surgical, histopathological, radiological, laboratory, and other reports. In order to obtain a more comprehensive understanding of patient cases with incomplete data, information from various sources was combined and stored as new variables. This method was exclusively employed for categorical variables.

The following section presents variables that are primarily based on information from one source (e.g., the operative report of the appendectomy), supplemented exclusively with information from one additional source (e.g., histopathological findings report), in cases where the information was imprecise or missing.

2.4.1 Combination of Surgical and Histopathological Findings

Specific descriptions in the surgical operation reports regarding the inflammatory stage of appendicitis, such as “unremarkable appendix, no signs of inflammation”, “catarrhal appendicitis”, “phlegmonous appendicitis”, “inflamed appendix with gangrenous component”, or “gangrenous-necrotic disintegrating appendix” allowed for clear classification of a case into one of the following categories (levels of the classification variable): 1. No acute appendicitis, 2. Catarrhal appendicitis, 3. Phlegmonous appendicitis, or 4. Gangrenous appendicitis. In cases with mixed information, such as “ulcero-phlegmonous appendicitis with gangrenous elements at the tip of the appendix”, the highest degree of inflammation (gangrenous) was considered for coding.

However, when the surgical reports had unspecific phrasing regarding the inflammatory stage of appendicitis, categories 1 to 4 could not be assigned. Therefore, such cases were assigned to category 5: Acute appendicitis without specification of severity.

For cases where no surgical report was available in the EHR, category 6 was assigned: No information regarding the degree of inflammation of the appendix.

To complete the missing or unspecific data, a new variable was created using the information presented in surgical reports and combining it with histopathological reports. This new variable was a copy of the variable representing surgical diagnosis of the inflammatory stage of appendicitis. For cases with variable levels 5 and 6, the histopathological category of the inflammatory state of the appendix was considered and replaced the previous variable level. For example, if a case was initially coded as “Acute appendicitis without specification of severity” based on the surgical report but was described as “gangrenous appendicitis” in the histopathological report, the new variable level was 4 in the combined variable.

2.5 Classification of Appendicitis

As presented in section 1.4, various definitions of CA have been used in the literature. In this study, CA is defined by a macroscopically inflamed-appearing appendix plus one of the following: gangrene of the appendix, perforation of the appendix, or abscess at the appendix. The selection of criteria is based on the common elements found in the WSES Jerusalem Guideline 2020 Update and the current AWMF guideline, indicating their fundamental agreement.

Factors such as peritonitis, intraabdominal fluid, intraabdominal pus, and intraabdominal abscesses, although often present in severe cases of appendicitis, lack the necessary specificity for identifying cases of primary appendicitis. It is important to recognize that certain conditions, such as Crohn's disease-associated terminal ileitis or inflammation of the right adnexa, can extend to the parietal peritoneum of the appendix. Consequently, if such criteria were employed, these cases would be classified as CA, even though the inflammation observed at the appendix would be secondary to these underlying diseases, suggesting a different etiology. Therefore, these factors lack appendix-specificity and are not employed in this study for methodological rather than pathophysiological considerations.

The WSES guideline suggests the "presence of appendicolith" as a potential criterion for classifying CA. However, several studies have demonstrated numerous cases of appendicoliths without clinical symptoms of acute appendicitis or histopathological evidence of appendix inflammation (see section 1.2). Given this information, although it is specific regarding localization, we refrain from utilizing the "presence of appendicolith" as a criterion to classify cases as CA.

2.5.1 Definition of Case Categories

In the present study, the cases are divided into the categories of UA, CA, and NA. Cases for which classification is not possible are grouped as “no assigned category” (NC). The following section will detail the circumstances under which a case was coded as UA, CA, NA, or NC.

A case is assigned to the category of UA if the following conditions are met: inflammation of the appendix is present, as indicated by the diagnoses of catarrhal appendicitis, phlegmonous appendicitis, or acute appendicitis without specification of the severity of inflammation. Additionally, there should be no periappendicular abscess or no information available regarding the presence of an abscess. Furthermore, there should be no perforation of the appendix or no information available regarding perforation.

A case is assigned to the category of CA if the following conditions are met: inflammation of the appendix is present, as indicated by the diagnoses of catarrhal appendicitis, phlegmonous appendicitis, or acute appendicitis without specification of the severity of inflammation. Additionally, there should be a periappendicular abscess or perforation of the appendix. Alternatively, a sufficient diagnosis of gangrenous appendicitis with or without periappendicular abscess or perforation of the appendix is considered.

A case is assigned to the category of NA if the following conditions are met: there is no inflammation of the appendix, as indicated by the absence of acute appendicitis. Additionally, there should be no periappendicular abscess or no information available regarding the presence of an abscess. Furthermore, there should be no perforation of the appendix or no information available regarding perforation.

A case is assigned to the NC group if the following condition is met: the case meets the inclusion criteria of this study, but cannot be assigned to categories UA, CA, or NA. This occurs when a case is diagnosed with a periappendicular abscess or perforation of the appendix, but no acute appendicitis is described.

In this study, data collected from clinical practice, encompassing surgical and histopathological information, is analyzed. Reports from both disciplines are utilized to evaluate the presence of inflammation in the appendix, as described in section 2.4.1. Regarding additional factors such as appendix perforation or abscess, solely surgical documentation was relied on. This approach was preferred due to the potential impact of various processes involved in handling the appendix, such as preparation, resection, and transportation, on the histopathological assessment.

2.6 Classification of Postoperative Complications

In this study, postoperative complications are classified according to the Dindo-Clavien classification (see section 1.6) by Dindo et al. (2004). In addition to the Dindo-Clavien classification, this study also individually captures several common postoperative complications. Table 3 presents the definitions of these specifically considered postoperative complications:

Table 3. Specific Postoperative Complications.

Complication	Definition
Acute kidney injury	Defined by an explicit mention in the case documentation or a postoperative alteration in laboratory values or changes in urine output according to the KDIGO Acute Kidney Injury Guidelines (Khwaja, 2012).
Ileus	Defined by an explicit mention of ileus or bowel obstruction in the case documentation, or the absence of bowel movement for more than 72 hours postoperatively together with the IV or IM administration of prokinetics or the application of enemas at any time during the postoperative period.
Cutaneous and subcutaneous wound healing disorders	Defined by an explicit mention of such wound healing disorders regarding the surgical skin incisions in the case documentation.
Elevation of body temperature	Defined by a body temperature measured at least 24 hours postoperatively, exceeding 37.0 °C.
Insufficient intraabdominal suture or staple line at the surgical site	Defined by an explicit mention of confirmed insufficient intraabdominal suture or staple line (usually during a revision surgery) in the surgical case documentation.
Intraabdominal abscess	Defined by an explicit mention in the surgical or radiological case documentation, referring to the entire peritoneal cavity.
Peritonitis	Defined by an explicit mention of clinically suspected peritonitis or mention of confirmed peritonitis in the surgical case documentation.
Sepsis	Defined by an explicit mention of a septic condition in the case documentation.

Case documentations include medication charts, reports about daily ward rounds detailing comprehensive annotations from healthcare professionals, discharge summaries, as well as reports from urgent follow-up visits, readmissions, and revision procedures within a 90-day period after surgery at Tübingen University Hospital.

2.7 Statistical Analysis

Statistical analyses of the data were conducted using IBM SPSS Statistics (Version: 28.0.0.0), Python (Version 3.11.0) and R (Version 4.1.3) software programs. To ensure transparency in the analyses, syntax scripts were created for all performed data analyses.

Frequencies in tables are presented as column percentages unless otherwise specified or clearly indicated in the table. If no information is provided regarding the proportion of missing data for a variable, the percentage values correspond to the valid proportions within the available data. Missing values are generally excluded from statistical analyses but mentioned separately in tables.

A statistical significance level of 0.05 was chosen for hypothesis testing. Due to the exploratory nature of the data analysis in this retrospective non-experimental study, predominantly non-directional statistical tests are used unless otherwise specified or clearly indicated in the text. In general, χ^2 of independence tests are used for analyses of 2x2 contingency tables as omnibus tests. In cases of insufficient sample size within the groups, Fisher's exact test is used for the analysis of 2x2 contingency tables. The corresponding odds ratios are provided.

For independent multinomial variables, the multinomial χ^2 test is used as omnibus test. In cases of significant results in multinomial χ^2 tests, post-hoc statistical tests are applied. For each level of nominal-scale variables, non-directional two-proportion Z-tests are employed if $n > 30$ in both groups typically comparing cases of UA and CA. For two-proportion Z-tests pooled proportions are used for calculating the standard error. For cases with $n < 30$ in any of the groups, binomial tests assuming equal frequencies in both groups are employed. In analyses where there are insufficient valid cases to utilize the binomial or two-proportion Z-test, no statistical post-hoc test is conducted.

For continuous variables that are assumed to follow a normal distribution, non-directional t-tests are performed when comparing two groups, unless stated otherwise. Levene tests are conducted to assess homogeneity of variances, and if signs of unequal variances are present, corrected test statistics are presented. To ensure transparency in the analyses, the p-values are presented with additional information about the specific statistical test used to calculate each p-value. Error bars in diagrams represent 95% confidence intervals. Mean values are supplemented with the ± symbol, indicating the standard deviation.

As previously mentioned, the analyses are based on a retrospective, rather than experimental study, and primarily serve an exploratory purpose. Therefore, the corresponding p-values can only be considered as rough estimates and do not allow for clear inferential statistical statements. Consequently, a Bonferroni correction for alpha errors is not employed.

2.8 Exclusion of Cases for Specific Analyses

In order to conduct an in-depth analysis of preoperative symptoms and diagnostics (clinical examination and imaging), six cases were excluded from the study due to exhibiting a symptom duration exceeding 30 days. However, these cases were included in the remaining analyses.

Regarding the analysis of laboratory parameters, five cases were identified as outliers and subsequently excluded from the laboratory parameter analyses (see section 3.2.5 Preoperative Laboratory Diagnostics). However, these cases were not excluded from the remaining analyses. This includes two cases of chronic lymphocytic leukemia, one case of acute lymphocytic leukemia, one case of preoperative acute kidney injury at AKIN/KDIGO-AKI stage 3, and one case with preexisting dialysis-dependent chronic kidney disease at stage G5A3 with glomerulosclerosis and previous thrombotic microangiopathy.

3 Results

In this chapter, first, the patient cohort is described, and then results on the course of symptoms, diagnostic approach, surgical procedure, and histopathological diagnoses are presented. These sections will be followed by an analysis of laboratory parameters, perioperative and postoperative antibiotic therapy, and the local microbial spectrum in appendicitis cases. Finally, complications, emergency re-visits, re-operations, and the comparison of intraoperative and postoperative microbiological culture results will be discussed.

All following tables refer to all cases (n = 1346) that meet the inclusion criteria for this study (see section 2.2). Figure 5 provides an overview of the distribution of the four patient groups.

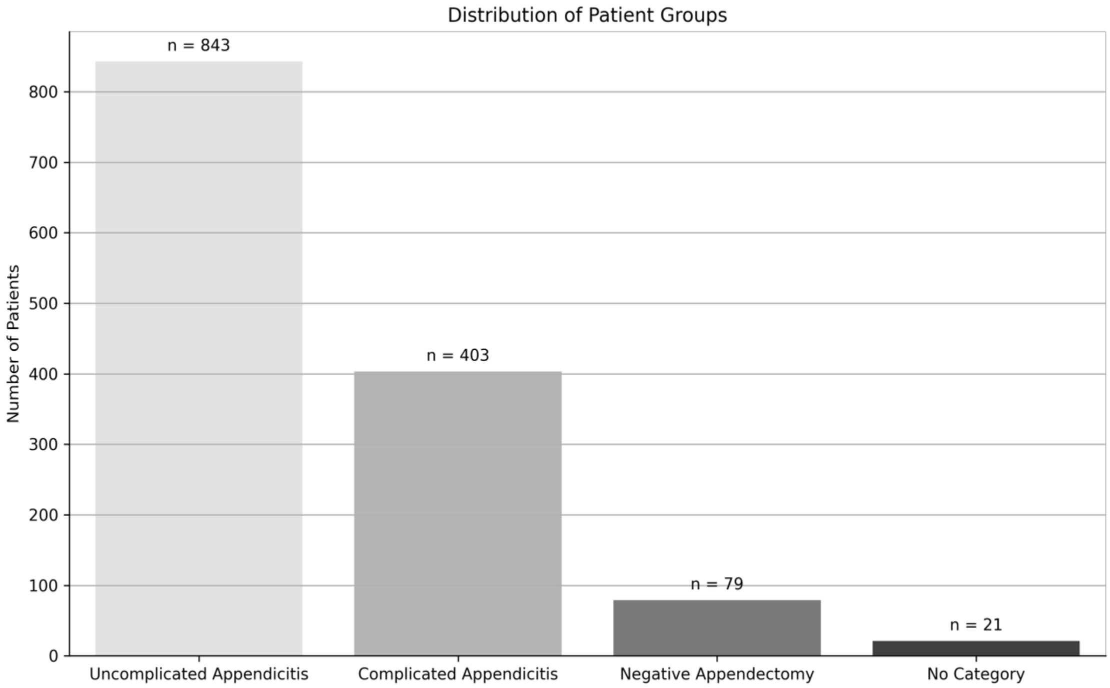

Figure 5. Distribution of Patient Groups.

Throughout the following chapter, the main focus lies on the differences between the UA and CA cases. An analysis of the NA and NC groups will be presented in selected sections.

3.1 Patient Characteristics

This section aims to highlight the differences in patient characteristics between patients with UA and those with CA by providing separate values for these two groups. When appropriate, statistical tests are conducted to provide a more accurate assessment of the differences between the groups.

3.1.1 Demographic Profile

Dividing the patient cohort into the subgroups UA and CA reveals that there are approximately twice as many cases of UA (n = 843) compared to CA (n = 403). The average Body Mass Index (BMI) is higher in the CA group (mean BMI ± SD; UA: 25.03 ± 5.02; CA: 26.50 ± 5.26). Despite a slightly higher proportion of male patients (UA: 51.6%; CA: 53.5%), the gender distribution is relatively balanced in both groups (Table 4).

Table 4. Epidemiological Data of the Study Population.

	Appendicitis Category		Statistic
	UA *(n=843)*	CA (*n=403)*	*p*
Number of Patients, *n* (%)*	843 (63.6%)	403 (30.4%)	-
Gender, (m : f)	435 : 408	215 : 188	.586$^{\chi}$
male, *n* (%)†	435 (51.6 %)	215 (53.3%)	-
female, *n* (%)†	408 (48.4 %)	188 (46.7%)	-
Age in years, Median (IQR)	28 (22-39)	52 (36-63)	<.001^{MWU}
Body Mass Index, Mean ± SD	25.03 ± 5.02	26.50 ± 5.26	<.001^{t}

Abbreviations: m = male; f = female; SD = standard deviation; IQR = interquartile range.
* Frequencies per row. Total sum is below 100% due to the exclusion of NA (n=79) and NC (n=21) cases.
† Frequencies per column. $^{\chi}$ Two-sided, non-directional χ^2 test. ^{MWU} Mann-Whitney U-Test. ^{t} Two-sided, non-directional t-test.

The median age differs significantly between the UA group and the overall older CA group (p < .001). This significant difference is visually represented in the following graph (Figure 6).

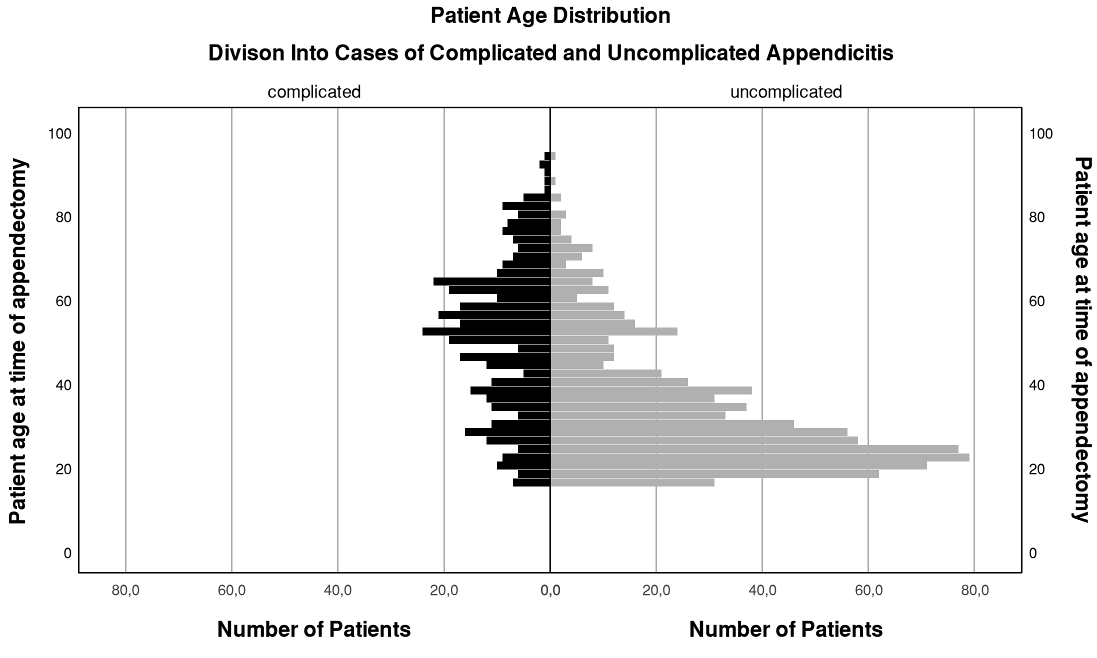

Figure 6. Patient Age Distribution by Type of Appendicitis.

It is visible that UA predominantly affects young patients, whereas CA is a condition which can be described as more uniformly distributed across all age ranges.

3.1.2 *Pre-existing Conditions, Medication Use and Prior Surgeries*

The patient population in the UA and CA groups exhibit significant differences in terms of pre-existing conditions. However, it is important to consider the significant age difference between UA and CA cases. Due to the relation of age and overall health status, no statistical tests are employed in this section.

The CA group demonstrates a higher proportion of oncological, nephrological, and cardiological diseases, as well as a greater prevalence of type 2 diabetes mellitus (Table 5). Consequently, the CA group has a higher percentage of individuals who regularly take medications (UA: 31.9%; CA: 50.6%).

Table 5. Pre-existing Conditions, Medication Use, and Prior Surgeries.

	UA *(n=843)*		CA (*n=403)*		Statistics
Pre-existing medical factor	*n*	*% of valid n*	*n*	*% of valid n*	*Odds Ratio (95% CI)*
Oncological condition	27	3.2%	44	10.9%	3.71 (2.26 – 6.09)
Chronic kidney disease	2	0.2%	11	2.7%	11.82 (2.61 – 53.56)
Type 1 diabetes mellitus	3	0.4%	4	1.0%	2.90 (0.65 – 13.02)
Type 2 diabetes mellitus	19	2.3%	20	5.0%	2.29 (1.21 – 4.34)
Heart failure	7	0.8%	11	2.7%	3.36 (1.29 – 8.72)
Intracardial device implant	5	0.6%	2	0.5%	0.84 (0.16 – 4.34)
Coagulopathy	10	1.2%	5	1.2%	1.05 (0.36 – 3.09)
Immunosupression	5	0.6%	1	0.2%	0.42 (0.05 – 3.56)
Sepsis	0	0.0%	1	0.2%	-
Liver cirrhosis	5	0.6%	6	1.5%	2.54 (0.77 – 8.36)
Regular medication use*	268	31.9%	203	50.6%	2.19 (1.72 – 2.80)
Anticoagulants	31	3.7%	50	12.4%	3.72 (2.33 – 5.92)
Immunosuppressants	13	1.5%	10	2.5%	1.64 (0.71 – 3.76)
Statins	15	1.8%	33	8.2%	4.94 (2.65 – 9.20)
History of abdominal surgery	146	17.3%	115	28.6%	1.91 (1.44 – 2.53)

* Including the regular use of oral contraceptives
Note that proportions are calculated relative to the number of cases for which the patient healthcare record provided information regarding a condition (*% of valid n*).

Considering the subgroup of women of childbearing age (15 - 44 years) no difference (Fisher's exact test: $p = .287$) in pregnancy frequency was detected between UA (1.2%, 4 out of 321 women) and CA (2.9%, 2 out of 68 women).

3.2 Preoperative Diagnostics

This section focuses on preoperative diagnostics, which consists of the following components: anamnesis of preoperative symptoms, resulting clinical suspected diagnosis, and, if necessary, additional radiological diagnostics, including sonography and cross-sectional imaging. Finally, preoperative laboratory diagnostics will be discussed.

For the purpose of a clear analysis, six cases (n = 1 UA, n = 3 CA, n = 1 NA, n = 1 NC) were excluded from the analysis of preoperative diagnostics (anamnestic course of preoperative symptoms, clinical suspected diagnosis, sonography, and cross-sectional imaging) due to a reported symptom duration of over 30 days. Furthermore, n = 47 cases (n = 25 UA, n = 17 CA, n = 3 NA, n = 2 NC) for which no information regarding preoperative symptom duration was available were also excluded from the aforementioned analyses. However, these cases were not excluded in the section discussing preoperative laboratory diagnostics, as it focuses on routinely collected measurements that are typically collected independent of the reported preoperative symptom duration.

3.2.1 Preoperative Course of Symptoms

The preoperative symptoms differed significantly between the groups regarding pain localization, as well as the presence of fever, nausea, digestive complaints, and dysuria. The median duration of symptoms was one day longer in the CA group (2 days, IQR = 1.0 – 3.5 days) compared to the UA group (1 day, IQR: 1.0 – 2.0 days; Mann-Whitney U test: $p < .001$).

3.2.1.1 Localization of Pain

A multinomial χ^2 test showed a significant difference ($\chi^2 = 37.62$, $p < .001$) in the distribution of localization of pain at presentation between cases of UA and CA. In both the UA and CA group, the right lower quadrant was the most common location of pain reported upon admission (UA: 79.4%; CA: 66.1%). The variability of pain locations was higher in the CA group.

Consequently, in the CA group, pain not restricted to the right lower abdomen, such as lower abdominal pain without specifying the side (UA: 8.2%; CA: 17.3%) and diffuse abdominal pain (UA: 3.3%; CA: 6.0%), were reported significantly more frequently. Reports of pain localization, such as left hemiabdomen, left lower abdomen, extraabdominal, or colicky, were rare, with frequencies of less than one percent in both groups.

3.2.1.2 Fever

During the admission and initial examination of patients, measurements of body temperature were not consistently recorded. As a result, the source of information regarding body temperature varied considerably in the admission reports. Some reports mentioned elevated body temperature reported by patients, while others referred to measurements taken by medical professionals. To address this issue, an additional category was introduced (see Table 6) to mark cases that showed both, systemic signs of infection, such as night sweats and chills, and also had documented body temperatures exceeding 38.5°C.

It is important to note that these categories do not represent distinct entities or commonly accepted severities of body temperature, and therefore, no comprehensive statistical test was employed in this analysis.

Table 6. Preoperative Course of Fever.

	UA *(n=817*)*			CA (*n=383**)		
Course of Fever	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Afebrile	427	52.3%	75.3%	132	34.47%	45.7%
Elevated body temperature[a]	105	13.0%	18.5%	90	23.5%	31.1%
Fever and chills[b]	35	4.3%	6.2%	67	17.5%	23.2%
Not specified	250	30.6%	-	94	24.5%	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.
[a] Elevated body temperature reported by the patient or medical professional.
[b] Temperature exceeding 38.5 °C, measured by medical professionals or reported by patients. Additionally, the patient reported experiencing night sweats and chills.

A descriptive examination of the data shows that a higher proportion of UA (75.3%) cases were found to be afebrile compared to cases of CA (45.7%). Additionally, a larger proportion of CA cases fell into the category of fever and chills, which is a more commonly accepted indication of systemic inflammation when compared to the other categories (UA: 6.2%; CA: 23.2%).

3.2.1.3 Vegetative Symptoms

Vegetative symptoms varied considerably between the groups. Symptoms of nausea and vomiting were significantly related to the severity of appendicitis ($\chi^2 = 21.59$, $p < .001$). In the CA group, a combination of vomiting and nausea, representing the most severe category for this variable (UA: 24.7%; CA: 35.5%; p = <.001), was significantly more frequent compared to UA. Digestive complaints were also significantly related to appendicitis severity ($\chi^2 = 49.58$, $p < .001$).

Diarrhea (UA: 18.5%; CA: 26.1%; p = .04), constipation (UA: 6.3%; CA: 14.2%; p < .001), as well as a mixed pattern of diarrhea and constipation (UA: 0.3%; CA: 3.0%; p < .001), were all more common in the CA group.

Table 7. Preoperative Course of Digestive Symptoms.

	UA (*n=817**)			CA (*n=383**)			Statistic
Digestive Symptom	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Nausea and vomiting	-	-	-	-	-	-	<.001$^{\chi}$
Not recalled	327	40.0%	42.3%	134	35.0%	37.8%	.148^{Z}
Nausea only	232	28.4%	30.0%	76	19.8%	21.4%	.003^{Z}
Vomiting only	23	2.8%	3.0%	19	5.0%	5.4%	.050^{Z}
Nausea and vomiting	191	24.7%	24.7%	126	32.9%	35.5%	<.001^{Z}
Not specified	44	5.4%	-	28	7.3%	-	-
Digestive complaints	-	-	-	-	-	-	<.001$^{\chi}$
Not recalled	559	68.4%	74.9%	191	49.9%	56.7%	<.001^{Z}
Softer stool or diarrhea	138	16.9%	18.5%	88	23.0%	26.1%	.004^{Z}
Harder stool or constipation	47	5.8%	6.3%	48	12.5%	14.2%	<.001^{Z}
Diarrhea and constipation	2	0.2%	0.3%	10	2.6%	3.0%	<.001^{Z}
Not specified	71	8.7%	-	46	12.0%	-	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.
$^{\chi}$ χ^2 test of independence
^{Z} Two-proportion Z-test

Presence of dysuria was documented in n = 25 cases of CA (9.8%) and n = 34 cases of UA (5.5%) during the medical history interview (Table 8). This corresponds to an odds ratio of 1.85 (95% CI: 1.09 – 3.23; χ^2 = 4.61, p = .032), suggesting a significantly higher proportion of dysuria cases in the CA group.

Table 8. Preoperative Course of Dysuric Symptoms.

	UA (*n=817**)			CA (*n=383**)		
Dysuric Symptoms	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Dysuria recalled	34	4.2%	5.5%	25	6.5%	9.8%
No recall of dysuria	583	71.4%	94.5%	230	60.1%	90.2%
Not specified	200	24.5%	-	128	33.4%	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.

The following section focuses on comparing the preoperatively clinically suspected diagnosis between the UA and CA groups, as well as the radiological diagnostic methods. It examines the commonly performed sonography and the less frequently used cross-sectional imaging. Finally, the preoperative laboratory diagnostics are discussed.

3.2.2 Preoperative Clinical Diagnosis

The study population consists of patients who underwent appendectomy, however, not all of them were initially diagnosed with appendicitis during clinical evaluation. Some cases presented with clinical symptoms and medical history that raised clinicians' suspicion of perforated or chronic appendicitis. In other instances, different conditions such as diverticulitis, cholecystitis, inflammatory bowel disease, ileus, or gynecological conditions were documented as the primary suspected diagnoses.

The results of the multinomial χ^2 test for independence were significant ($\chi^2 = 89.66$, $p < .001$), indicating an association between the groups (UA or CA) and the clinical diagnosis established before radiographic assessment. Table 9 presents the distribution of preclinical diagnoses for UA and CA.

Table 9. Preoperative Clinical Diagnosis.

Clinical Diagnosis	UA (*n=817**)			CA (*n=383**)			Statistic
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Acute appendicitis	759	92.9%	96.2%	297	77.5%	82.5%	<.001^Z
Perforated acute appendicitis	2	0.2%	0.3%	21	5.5%	5.8%	<.001^Z
Chronic appendicitis	1	0.1%	0.1%	0	0.0%	0.0%	.499^Z
Other than appendicitis	-	-	-	-	-	-	-
Tumour	1	0.1%	0.1%	3	0.8%	0.8%	.059^Z
Diverticulitis	3	0.4%	0.4%	8	2.1%	2.2%	.003^Z
Perforation of gastrointestinal tract or another intraabdominal organ	1	0.1%	0.1%	11	2.9%	3.1%	<.001^Z
Cholecystitis or choledocholithiasis	5	0.6%	0.6%	5	1.3%	1.4%	.201^Z
Bowel obstruction	2	0.2%	0.3%	6	1.6%	1.7%	.008^Z
Gynecological disease	2	0.2%	0.3%	1	0.3%	0.3%	.94^Z
Crohn's disease or ulcerative colitis	0	0.0%	0.0%	2	0.5%	0.6%	.036^Z
Other focus	13	1.6%	1.6%	6	1.6%	1.7%	.981^Z
Not specified	28	3.4%	-	23	6.0%	-	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.
^{Z} Two-proportion Z-test

During preoperative clinical diagnostics, the diagnosis of perforated acute appendicitis (UA: 0.3%; CA: 5.8%; $p < .001$) was more frequently observed in the CA group. The proportions of diagnoses other than appendicitis also varied between the UA and CA groups, with statistical analysis indicating significant differences for diverticulitis ($p = .003$), perforation of the gastrointestinal tract or other intraabdominal organs ($p < .001$), bowel obstruction ($p = .008$), and inflammatory bowel disease ($p = .036$). No statistically significant differences were found between the UA and CA groups with regard to the proportion of diagnoses of tumors, cholecystitis or choledocholithiasis, or gynecological diseases.

3.2.3 Preoperative Ultrasound Examination

The radiological baseline diagnostic method, specifically the sonographic examination, was performed more frequently in the UA group (95.7%) compared to the CA group (78.9%). In cases with a visible appendix, signs of appendicitis, as well as additional signs of covered (UA: 1.3%; CA: 7.6%; $p < .001$) or open perforation (UA: 0.1%; CA: 4.6%; $p < .001$), were more frequently described in the CA group (Table 10). For cases where the appendix was not visible during ultrasound examination, the presence of indirect signs of appendicitis also significantly differed between UA (12.9%) and CA cases (19.9%; $p = .004$).

Table 10. Preoperative Ultrasound Diagnostics.

	UA *(n=817*)*			CA (*n=383**)			Statistic
Ultrasound of the appendix	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Appendix visible	-	-	-	-	-	-	-
No signs of appendicitis	28	3.4%	3.6%	5	1.3%	1.7%	.098^Z
Indirect signs of appendicitis	432	52.9%	55.2%	116	30.3%	38.4%	<.001^Z
Non-perforated appendicitis	93	11.4%	11.9%	28	7.3%	9.3%	.219^Z
Perforated appendicitis	-	-	-	-	-	-	-
Covered perforation	10	1.2%	1.3%	23	6.0%	7.6%	<.001^Z
Open perforation	1	0.1%	0.1%	14	3.7%	4.6%	<.001^Z
Appendix not visible	-	-	-	-	-	-	-
No signs of appendicitis	117	14.3%	15.0%	56	14.6%	18.5%	.149^Z
Indirect signs of appendicitis	101	12.4%	12.9%	60	15.7%	19.9%	.004^Z
No ultrasound of appendix	35	4.3%	-	81	21.1%	-	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.

^Z Two-proportion Z-test

Taking into consideration only those cases in which the sonographic findings provided information regarding the presence of free intraabdominal fluid (total UA: n = 774, CA: n = 291, NA: n = 69, NC: n = 10), the following observations were made: In the UA group, free fluid was described in 36.2% of the cases, while in the CA group, it was observed in 46.4% of the cases under consideration. Therefore, the odds ratio for CA when free abdominal fluid was detected in the sonographic findings was statistically significant, with an OR = 1.53 (95% CI: 1.16 - 2.01; $\chi^2 = 8.86$; $p = .003$).

3.2.4 Preoperative Cross-Sectional Imaging

Cross-sectional imaging was not routinely performed in cases of suspected appendicitis, as in most instances, clinical diagnosis supplemented by ultrasound was sufficient for diagnosing acute appendicitis.

Cross-sectional imaging was performed in 354 cases (27.4%). This was significantly more frequent in the CA group compared to the UA group (UA: n = 117; CA: n = 207; NA: n = 18; NC: n = 12). The most common reasons for performing cross-sectional imaging in both groups were inconclusive findings from ultrasound (UA: 47.0%; CA: 40.1%), as well as obesity (UA: 12.0%; CA: 7.2%) or severe clinical symptoms and suspicion of bowel perforation (UA: 6.0%; CA: 23.2%). Additionally, cross-sectional imaging was chosen in some cases with suspicion of diagnoses other than acute appendicitis, such as urolithiasis (UA: 6.8%; CA: 1.4%) or diverticulitis (both groups: 3.4%). Radiological reports with specific information about the appendix are available for a total of n = 348 cases, accounting for 98.3% (UA: n = 114; CA: n = 205; NA: n = 17; NC: n = 12) of all cases with any preoperative cross-sectional imaging (Table 11).

The results of the multinomial χ^2 test for independence were significant ($\chi^2 = 86.40$, $p < .001$), indicating an association between the groups (UA or CA) and the preoperative cross-sectional findings.

In cases with a non-visible appendix, no significant differences regarding the frequency of indirect signs of appendicitis were observed. However, there were significant differences between the groups for cases with visible appendix. The diagnosis of appendicitis without any signs of perforation was significantly more common in the UA group (UA: 65.8%, CA: 28.3%). Consequently, diagnosis of appendicitis with covered (UA: 3.5%; CA: 36.1%) or open (UA: 0.0%, CA: 16.6%) perforation was significantly more frequent in the CA group compared to the UA group.

Table 11. Preoperative Cross-sectional Imaging.

Cross-section of the appendix	UA (*n=817**)			CA (*n=383**)			Statistic
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Appendix visible	-	-	-	-	-	-	-
No signs of appendicitis	1	0.1%	0.9%	2	0.5%	1.0%	$.93^{Z}$
Indirect signs of appendicitis	31	3.8%	27.2%	31	8.1%	15.1%	$.009^{Z}$
Non-perforated appendicitis	75	9.2%	65.8%	58	15.1%	28.3%	$<.001^{Z}$
Perforated appendicitis	-	-	-	-	-	-	-
Covered perforation	4	0.5%	3.5%	74	19.3%	36.1%	$<.001^{Z}$
Open perforation	0	0.0%	0.0%	34	8.9%	16.6%	$<.001^{Z}$
Appendix not visible	-	-	-	-	-	-	-
Indirect signs of appendicitis	0	0.0%	0.0%	5	1.3%	2.4%	$.09^{Z}$
No signs of appendicitis	3	0.4%	2.6%	1	0.3%	0.5%	$.10^{Z}$
Not specified	3	0.4%	-	2	0.5%	-	-
No cross-section of appendix	700	85.7%	-	176	46.0%	-	-

*Total cases after exclusion of n=6 cases with symptom duration of > 30 days, and n=47 cases with missing information regarding duration of preoperative symptoms.
^{Z} Two-proportion Z-test

Cross-sectional imaging reports provided information about the presence of free intraabdominal air in a total of n = 293 cases (UA: n = 100, CA: n = 169, NA: n = 15, NC: n = 9). In the UA group, free air was observed in 3.0% of the cases, whereas in the CA group, it was described in 28.4% of the cases examined. The odds ratio for CA with a positive imaging finding of free intraabdominal air was OR = 12.83 (95% CI: 3.88 - 42.44, $\chi^2 = 26.39$, p < .001).

3.2.5 Preoperative Laboratory Diagnostics

The following section presents analyses of preoperatively routinely examined laboratory parameters, including leukocyte- and platelet-count, as well as hemoglobin-, creatinine-, bilirubin- and c-reactive-protein (CRP) levels. As previously mentioned in section 2.8 (Exclusion of Cases for Specific Analyses), n = 5 cases were identified as outliers and were excluded from the subsequent analyses for better interpretability of the results.

Among the preoperatively routinely examined laboratory parameters (see Table 12), leukocyte counts showed a significantly higher mean value in the CA group (14,383 per µl) compared to the UA group (12,831 per µl; p < .001). No significant difference was found in hemoglobin levels between the two groups (UA: 14.11 g/dl, CA: 13.96 g/dl; p = .101) or in platelet counts (UA: 244, CA: 247; p = .482). CRP levels showed a significantly higher value in the CA group (11.54 mg/dl) compared to the UA group (3.46 mg/dl; p < .001).

The mean creatinine levels were significantly higher in the CA group (0.87 mg/dl) compared to the UA group (0.77 mg/dl; p < .001). Similarly, mean bilirubin levels were significantly higher in the CA group (1.18 mg/dl) compared to the UA group (1.00 mg/dl; p < .001). It is important to consider the significantly increased age in the CA group (see section 3.1.1) and the physiologic association of age and serum-creatinine levels.

Table 12. Preoperative Laboratory Diagnostics.

	Uncomplicated Appendicitis		Complicated Appendicitis		Statistic
Laboratory parameters*	*n*	*Mean (95% CI)*	*n*	*Mean (95% CI)*	*p*
Leukocytes [per µl]	842	12831 (12540 – 13121)	401	14383 (13925 – 14841)	<.001
Hemoglobin [g/dl]	842	14.11 (14.01 – 14.21)	401	13.96 (13.80 – 14.12)	.101
Platelets [1000/µl]	842	244 (240 – 248)	401	247 (240 – 255)	.482
Creatinine [mg/dl]	826	0.77 (0.76 – 0.80)	390	0.87 (0.83 – 0.90)	<.001
Bilirubin [mg/dl]	803	1.00 (0.95 – 1.05)	382	1.18 (1.10 – 1.26)	<.001
CRP [mg/dl]	839	3.46 (3.18 – 3.74)	399	11.54 (10.68 – 12.40)	<.001

Abbreviations: CI = Confidence interval
* Reference laboratory values: leukocytes (3800 - 10300 per µl); hemoglobin (4.0 - 18.0 g/dl); platelets in thousands (150 - 450 per µl); creatinine (0.6 - 1.1 mg/dl); bilirubin (0 - 1.1 mg/dl); c-reactive-protein (0 - 0.5 mg/dl)
All p-values derived from two-sided, non-directional t-tests. Levene tests conducted to assess equality of variances.

Figure 7 presents histograms and receiver operator characteristics (ROC) for leukocyte- and platelet-count, as well as, hemoglobin- and CRP levels, as these variables correspond to markers of inflammation or parameters relevant to the patients' suitability for undergoing surgery. For smoothing of the distributions, kernel density estimates were added to histograms and shown on the plot as two lines, one for UA and one for CA respectively.

The ROC curves for classifying CA vs UA show variations in the AUCs (Area under the curve), ranging from values below 0.5 (AUC = 0.48 for hemoglobin; AUC = 0.49 for platelets), suggesting no difference in preoperative levels, to AUCs above 0.5 such as AUC = 0.59 for leukocytes and AUC = 0.82 for CRP, suggesting a difference in preoperative levels. Statistical testing for the comparison of these distributions confirms the AUC results (see Table 12).

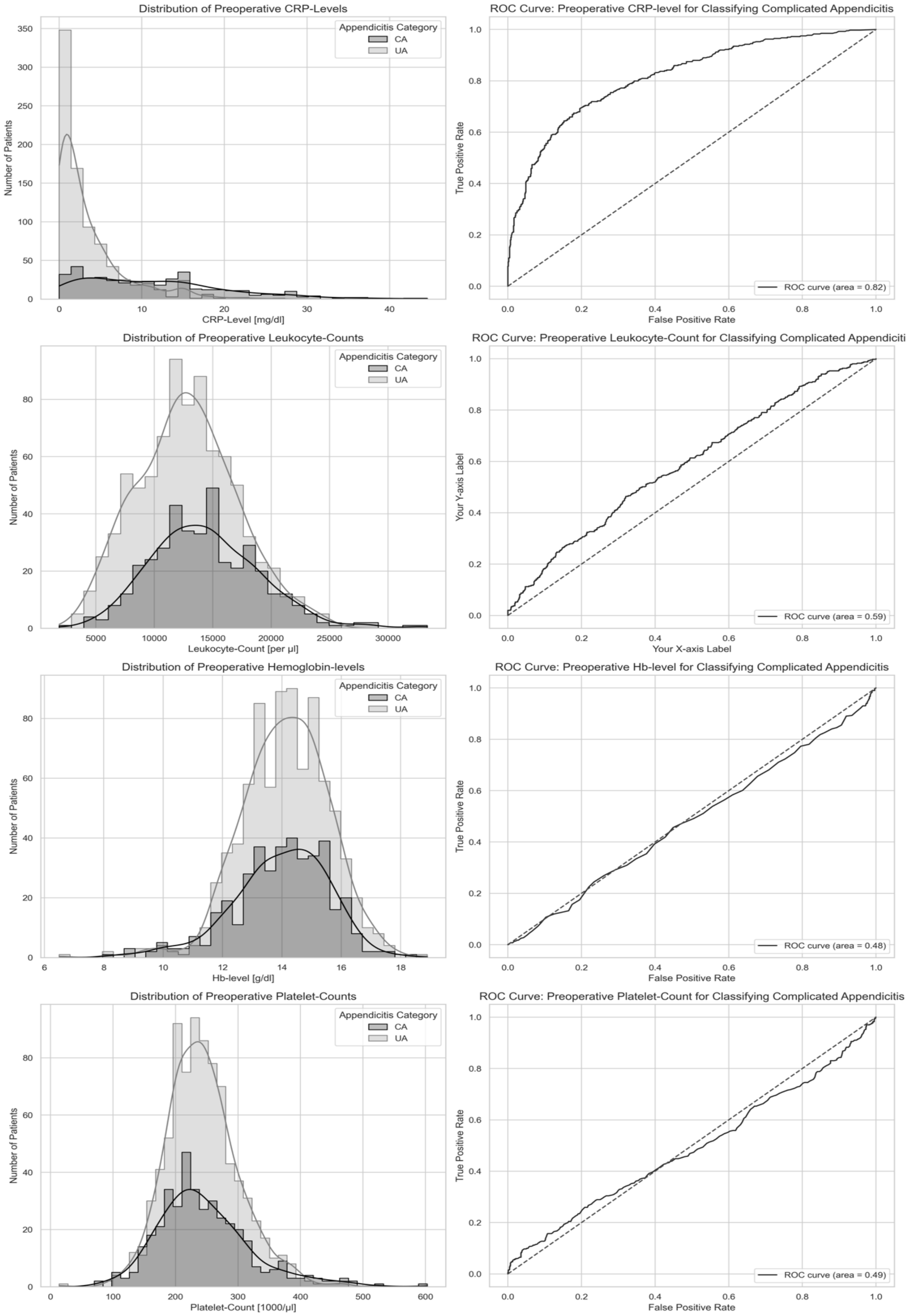

Figure 7. Histograms and ROC Curves of Preoperative Laboratory Tests.

3.3 Primary Surgical and Antibiotic Therapy

The following section presents the analyses of surgical procedures, including selected approaches, tools, and operation duration. To provide a better understanding of the differences in surgical approach between UA and CA, the results are presented together with the distribution of ASA (American Society of Anesthesiologists) scores. Subsequently, intraoperative findings are presented. The chapter concludes by addressing the perioperative antibiotic therapy.

3.3.1 ASA Scores, Surgical Procedure and Iatrogenic Injuries

The distribution of ASA scores varied among the groups, with median values of ASA = 1 for UA and ASA = 2 for CA (see Table 13). A two-sided Mann-Whitney U-test was conducted to compare the groups, resulting in a statistically significant finding ($p < .001$), indicating an overall difference in patient health and fitness between the two groups.

Table 13. Preoperative ASA Scores.

	UA *(n=843)*			CA (*n=403)*		
ASA Score	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
ASA 1	523	62.0%	62.0%	137	34.0%	34.0%
ASA 2	294	34.9%	34.9%	206	51.1%	51.1%
ASA 3	26	3.1%	3.1%	58	14.4%	14.4%
ASA 4	0	0.0%	0.0%	2	0.5%	0.5%
Not specified	0	0.0%	-	0	0.0%	-

The surgical procedure differed in several aspects between patients with UA and CA (Table 14). For instance, the average duration of the operation for CA cases was approximately half an hour longer than for UA cases (CA: 79.1 ± 47.2 minutes; UA: 50.5 ± 19.8 minutes; $t = 11.65$, $p < .001$).

Coecectomy (21.8%) and ileocoecal resection rates (6.0%) were performed significantly more often in CA compared to UA procedures (3.7% and 0.1%). The primary use of an open approach (4.2% vs. 0.5%, $p < .001$) or conversion from laparoscopic to open surgery (8.2% vs 0.2%, $p < .001$) was also significantly more common in the CA, compared to the UA group. Contraindications to laparoscopic approaches were reported in an overall of n = 5 cases, including n = 2 cases with surgical contraindications due to previous abdominal surgeries and n = 3 cases with anesthesiologic contraindications due to cardiorespiratory disease.

Table 14. Surgical Procedure, Approach and Tools for Appendectomy.

Details of Surgery	UA *(n=843)*			CA (*n=403)*			Statistic
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Surgical procedure	-	-	-	-	-	-	<.001$^{\chi}$
Appendectomy	811	96.2%	96.2%	291	72.2%	72.2%	<.001^{Z}
Resection of coecum	31	3.7%	3.7%	88	21.8%	21.8%	<.001^{Z}
Ileocoecal resection	1	0.1%	0.1%	24	6.0%	6.0%	<.001^{Z}
Not specified	0	0.0%	-	0	0.0%	-	-
Surgical approach	-	-	-	-	-	-	<.001$^{\chi}$
Laparoscopic	837	99.3%	99.3%	353	87.6%	87.6%	<.001^{Z}
Open	4	0.5%	0.5%	17	4.2%	4.2%	<.001^{Z}
Conversion to open	2	0.2%	0.2%	33	8.2%	8.2%	<.001^{Z}
Not specified	0	0.0%	-	0	0.0%	-	-
Surgical tool	-	-	-	-	-	-	.001$^{\chi}$
Stapler	806	95.6%	95.6%	373	92.6%	92.6%	.025^{Z}
Ligation	32	3.8%	3.8%	17	4.2%	4.2%	.720^{Z}
Other	5	0.6%	0.6%	13	3.2%	3.2%	<.001^{Z}
Not specified	0	0.0%	-	0	0.0%	-	-

$^{\chi}$ χ^2 test of independence
^{Z} Two-proportion Z-test

Differences were also observed in the usage of surgical tools for the procedure (χ^2 = 13.47, p = .001). Staplers were more commonly used in UA cases (95.6%) compared to CA (92.6%; p < .001). A combination of stapler and ligation was more frequently used in cases of CA (UA: 0.6%; CA: 3.2%; p < .001).

There were no missing values for surgical procedure, surgical approach, and surgical tools in the UA and CA groups. Intraoperative findings and further details regarding the surgical technique are discussed in section 3.3.2.

3.3.1.1 Intraabdominal Drain Placement

The proportion of cases for which surgeons decided to place an intraabdominal drain at the end of the surgery varied considerably between the groups (χ^2 = 496.08, p < .001; see Table 15). Drains were placed significantly more frequently in the CA group (62.0%) compared to the UA group (4.6%, p < .001).

Table 15. Intraabdominal Drain Placement During Surgery.

Drain placement	UA *(n=843)*			CA (*n=403)*			Statistic
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Drain placed	38	4.5%	4.6%	248	61.5%	62.0%	<.001^{Z}
No drain placed	793	94.1%	95.4%	152	37.7%	38.0%	<.001^{Z}
Not specified	12	1.4%	-	3	0.7%	-	-

^{Z} Two-proportion Z-test

3.3.1.2 Iatrogenic Injuries During Appendectomy

Iatrogenic injuries occurred in n = 24 of n = 1346 cases. Among them, n = 8 cases involved accidental perforations of the appendix, some of which had already progressed to gangrenous or fragile wall structures. Other types of injuries included serosal defects (n = 9), injuries to the epigastric vessels (n = 1), as well as perforations of the bladder (n = 1) or small intestine (n = 3). The majority of iatrogenic injuries occurred during laparoscopic appendectomies (n = 21).

3.3.2 Intraoperative Findings

The following chapter covers intraoperative findings such as perforation of the appendix, as well as the presence of intraabdominal fluid, abscesses, or peritonitis. The most common description of appendix localization was retrocecal, however, as data regarding the intraoperative position of the appendix was available for less than half of all cases, only n = 10 notable cases which displayed unconventional positions of the appendix are described here. These positions included subhepatic (n = 4), left abdomen secondary to malrotation (n = 1), appendix within a previously inserted intraabdominal drain (n = 1), or appendix within a hernia (n = 4). Notably, two of these cases involved Amyand's hernias.

3.3.2.1 Intraabdominal Collection of Cloudy Fluid

In approximately half of the cases, surgical reports lacked information regarding the presence or absence of cloudy intraabdominal fluid (Table 16). Therefore, no statistical tests were calculated for this variable. It is notable that among all UA patients, 23.3% had cloudy intraabdominal fluid described.

Table 16. Intraabdominal Cloudy Fluid Collection.

	UA *(n=843)*			CA (*n=403)*		
Cloudy intraabdominal fluid	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Described as present	196	23.3%	53.6%	181	44.9%	83.8%
Explicitly excluded	170	20.2%	46.4%	35	8.7%	16.2%
Not specified	477	56.6%	-	187	46.4%	-

3.3.2.2 Intraabdominal Abscesses

It should be noted that by the definition of CA and UA employed in this study, there are only UA cases for which periappendicular abscesses were explicitly excluded in surgical reports or no information about periappendicular abscesses was available. As this variable is correlated to CA and UA by definition, no statistical tests were calculated for this variable. Surgical reports made no reference to the presence or absence of abscesses in approximately half of the cases (Table 17). Periappendicular abscesses were reported in 77.1% of valid CA cases.

Table 17. Periappendicular Abscesses.

Abscess at appendix	UA *(n=843)*			CA (*n=403)*		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Described as present	0	0.0%	0.0%	155	38.5%	77.1%
Explicitly excluded	412	48.9%	100%	46	11.4%	22.9%
Not specified	431	51.1%	-	202	50.1%	-

Further analysis of the presence of non-periappendicular but intraabdominal abscesses during surgery revealed that both UA and CA cases had a median of zero intraabdominal non-periappendicular abscesses, with a range of 0 to 1 for UA and 0 to 8 for CA, demonstrating a significant difference between the two groups tested by the Mann-Whitney U-test ($p < .001$).

3.3.2.3 Perforation of the Appendix

In accordance with the explanation from section 3.3.2.2 regarding intraabdominal abscesses, statistical tests were not conducted to compare the incidence of appendix perforation between UA and CA cases. Among CA cases, appendix perforation was described in 76.9% of all, and 91.5% of valid cases (Table 18).

Table 18. Perforation of the Appendix.

Perforation of the appendix	UA *(n=843)*			CA (*n=403)*		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Described as present	0	0.0%	0.0%	310	76.9%	91.5%
Explicitly excluded	450	53.4%	100%	29	7.2%	8.5%
Not specified	393	46.6%	-	64	15.9%	-

3.3.2.4 Peritonitis

In approximately half of the cases (UA: 46.4%, CA: 57.1%), surgical reports mentioned the presence or absence of peritonitis. Two levels of severity (localized peritonitis and extensive peritonitis) are presented in Table 19. Statistical testing for independence between both variables showed a significant relationship between UA and CA groups to severity and presence of peritonitis

(χ^2 = 263.15, p < .001). Among patients with UA, 1.3% (n = 5), compared to 33.5% (n = 77) of patients with CA had extensive peritonitis described (p < .001).

Table 19. Peritonitis.

Peritonitis	UA *(n=843)*			CA *(n=403)*			Statistic
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Extensive peritonitis*	5	0.6%	1.3%	77	19.1%	33.5%	<.001^{Z}
Localized peritonitis	60	7.1%	15.3%	107	26.6%	46.6%	<.001^{Z}
Peritonitis explicitly excluded	326	38.7%	83.4%	46	11.4%	20.0%	<.001^{Z}
Not specified	452	53.6%	-	173	42.9%	-	-

* corresponds to an explicit mention of “extensive” or “diffuse” peritonitis or peritonitis ranging over ≥ 2 quadrants.
^{Z} Two-proportion Z-test

In line with that, 15.3% (n = 60) of UA cases had localized peritonitis described, compared to 46.6% (n = 107) of CA cases (p < .001). On the other hand, 83.4% (n = 326) of surgical reports for UA cases had excluded peritonitis, compared to 20.0% (n = 46) of CA cases (p < .001).

3.3.3 Perioperative Antimicrobial Prophylaxis

This section focuses on the administration of antibiotics following a documented surgical indication for the definitive operative treatment of appendicitis. The time frame considered extends from a maximum of 24 hours prior to the start of the operation to the point of the completion of the procedure.

A perioperative single-shot antimicrobial prophylaxis was documented for 99.3% of patients with UA and 98.8% of patients with CA. Median values for the number of distinct perioperative single-shot antibiotics were n = 2 for both UA and CA cases. A bar chart representing the distribution of the number of distinct antibiotic agents for perioperative antimicrobial prophylaxis in appendectomies is presented in Figure 8.

Of the total n = 1346 cases included in the study, n = 13 cases did not have any documentation of perioperative antimicrobial prophylaxis in the anesthesia protocol or surgical reports. Additionally, information regarding perioperative antibiotic use is not available for n = 4 cases due to the unavailability of reports.

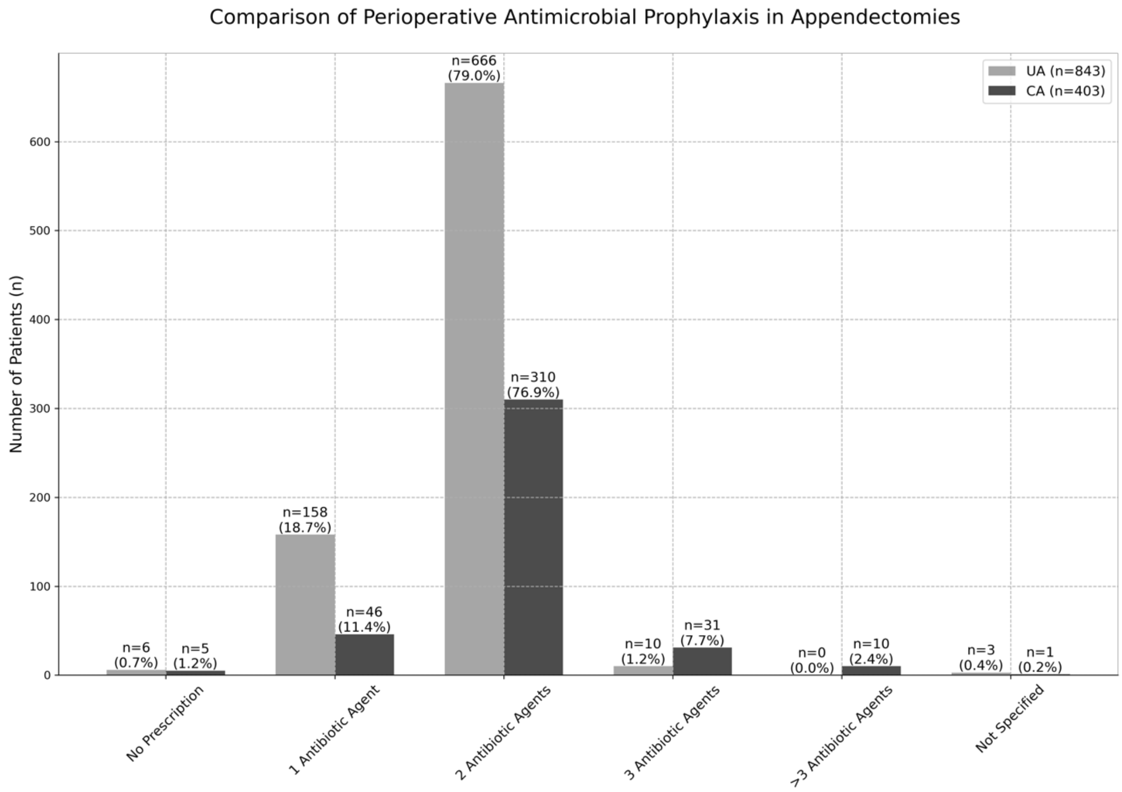

Figure 8. Comparison of Perioperative Antimicrobial Prophylaxis.

In n = 219 cases, one single-shot antibiotic agent was administered. The most commonly used medications in this group were Cefotaxime (n = 175; 79.9%), Piperacillin - Tazobactam (n = 26; 11.9%), and Metronidazole (n = 8; 3.7%).

The following heatmap (Figure 9) represents the combinations of antibiotic agents for perioperative antimicrobial prophylaxis as color intensity levels in each cell. On visual inspection, it is evident that Cefotaxime & Metronidazole (n = 972; 92.1%) was the most frequent combination of antibiotic agents administered for antimicrobial prophylaxis in this patient cohort. It is notable that a variety of combinations was applied in less than 1% of cases.

It is important to note that, for reasons of enhanced visualization, only patients who received exactly two antibiotic agents are included (n = 1056). Patients who received no perioperative antimicrobial prophylaxis (n = 13), only one antibiotic agent (n = 219), or ≥3 antibiotic agents (n = 54) are not included in this figure.

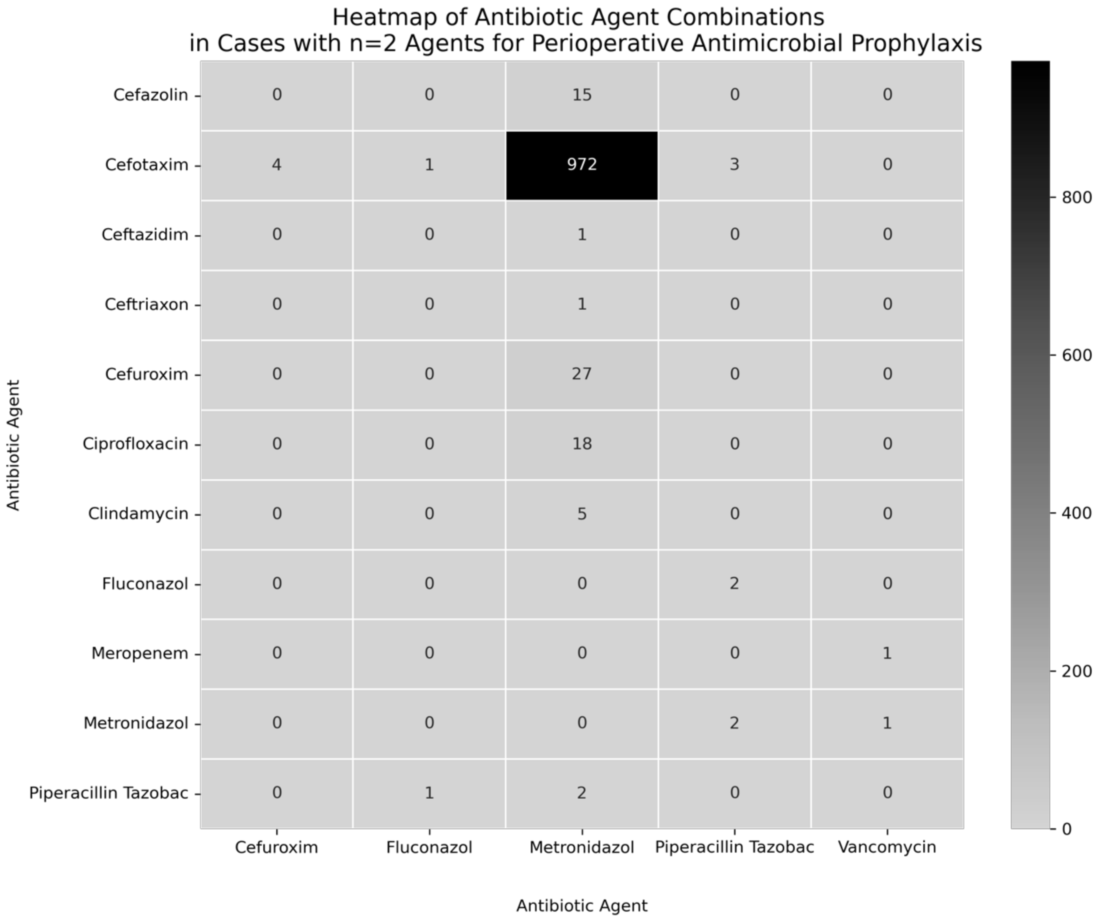

Figure 9. Antibiotic Agent Combinations for Perioperative Antimicrobial Prophylaxis During Appendectomy.

3.4 Surgical and Histopathological Assessment of the Appendix

This chapter presents and compares the diagnoses found in surgical operation reports and histopathological examination findings. Both perspectives are considered to provide a comprehensive evaluation of the severity of appendicitis. It is important to note that certain cases revealed the presence of additional pathological conditions alongside the presentation of appendicitis. In cases of NA the clinical suspicion of appendicitis could not be verified.

3.4.1 Intraoperative Surgical Diagnosis

Analysis of the surgical reports revealed the following distribution patterns of diagnoses regarding the severity of appendicitis: Among CA cases, gangrenous appendicitis represented the majority of diagnoses (51.9%). For UA, phlegmonous and catarrhal appendicitis were the most prevalent, accounting for 75.9% and 16.8% of cases. In some reports, the grade of appendicitis severity was not specified any further than “Acute appendicitis”. This category is presented as “Acute Appendicitis (not otherwise specified)” in Table 20. Since the classification applied in this study is based on appendicitis severity, no statistical tests were employed for this variable.

Table 20. Surgical Diagnoses in Operation Reports of Uncomplicated and Complicated Appendicitis.

Surgical Diagnosis	UA *(n=843)*			CA (*n=403)*		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Catarrhal appendicitis	141	16.7%	16.8%	1	0.2%	0.2%
Phlegmonous appendicitis	638	75.7%	75.9%	53	13.2%	13.2%
Gangrenous appendicitis	0	0.0%	0.0%	209	51.9%	51.9%
Acute appendicitis (not otherwise specified)	62	7.4%	7.4%	140	34.7%	34.7%
No acute appendicitis	0	0.0%	0.0%	0	0.0%	0.0%
Surgical report not available	2	0.2%	-	0	0.0%	-

It is worth noting that a considerable number of cases in the NA category (16.9%) and NC category (71.4%) fell into the group of “Acute Appendicitis (not otherwise specified)” in the surgical reports. An explanation for this is provided in section 2.5.1 (Definition of Case Categories). Table 21 provides a detailed overview of the distribution of surgical diagnoses listed in operation reports for NA and NC cases.

Table 21. Surgical Diagnoses in Operation Reports of Negative Appendectomies and Non-Classified Cases.

Surgical Diagnosis	NA *(n=79)*			NC *(n=21)*		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Catarrhal appendicitis	0	0.0%	0.0%	0	0.0%	0.0%
Phlegmonous appendicitis	0	0.0%	0.0%	0	0.0%	0.0%
Gangrenous appendicitis	0	0.0%	0.0%	0	0.0%	0.0%
Acute appendicitis (not otherwise specified)	13	16.5%	16.9%	15	71.4%	71.4%
No acute appendicitis	64	81.0%	83.1%	6	28.6%	28.6%
Surgical report not available	2	2.5%	-	0	0.0%	-

In a total of n = 125 cases, diagnoses other than appendicitis were reported additionally to or instead of acute appendicitis. The most frequently observed diagnoses were attributed to the field of gynecology (n = 90). These included follicular cysts (n = 28), endometriosis (n = 11), tuboovarian abscesses (n = 6), adnexitis (n = 3), as well as other gynecological conditions (n = 42). Additionally, there were instances of gastroenterological / visceral surgical conditions such as enteritis (n = 12), ileus (n = 10), and n = 14 oncological diagnoses, including n = 3 cases of peritoneal carcinomatosis.

3.4.2 Comparison of Surgical and Histopathological Assessment

The surgical assessment of the appendix does not necessarily correspond to the histopathological assessment. The following section aims at comparing the surgical and histopathological reports.

3.4.2.1 Inflammation and Gangrene of Appendiceal Tissue

The frequency of histopathologically confirmed inflammation and gangrene in the examined tissue varied considerably between UA and CA cases, as presented in Table 22. In histopathological reports, inflammation was described more frequently in cases of CA with a rate of 99.5%, as compared to cases of UA with a rate of 90.6% ($\chi^2 = 33.94$, $p < .001$).

Table 22. Histopathological Assessment of Inflammation and Gangrene.

	UA *(n=843)*			CA *(n=403)*			Statistic
Analysis of specimen tissue	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Inflammation present	763	90.5%	90.6%	401	99.5%	99.5%	<.001^{Z}
No inflammation	79	9.4%	9.4%	2	0.5%	0.5%	<.001^{Z}
Not specified	1	0.1%	-	0	0.0%	-	-
Gangrene present	25	3.0%	3.0%	108	26.8%	26.8%	<.001^{Z}
No gangrene	818	97.0%	97.0%	295	73.2%	73.2%	<.001^{Z}
Not specified	0	0.0%	-	0	0.0%	-	-

^{Z} Two-proportion Z-test

Gangrenous tissue could be identified in approximately a quarter of the CA cases (26.8%). Histopathological analysis also revealed that a small proportion of UA cases had gangrenous tissue in the resected specimen (3.0%). A χ^2 test of independence for presence of gangrene and the appendicitis severity grouping variable was statistically significant ($\chi^2 = 159.94$, $p < .001$), so that post-hoc two-proportion Z-tests were performed.

3.4.2.2 Presence of Appendicoliths

Since, in some cases, appendicoliths were described during the operation but not always sent in for histopathological evaluation, statements from surgical and histopathological reports were considered for the analysis. Appendicoliths were significantly more common in CA (24.1%) compared to the UA group (11.9%), with an odds ratio of 2.36 (95% CI: 1.73 - 3.21; $\chi^2 = 30.52$; $p < .001$).

3.4.2.3 Comparison of Surgical and Histopathological Diagnosis

The following section presents the overlap of the histopathological and surgical diagnoses. The surgical diagnosis “phlegmonous appendicitis” was histopathologically confirmed in 82.5% of the cases (see Table 23). In contrast, for the surgical diagnosis “gangrenous appendicitis”, the same diagnosis was made by histopathology in only 31.1% of the cases, while a milder histopathological diagnosis such as “phlegmonous appendicitis” was more commonly observed (59.3% of cases).

The category “erosive appendicitis” was used exclusively in histopathological reports and not in surgical reports. Therefore, this category is not included in the list of surgical diagnoses.

Table 23. Surgical and Histopathological Assessment of Appendicitis.

		Surgical Diagnosis				
		No acute appendicits (n=70)	Catarrhal appendcitis (n=142)	Phlegmonous appendicitis (n=690)	Gangrenous appendicitis (n=209)	Acute appendicitis NOS (n=230)
Histopathological Diagnosis	No acute appendicits (n=205)	48 (68.6%)	63 (44.4%)	55 (8.0%)	11 (5.3%)	28 (12.2%)
	Catarrhal appendcitis (n=54)	7 (10.0%)	31 (21.8%)	14 (2.0%)	0 (0.0%)	2 (0.9%)
	Erosive appendicitis (n=14)	2 (2.9%)	5 (3.5%)	3 (0.4%)	0 (0.0%)	4 (1.7%)
	Phlegmonous appendicitis (n=882)	10 (14.3%)	31 (21.8%)	569 (82.5%)	124 (59.3%)	148 (64.3%)
	Gangrenous appendicitis (n=133)	0 (0.0%)	0 (0.0%)	32 (4.6%)	65 (31.1%)	36 (15.7%)
	Acute appendicitis NOS (n=53)	3 (4.7%)	12 (8.5%)	17 (2.5%)	9 (4.3%)	12 (5.2%)

* Acute Appendicitis NOS = Acute Appendicitis without specification of severity (Not otherwise specified)

The histopathological assessment of tissue continuity or perforation of the appendix wall significantly corresponds to the surgical assessment ($\chi^2 = 434.56$, $p < .001$; see Table 24). Histopathological confirmation of perforation was achieved in 85.4% of cases with surgical reports indicating perforation.

Table 24. Surgical and Histopathological Assessment of Tissue Perforation.

		Surgical assessment of the appendix	
		Non perforated (n=468)	Perforated (n=268)
Histopathological assessment of the appendix	Non perforated (n=467)	428 (91.5%)	39 (14.6%)
	Perforated (n=269)	40 (8.5%)	229 (85.4%)

Percentages according to frequencies in columns.

3.4.3 Combination of Surgical and Histopathological Diagnosis

In accordance with the explanation provided in section 2.4.1 (Combination of Surgical and Histopathological Findings), partially missing information in surgical reports regarding the severity of appendix inflammation was substituted, whenever appropriate, with histopathological data. In n = 4 cases, no surgical assessment was available. In n = 230 cases, the surgical report provided a non-specific diagnosis classified as "acute appendicitis (not otherwise specified)" in this study. For these cases, the histopathological diagnosis is used instead of the missing or imprecise surgical diagnosis, resulting in a combined variable that serves as the basis for categorizing cases into UA, CA, NA, and NC in this study. Cases from the NA group (n = 79) and the NC group (n = 21) all fall, by definition, into the category of "no acute appendicitis", as presented in Figure 10.

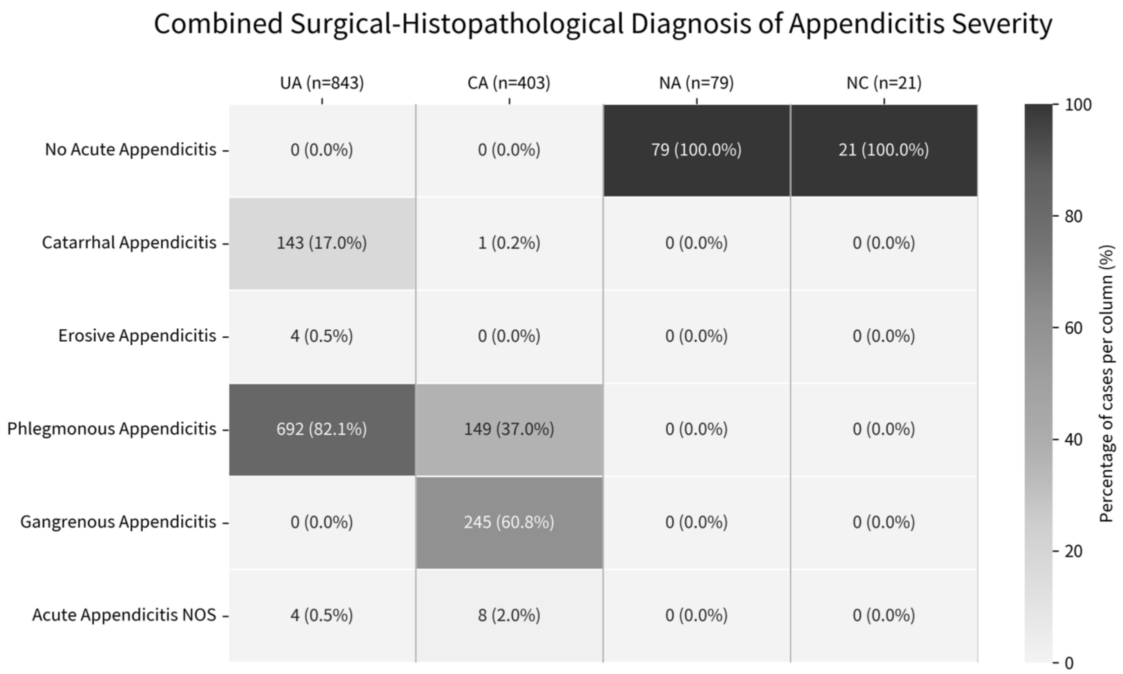

Figure 10. Combined Surgical-Histopathological Diagnosis of Appendicitis Severity.

3.5 Microbiological Analysis of Intraoperative Samples

In this chapter, the microbiological findings obtained from intraoperative, intraabdominal swab samples are presented. Swabs from the surgical site were not routinely collected; rather, they were taken based on the indications provided by the operating surgeon (see section 3.3.2). In total, samples for microbiological diagnostics were taken and examined in 52.45% of all patients (n = 706). The following sections discuss the availability of intraoperative swab results and the observed spectrum of microorganisms. Overall, the genera Bacteroides, Escherichia, Streptococcus, and Enterococcus were most frequently identified in intraabdominal swabs.

3.5.1 Validity of Intraoperative Samples for Microbiological Analysis

Out of the n = 706 patients with microbiological samples obtained intraoperatively, only intraabdominal swabs directly related to the appendectomy are considered for the subsequent analyses. Excluded from consideration are n = 4 extraabdominal swabs, n = 3 swabs lacking localization information, and n = 1 intraabdominal swab which was performed in the context of a ruptured ovarian cyst and intraoperative suspicion of endometriosis, thus being unrelated to appendicitis. However, two of these patients with invalid intraoperative swabs had another valid swab taken, so that the total number of patients with valid samples is n = 700 (UA: n = 342 / 843; CA: n = 317 / 403; NA: n = 27 / 79; NC: n = 14 / 21).

The distribution of collection sites of the intraoperatively obtained intraabdominal swabs, which were directly related to the appendectomy (i.e., valid swab samples), is detailed in Table 25.

Table 25. Collection Sites of Intraoperative Intraabdominal Swab Samples.

Intraoperative Collection Site	UA (*n=843*)			CA (*n=403*)		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Intraabdominal Abscess	2	0.2%	0.6%	49	12.2%	15.5%
Intraabdominal Fluid	27	3.2%	7.9%	22	5.5%	6.9%
Peritoneum	165	19.6%	48.2%	143	35.5%	45.1%
Intraabdominal not otherwise specified	148	17.6%	43.4%	103	25.6%	32.5%
No valid swab	501	59.4%	-	86	21.3%	-

It is notable that the availability of valid samples is significantly higher in the CA group (78.67%) compared to the UA group (40.57%), as indicated by a two-proportion Z-test ($Z = 12.6$, $p < .001$).

3.5.2 Microbial Spectrum of Intraoperative Samples

Microbiological culture results were positive (detection of at least one bacterial species) in n = 394 (UA: n = 116 / 342; CA: n = 263 / 317; NA: n = 3 / 27;

NC: n = 12 / 14) out of the n = 700 patients who had valid intraoperative samples. This result corresponds to a positive culture result rate of 56.29%.

Two valid intraoperative swabs were taken in n = 68 patients. Therefore, a number of n = 768 intraoperative swabs were available for analysis. Figure 11 provides an overview of bacterial species per culture for UA and CA cases.

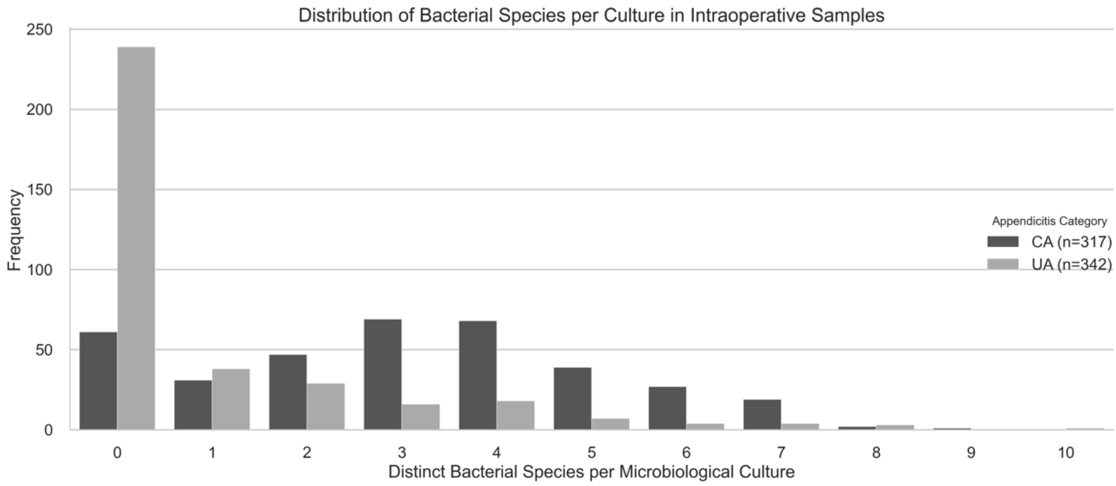

Figure 11. Bacterial Species per Culture in Intraoperative Samples.

Regarding all patients with valid intraoperative sampling (UA, CA, NA, and NC), it can be noted that n = 328 cultures showed no growth of bacteria (42.7%), n = 72 cultures showed single species infections (9.4%), and n = 368 cultures showed mixed species infections (47.9%).

The average number of different species identified in valid intraoperative swabs independent of a positive or negative culture result was 0.96 ± 1.76 for UA and 3.05 ± 2.07 for CA ($t = -13.93$; $p < .001$). Anaerobes were detected in n = 317 out of all patients (UA: n = 78 / 342; CA: n = 227 / 317; NA: n = 3 / 27; NC: n = 9 / 14) with valid samples independent of a positive or negative culture result (n = 700). This corresponds to rates of 22.8% for UA and 71.6% for CA cases.

When considering only positive culture results, the average number of different species identified was 2.83 ± 1.95 for UA and 3.67 ± 1.69 for CA ($t = -4.28$; $p < .001$). Anaerobes were present in 80.48% of cases with positive culture results. Further analysis showed rates of 67.24% for UA (n = 78 / 116) and 86.31% for CA (n = 227 / 263) cases regarding the presence of anaerobes, corresponding to an Odds Ratio of 3.07 (95% CI: 1.82 – 5.19; χ^2 =17.44, $p < .001$) for the presence of anaerobes in positive cultures for CA.

3.5.2.1 Presence of Anaerobic Bacteria in Microbiological Culture Results

The average number of distinct bacterial species in cases with positive microbiological cultures is illustrated in Figure 12. Culture results are grouped into either the category of exclusively aerobic bacteria present or the category of ≥ 1 anaerobic bacterium present (includes cases with mixed aerobic-anaerobic cultures, as well as cases with exclusively anaerobic culture results). The results are further divided into the UA and CA groups. Note that error bars represent 95% confidence intervals.

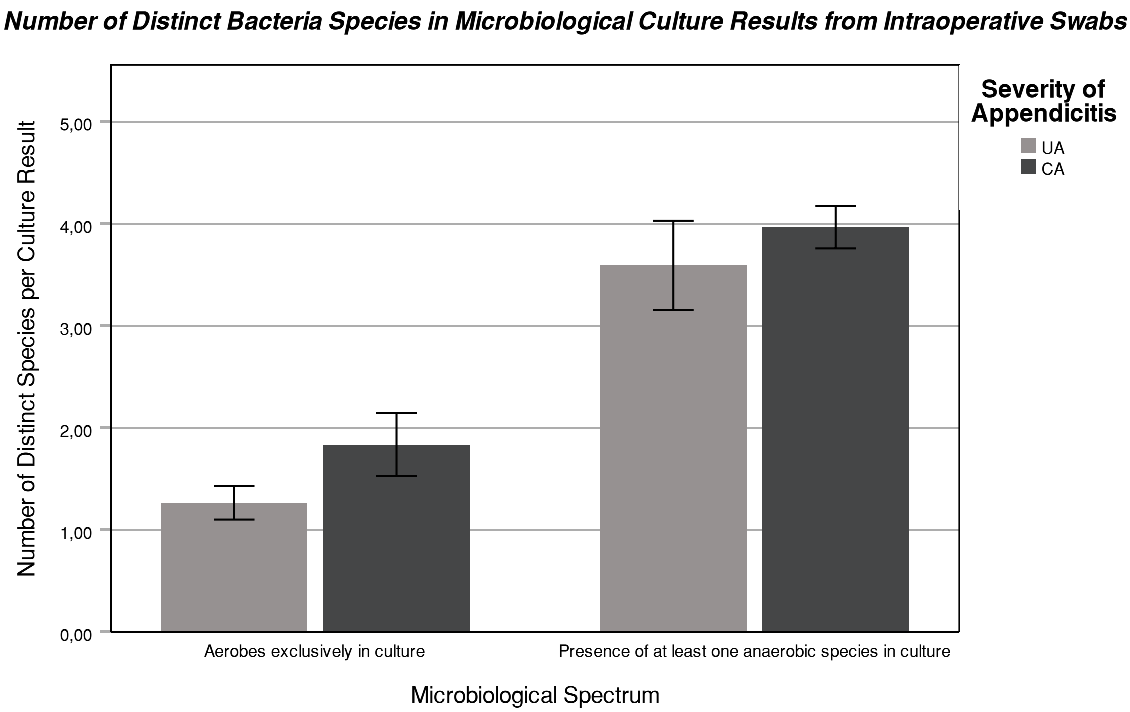

Figure 12. Number of Distinct Bacterial Species in Microbiological Culture Results from Intraoperative Swab Samples.

The grouping variable UA/CA did show an effect on the number of distinct species per culture in cultures including exclusively aerobes (UA: 1.26 ± 0.50, CA: 1.83 ± 0.91; $t = -3.31$; $p = .002$), but not in cultures where anaerobes were detected (UA: 3.59 ± 1.94, CA: 4.97 ± 1.59; $t = -1.54$; $p = .127$). It can be observed that in culture results with ≥1 anaerobic bacterial species present (n = 317, 3.83 ± 1.69), regardless of the severity of appendicitis, a significantly higher number of microorganisms per culture was detected compared to cultures including exclusively aerobes ($n = 77$, 1.60 ± 0.83; $t = 16.67$, $p < .001$). However, it is important to consider the results of the previous section indicating higher odds for the presence of anaerobes in CA samples.

3.5.2.2 Overview of Bacterial Genera and Species in Microbiological Culture Results from all Valid Intraoperative Intraabdominal Swab Samples

The following sunburst chart (Figure 13) provides an overview of the entire microbial spectrum identified in cultures derived from all patients ($n = 700$) with valid intraoperative intraabdominal swabs.

To provide a comprehensive representation of the microbial spectrum across the patient cohort in this study, for patients in which multiple swabs were taken, all microorganisms from all valid intraoperative samples are listed. Therefore, the legends (shading intensity) on the subsequent graphs indicate the absolute frequency of bacterial species or genera detected in microbiological cultures, rather than the count of patients in whom these species or genera were found.

In the intraoperative intraabdominal swabs the genera Bacteroides ($n = 298$, 42.57%), Escherichia ($n = 233$, 33.29%, of which $n = 7$ MDRGN), and Streptococcus ($n = 110$, 15.71%) followed by, Enterococcus ($n = 100$, 14.29%, of which $n = 2$ VRE faecium), Bilophila ($n = 68$, 9.71%), Pseudomonas ($n = 66$, 9.43%), Parabacteroides ($n = 37$, 5.29%), Klebsiella ($n = 33$, 4.71%), Eggerthella ($n = 30$, 4.29%) and Staphylococcus ($n = 23$, 3.29%) were the most commonly identified.

For a table regarding frequencies of bacterial species and a comparison of the intraoperative and postoperative bacterial spectrum, see section 3.9.4. Out of the total $n = 317$ CA patients with valid swab collection, positive microbiological culture results were found in $n = 263$ patients (82.97%). In comparison, in the UA group, only 33.92% of patients with valid swab samples had positive microbiological culture results.

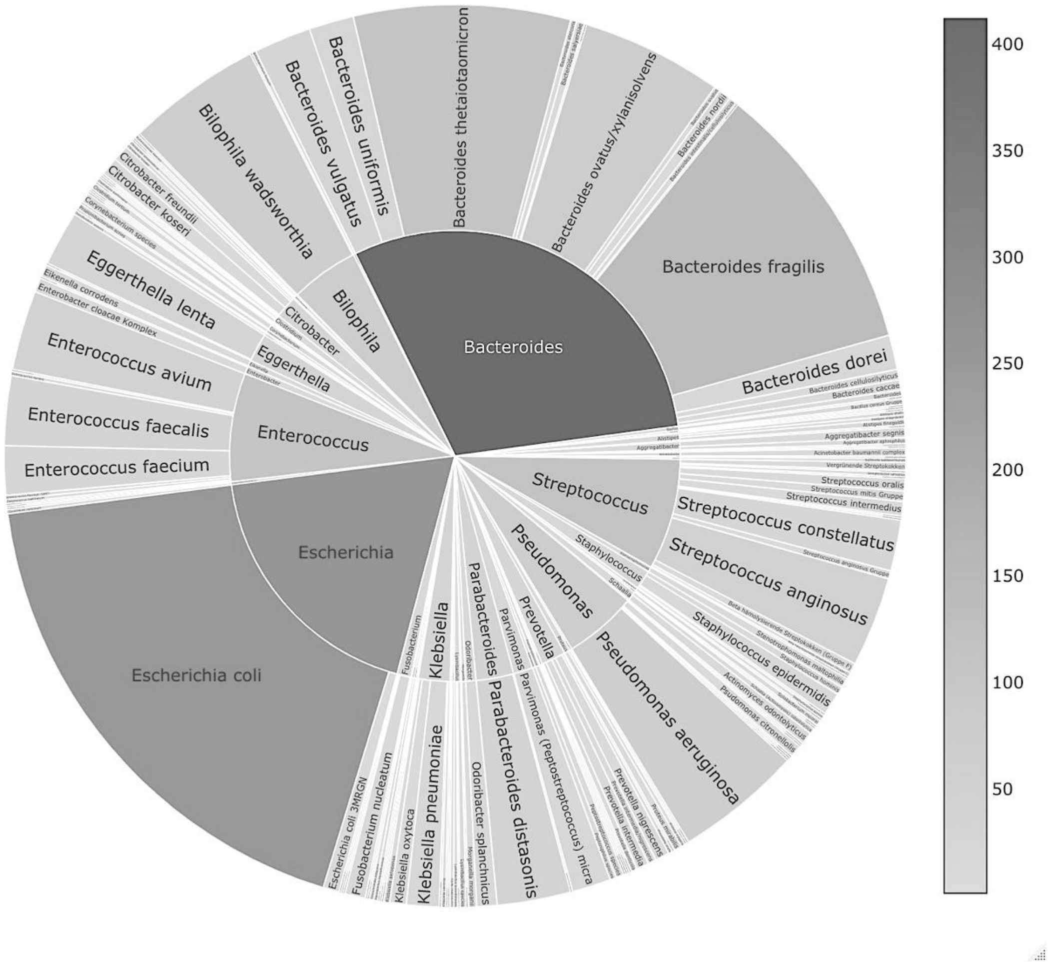

Figure 13. Microbial Spectrum of all Intraoperative Samples.

3.5.2.3 Microbial Spectrum of Uncomplicated Appendicitis

Analysis of microbiological culture results from all valid intraoperative intraabdominal swab samples in cases of UA showed positive cultures in n = 116 of n = 342 UA cases (33.92%). An overview of the microbial spectrum identified in these cultures is presented in Figure 14.

The five most frequently identified bacterial genera, in descending order, were Bacteroides spp. (n = 70), Escherichia spp. (n = 51), Streptococcus spp. (n = 22), Enterococcus spp. (n = 22), and Pseudomonas spp. (n = 22). It was observed that numerous genera were detected in a limited number of patients, and some genera, such as Clostridium spp., Pseudomonas spp., or Klebsiella spp., in less than five patients each.

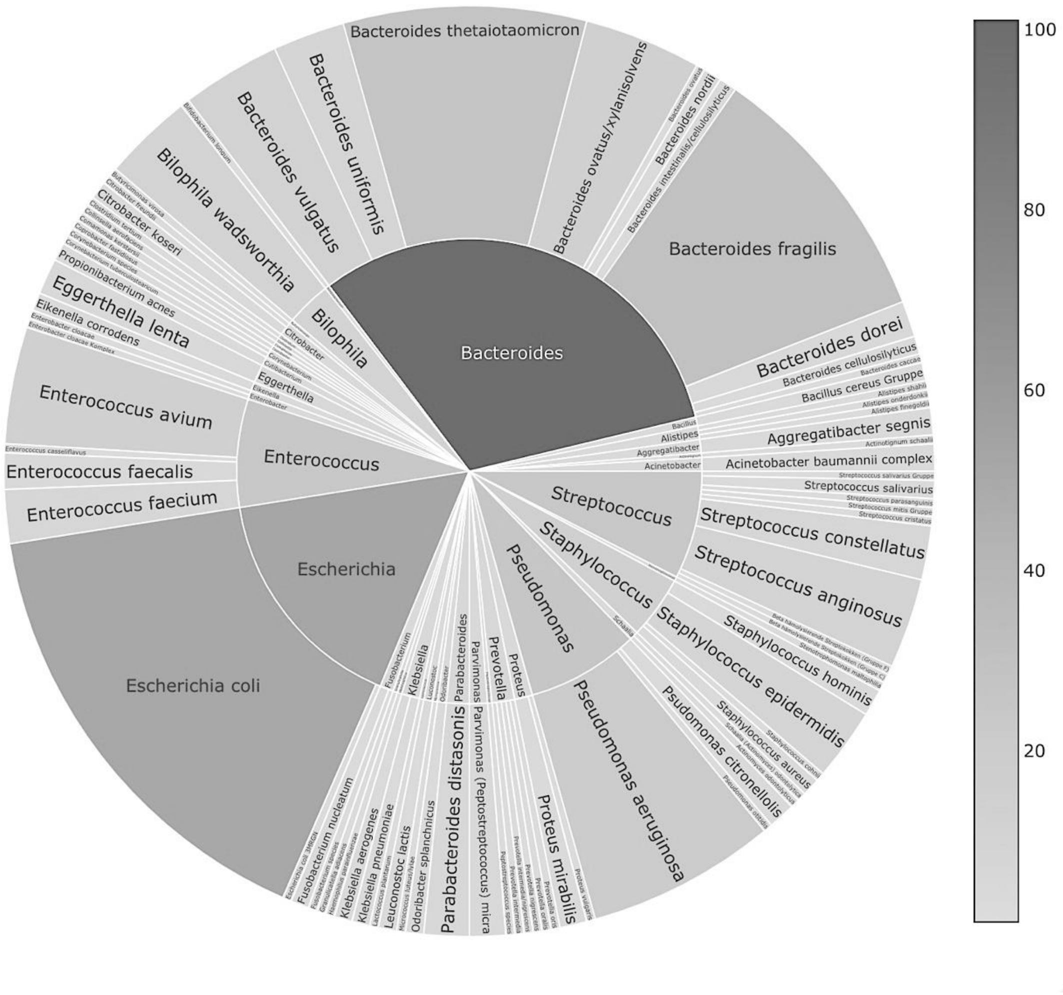

Figure 14. Microbial Spectrum of Uncomplicated Appendicitis.

3.5.2.4 Overview of Bacterial Genera and Species in Microbiological Culture Results in Cases of Complicated Appendicitis

As the majority of all positive microbiological culture results were based on valid swab samples collected from CA cases, the microbial spectrum distribution in this group resembles that which includes all patients (see Figure 13). An overview of the whole microbial spectrum identified in CA cultures is presented in Figure 15. The three most frequently identified bacterial genera were in the same order as in UA (see Figure 14): Bacteroides (n = 219), Escherichia (n = 178), and Streptococcus (n = 84). These were followed by Enterococcus (n = 76), Bilophila (n = 56), Pseudomonas (n = 43), Parabacteroides (n = 30), Klebsiella (n = 26), and Eggerthella (n = 24), however different from the order of species in the UA group.

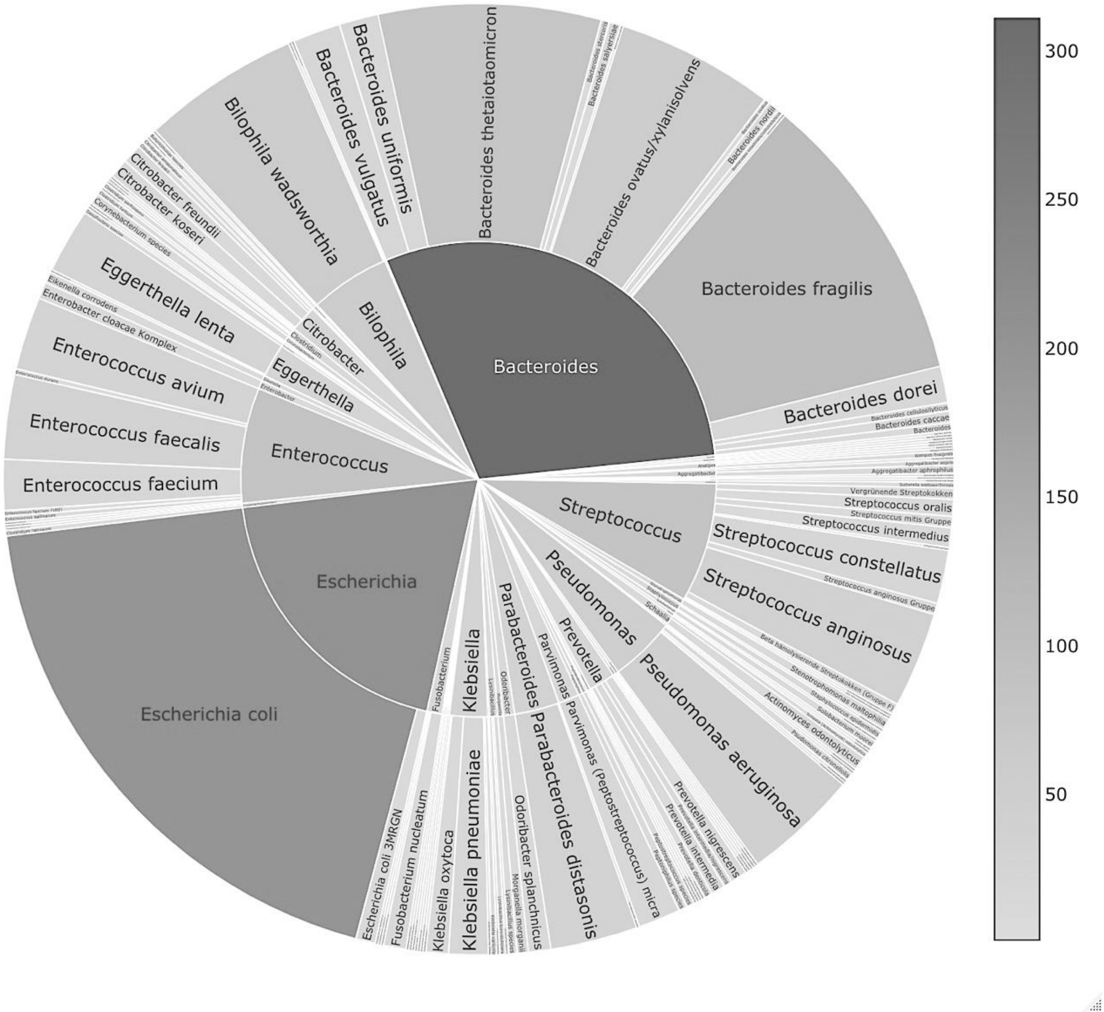

Figure 15. Microbial Spectrum of Complicated Appendicitis.

3.5.2.5 Comparison of Frequent Genera in Microbiological Culture Results from Intraoperative Sampling

To complete the analysis of positive cultures, the following bar chart (Figure 16) presents the most common genera from intraoperative sampling. It compares the frequency of detection of at least one species of this genus relative to the amount of all valid intraoperative samples in the UA and CA groups.

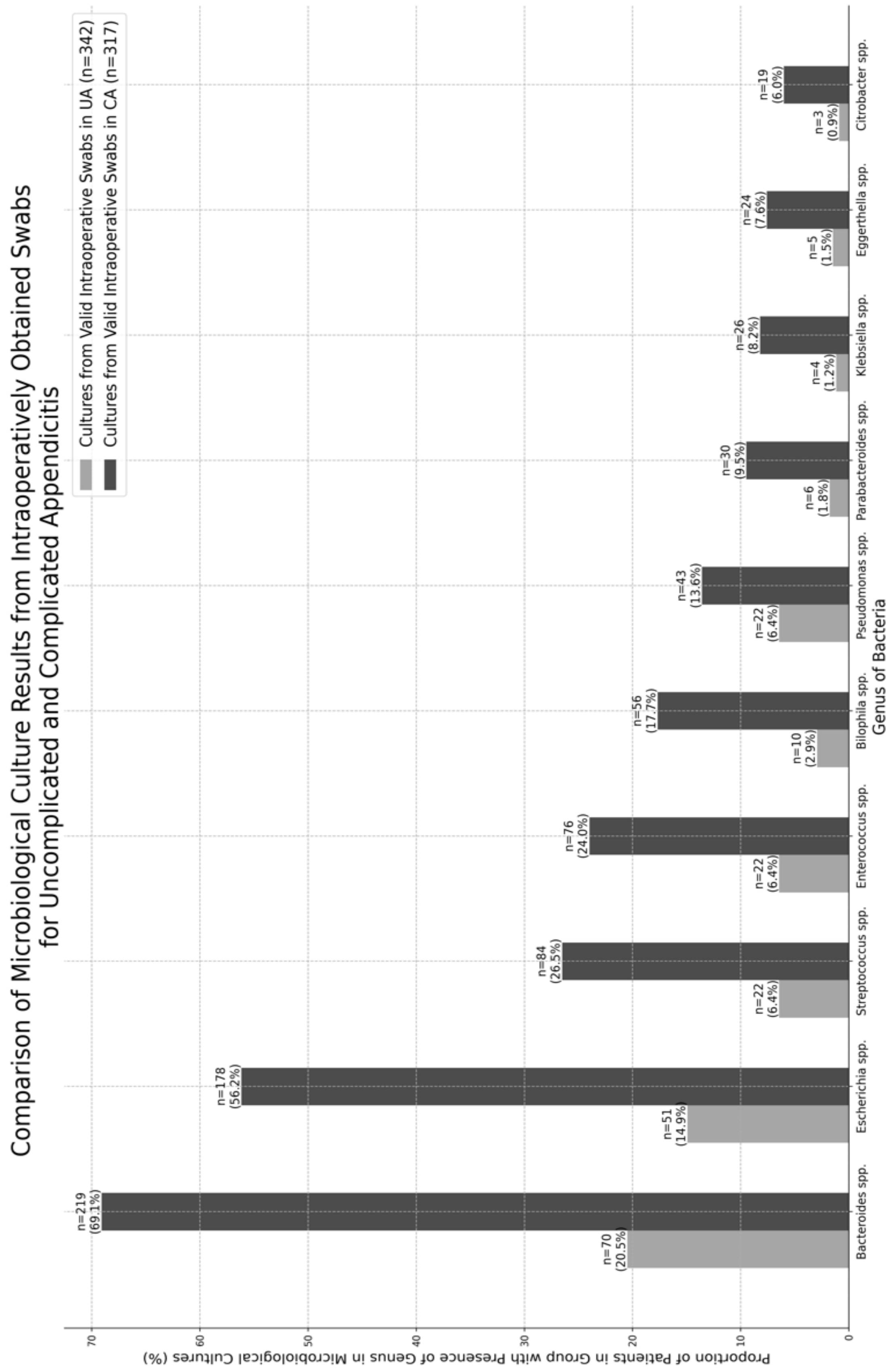

Figure 16. Comparison of Intraoperative Microbiological Culture Results.

It is notable that the distribution of genera is similar between the UA and CA groups, as in both groups, the bars decrease in a similar proportion from left to right on the plot. However, the main difference between the groups is the positive culture rate. For example, in the CA group, Bacteroides spp. were found in 69.1% of patients with cultures from valid intraoperative swabs, whereas in the UA group, this was only the case for 20.5% of patients. This corresponds to the positive culture rate for Bacteroides spp. being 3.4 times higher in the CA group. Overall, for the ten most common genera from intraoperative swabs, the frequency of positive cultures for a given genus in cultures is approximately 2 to 6 times higher in the CA group compared to UA.

3.6 Postoperative Course

In this section, differences in the postoperative course between the UA and CA groups will be examined. Focus areas include hospital stay duration, postoperative laboratory trends, and postoperative antibiotic therapy. Postoperative complications will be presented in chapter 3.8.

3.6.1 Duration of Hospital Stay

The average postoperative hospital stay duration, measured in days, across all cases, was 2.90 ± 3.03 SD (range: 0 to 56 days) and differed significantly among UA cases (1.97 ± 0.94), CA cases (4.77 ± 4.51), and NA cases (2.84 ± 3.67) ($F = 1070.912$; $p < .001$).

The distribution of postoperative hospital stay duration of UA and CA patients is visualized by a cumulative incidence plot of hospital discharges presented in Figure 17. Dotted lines have been added to mark the days on which 50% and 90% of patients have been discharged. The 50% line corresponds to the median hospital stay duration, which was four days in the CA and two days in the UA group.

By the end of the second postoperative day, over 80% of UA cases have been discharged. On the third postoperative day, over 90% of UA cases have been discharged. For the CA group, the 90% mark is reached by day 8. A small number of UA cases were already discharged on the day of surgery (equivalent to day 0).

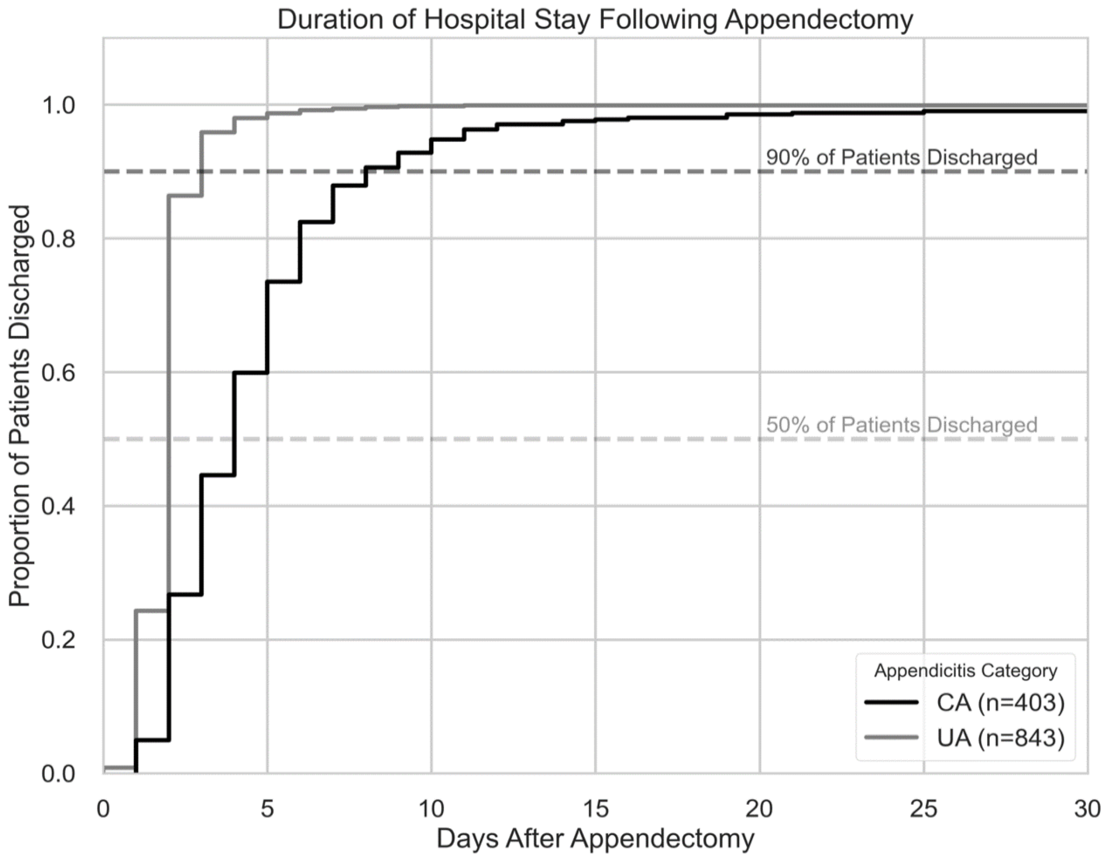

Figure 17. Duration of Hospital Stay Following Appendectomy.

3.6.2 Postoperative Course of Laboratory Tests

The following section presents the course of certain laboratory parameters, such as leukocyte count, hemoglobin levels, etc., during the first seven postoperative days for the UA and CA groups. Note that five cases previously identified as outliers in section 3.2.5 (Preoperative Laboratory Diagnostics) are excluded in the following analyses. Before analyzing the course of those laboratory values, it is important to consider the decreasing amount of blood samples over the postoperative one-week period.

The indications for postoperative blood sampling and the specific laboratory parameters examined varied individually based on patients' pre-existing conditions and their current health status. In the UA and CA groups, the number of blood samples collected, and consequently, the retrospective availability of laboratory parameters during the postoperative course, decreased logarithmically over the postoperative one-week period. This limited data availability is mainly due to the length of the postoperative hospital stay duration, so that blood sampling was performed in less than half of the cases in both groups as early as the second postoperative day.

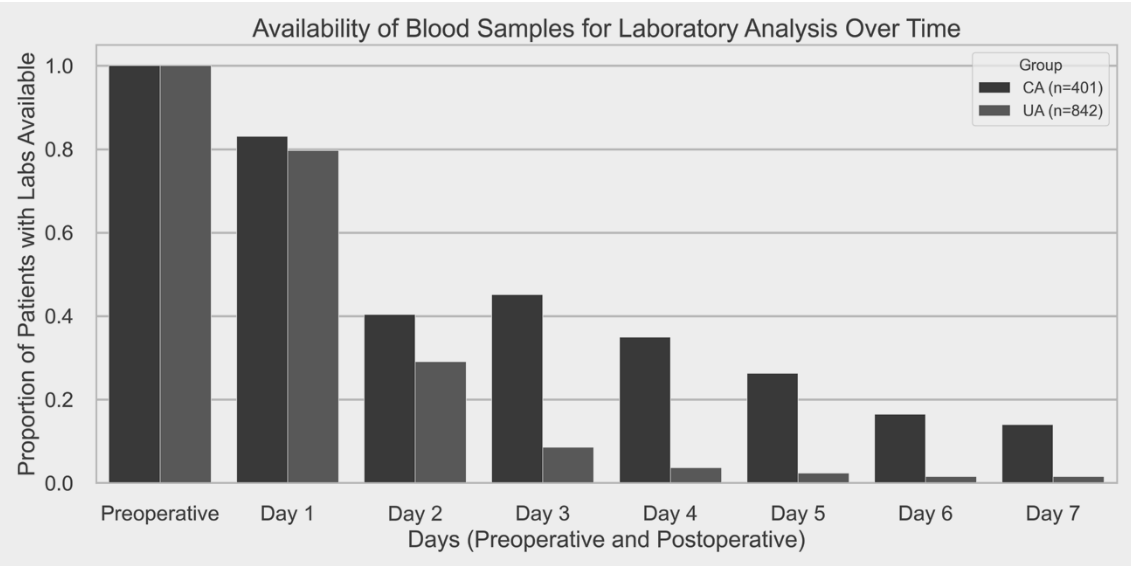

Figure 18. Perioperative Availability of Laboratory Parameters.

In the following section, the postoperative course of leukocyte count, hemoglobin level, platelet count, creatinine level, total bilirubin level and CRP level, are presented. These values are presented separately for the groups UA and CA, along with their respective mean values and 95% confidence intervals. It is notable that the confidence intervals increase over the one-week period for all laboratory parameters and findings after the dismission of the majority of patients (UA: 2 days; CA: 4 days) are only available for a non-representative subset of UA and CA cases. Values and comparisons are therefore only considered as representative until the second postoperative day. For a visualization of the non-representative nature of the values from postoperative day 3 to 7, these values are displayed with a decreased opacity in the following graphics. For details regarding this topic, see section 4.2.3.

The trend in mean leukocyte count is presented in Figure 19. Values decrease constantly until postoperative day 2 in both groups. The relative decrease is more significant in the UA than in the CA group.

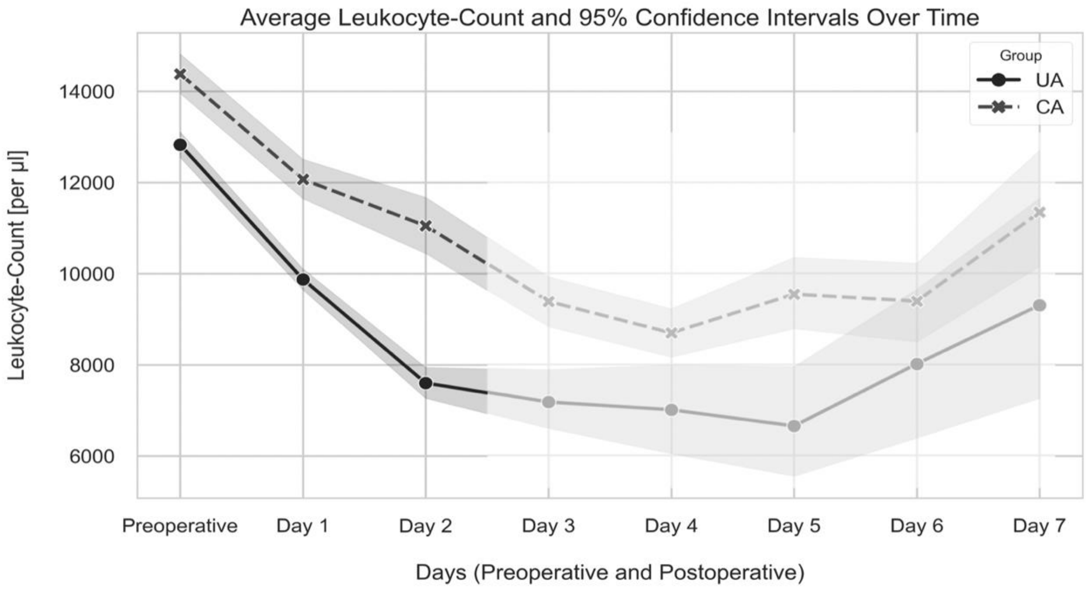

Figure 19. Perioperative Course of Leukocyte Count.

The mean preoperative hemoglobin levels are approximately 14 g/dl in both groups. The levels significantly decrease between the preoperative baseline and the first postoperative day in both groups by approximately 1.5g/dl (Figure 20).

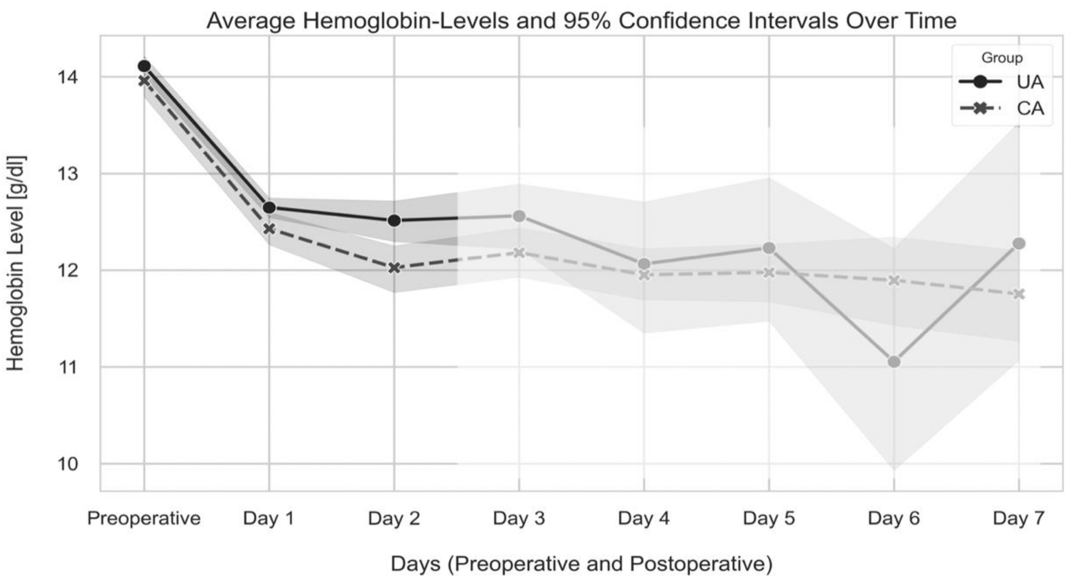

Figure 20. Perioperative Course of Hemoglobin Levels.

The course of the average platelet count is comparable between both groups. Initially, values in both groups decrease from preoperative to the first postoperative day and increase on the second postoperative day (Figure 21), however, not yet reaching preoperative levels.

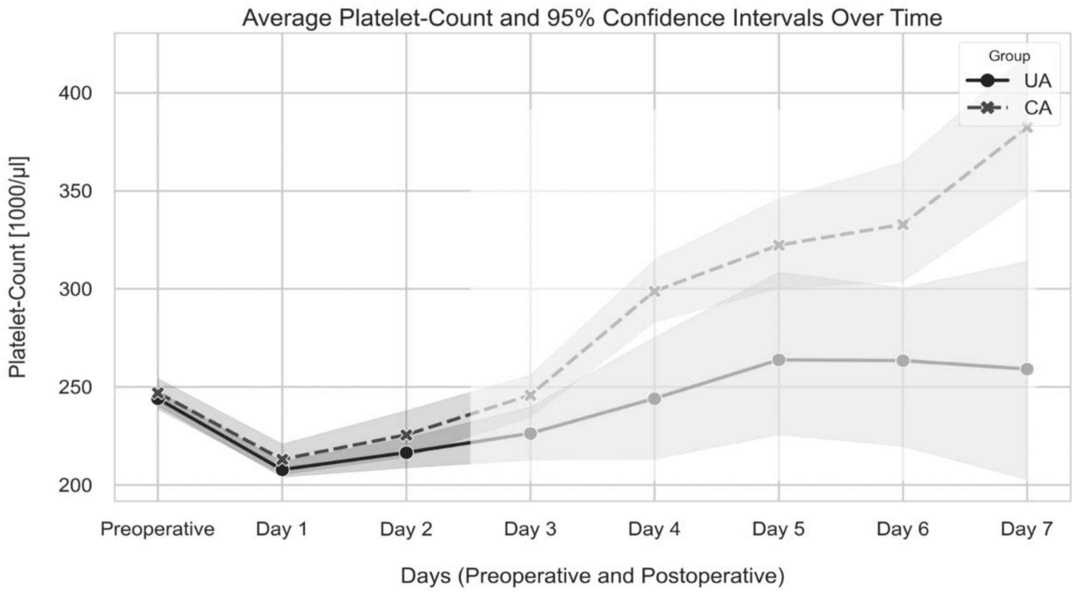

Figure 21. Perioperative Course of Platelet Count.

The postoperative trend of serum creatinine levels is similar across both groups with average values being stable the postoperative time-course (Figure 22). This is true for both, the representative timeframe until the second postoperative day, as well as, until day 7.

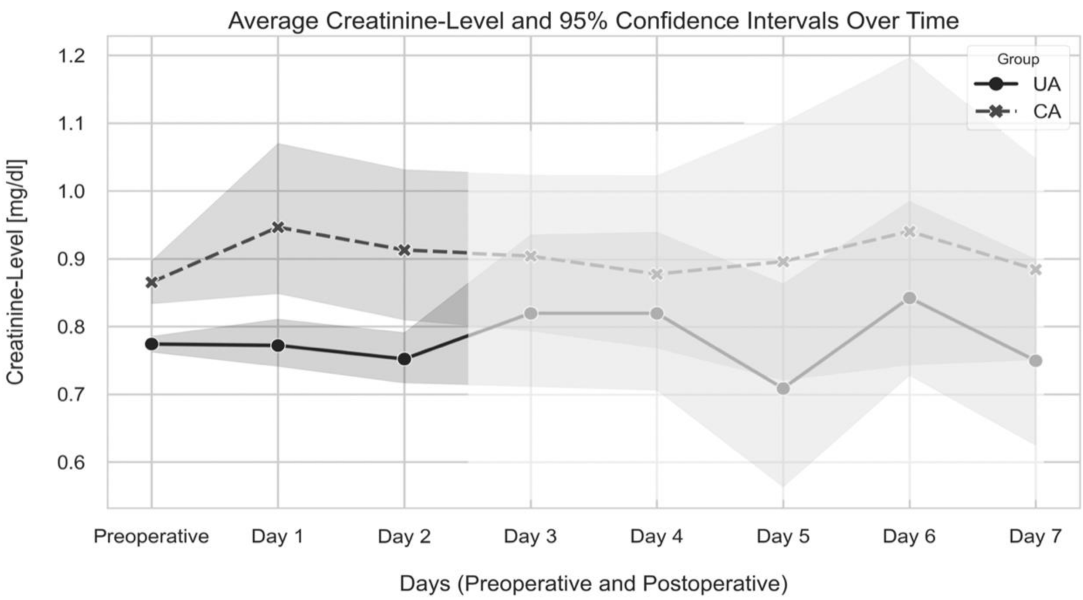

Figure 22. Perioperative Course of Serum Creatinine.

The postoperative trend of total bilirubin levels until postoperative day 2 is comparable between the UA and CA group showing no significant changes from preoperative levels (Figure 23).

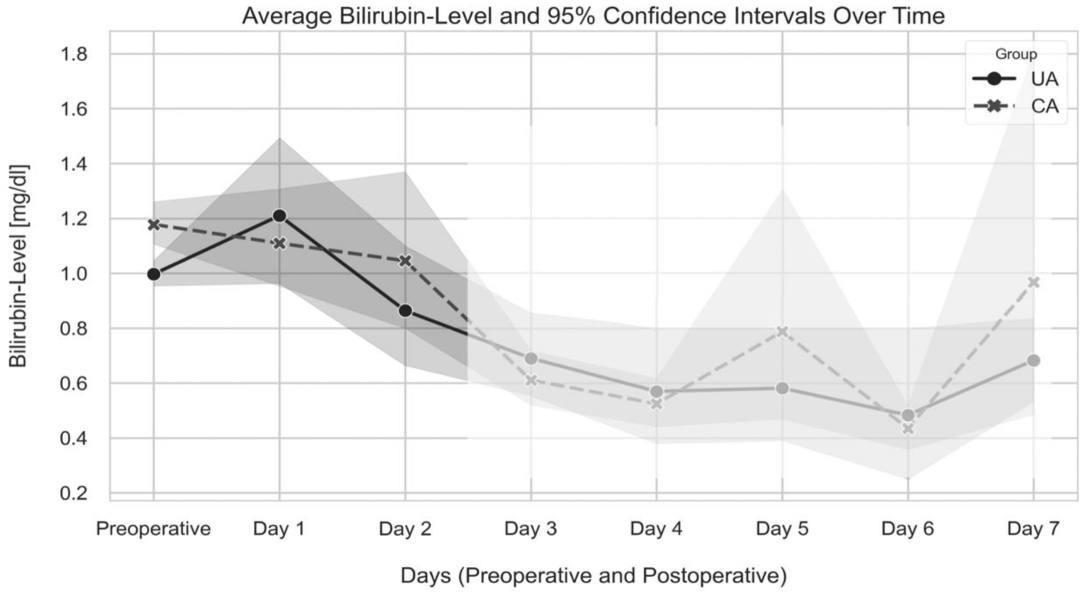

Figure 23. Perioperative Course of Total Bilirubin Levels.

The course of the laboratory parameter CRP varied among the groups (Figure 24). By the first postoperative day, mean CRP levels increased to over twice the preoperative level in the UA and CA groups. In the CA group, mean CRP levels continued to increase significantly from day 1 to day 2, so that they reach twice the preoperative level on day 2.

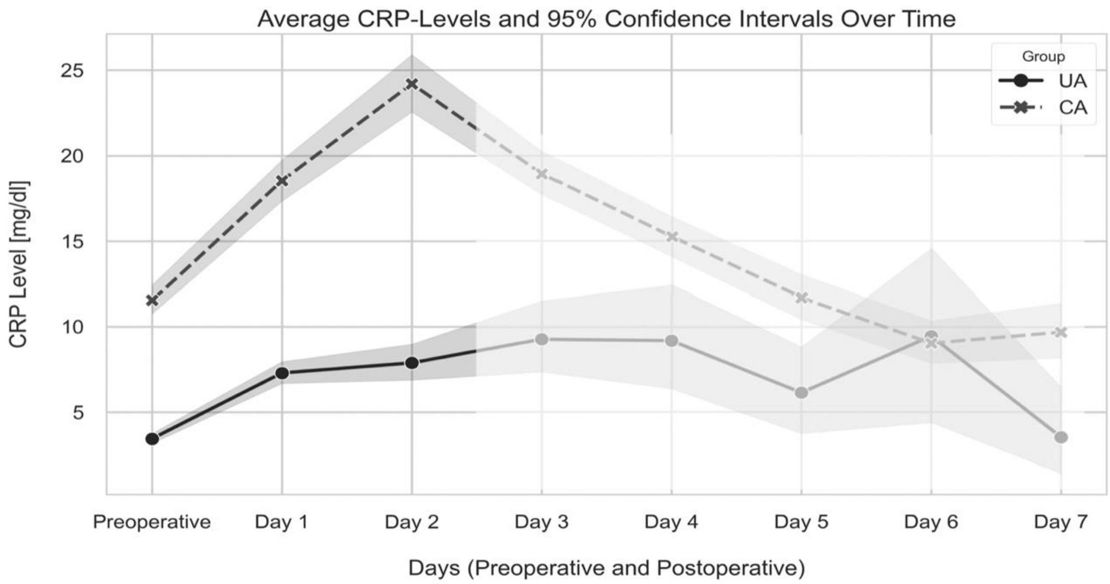

Figure 24. Perioperative Course of C-Reactive Protein Levels.

3.7 Postoperative Antibiotic Therapy

The following chapter presents an analysis of all postoperative administrations of antibiotics related to appendicitis or its complications. Information regarding postoperative antibiotic therapy is not available for n = 4 cases. Considering all other cases included in the study, including NA and NC (n = 1342), it is noteworthy that a primary postoperative empirical antibiotic therapy was prescribed in less than half of all patients (n = 550; 40.98%). The frequency of these prescriptions was significantly higher in the CA group (n = 332; 82.4%) compared to UA (n = 173; 20.5%) ($\chi^2 = 430.31$, $p < .001$) with an Odds Ratio of 18.11 (95% CI: 13.34 – 24.59) (see Table 27 in section 3.7.3).

In the CA group, a higher number of distinct antibiotic agents for empirical therapy were prescribed compared to the UA group (Mann-Whitney U-Test; Z = 20.59; $p < .001$). The average duration of the primary postoperative empirical antibiotic therapy until changing to other agents or termination of treatment was, on average, shorter in the UA group at 1.67 days (SD = 2.01) compared to the CA group at 3.69 days (SD = 2.06) ($t = -10.60$; $p < .001$). Data regarding the duration of postoperative empirical antibiotic therapy is not available for n = 5 cases (0.4%).

3.7.1 Combinations of Antibiotic Agents for Empirical Therapy

Considering cases with UA, CA, and NA, when empirical antibiotic therapy was prescribed, the most common regimens included a combination of two (n = 300; 22.3% of all cases) or a single antibiotic agent (n = 229; 17.0% of all cases). More than two antibiotic agents were prescribed in n = 21 cases (1.5%). In patients, where only one empirically selected antibiotic agent was administered postoperatively, the drugs Piperacillin-Tazobactam (n = 177; 77.3%), Ciprofloxacin (n = 17; 7.4%), Cefotaxime (n = 10; 4.4%), and Amoxicillin-Clavulanic Acid (n = 7; 3.1%) were the most commonly prescribed. The most frequently prescribed combinations for cases, who received two antibiotic agents, are presented in Figure 25.

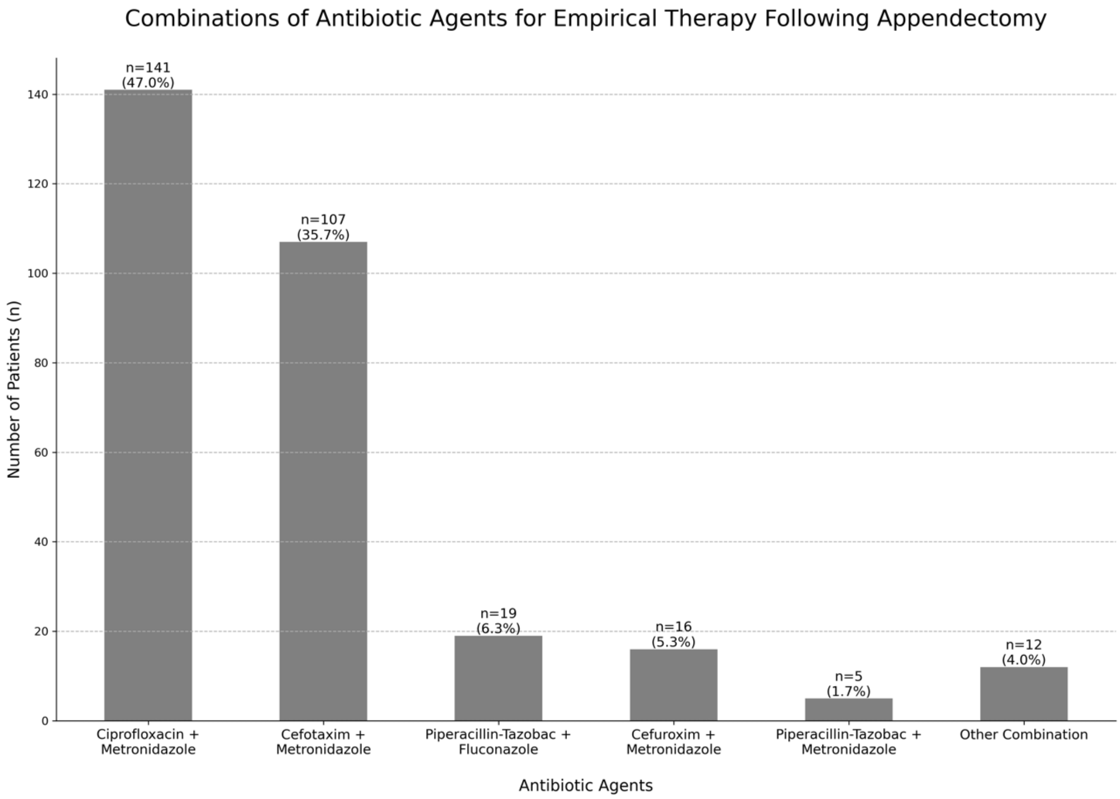

Figure 25. Combinations of Antibiotic Agents for Empirical Therapy Following Appendectomy.

The category “Other combinations” (n = 12; 4.0%) included combinations that were prescribed each in less than 1.0% of cases. These included Cefazolin + Metronidazole (n = 2), Ampicillin-Sulbactam + Metronidazole (n = 2), and agents such as Anidulafungin, Clarithromycin, Meropenem, Tigecycline, and Vancomycin. It is important to note that this graph only includes cases in which an empirical combination of two antibiotic agents was administered postoperatively (n = 300). Cases in which no antibiotics (n = 792), only one antibiotic (n = 229), or more than two antibiotic agents (n = 21) were given postoperatively are not considered.

3.7.2 Antibiogram-Based Assessment of Antibiotic Coverage

Information regarding the coverage of the microbial spectrum and resistance pattern by the primary empirical postoperative antibiotic therapy can only be provided for the subset of cases in which valid intraabdominal swabs were obtained intraoperatively (see section 3.5.1). Intraoperative swabs and antibiograms were available for n = 342 (40.6%) of UA cases and n = 317 (78.7%) of CA cases.

The analysis of microbial spectrum coverage presented in this section (see Table 26) is based on the theoretical fit of the primary empirical postoperative antibiotic therapy prescribed and the antibiogram results, regardless of dosage or duration of treatment. Cases lacking antibiotic resistance testing specifically for the agents prescribed for primary empiric antibiotic therapy are categorized as "Spectrum coverage unclear".

Table 26. Coverage of the Microbial Spectrum and Resistance Pattern by the Primary Empirical Postoperative Antibiotic Therapy.

	UA *(n=342*)*			CA (*n=317*)*		
Coverage of microbial spectrum	*n*	*% of cases with antibiogram*	*% of positive culture results (n=116)*	*n*	*% of cases with antibiogram*	*% of positive culture results (n=263)*
Spectrum not covered	89	26.0%	76.7%	113	35.7%	43.0%
Spectrum covered	24	7.0%	20.1%	131	41.3%	49.8%
Spectrum coverage unclear	3	0.9%	2.6%	19	6.0%	7.2%
Negative culture results	226	66.1%	-	54	17.0%	-

*Note that this is a subgroup of patients (40.6% of UA and 78.7% of CA) in whom valid intraabdominal swabs were obtained intraoperatively and a corresponding antibiogram was available.

Negative microbiological culture results represent a special case of the antibiogram-antibiotic therapy fit and are, therefore, listed in a separate category, which is excluded for analysis in two of the columns in Table 26 so that the coverage can be either assessed irrespective of culture results or for cases with positive cultures exclusively.

3.7.3 Course of the Postoperative Antibiotic Therapy

The primary postoperative empirical antibiotic therapy, which was prescribed in less than half of all patients (n = 550), was continued without any changes until completion in 71.1% (n = 391) of these patients (UA: 89.0%; CA: 61.4%). In other cases, the therapeutic regimen was adjusted in response to changes in the clinical presentation of the patient, laboratory abnormalities, or availability of antibiograms. Other reasons for modifying the primary empiric antibiotic therapy included oralization of medication or switching due to suspicion of allergic reactions. Table 27 provides an overview of the course of the primary postoperative antibiotic therapy for UA and CA cases.

As antibiotics with similar spectra of activity and comparable antibiotic efficacy were substituted for others in some instances, not all changes can be categorized as escalations or de-escalations of antibiotic therapy. Note that oralization, even though typically seen as part of a de-escalation strategy, is not classified as such in Table 27. This is due to the variety of reasons for oralization in the patient cohort, of which some could be classified as escalation, some as de-escalation, and others such as oralization due to pharmacokinetic considerations, or patient-specific factors such as limited IV access could not be classified.

Table 27. Course of the Primary Empiric Postoperative Antibiotic Therapy.

Primary empiric antibiotic therapy	UA *(n=843)*			CA (*n=403)*		
	n	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Termination without change of agents	154	18.3%	89.0%	204	50.6%	61.4%
De-escalation of agents	5	0.6%	2.9%	18	4.5%	5.4%
Escalation of agents	4	0.5%	2.3%	30	7.4%	9.0%
Change of agents for other reason*	10	1.2%	5.8%	80	19.9%	24.1%
No primary empiric antibiotic therapy	666	79.0%	-	71	17.6%	-
No information available	4	0.5%	-	0	0.0%	-

*Including: Suspicion of allergic reaction (UA: n = 0; CA: n = 3), Oralization (UA: n = 8; CA: n = 64), and switch to an equivalent substitute without specification of reasons (UA: n = 2; CA: n = 13).

The frequency of primary empiric postoperative antibiotic therapy prescriptions was significantly higher in the CA group compared to UA (see introduction of section 3.7). In line with that, there are also notable differences in the course of this therapy comparing UA and CA cases: While in the UA group 89.0% of antibiotic regimens were continued without any change until termination, 4.6% oralized and only 2.3% escalated, in the CA group fewer antibiotic regimens were continued unchanged until termination (61.4%) and more oralized (19.2%) or escalated (9.0%).

An analysis of the reasons for the n = 30 CA cases with escalations of the primary empiric antibiotic therapy showed that antibiograms were considered in more than half of these cases (56.7%, n = 17). In the other cases of escalations in the CA group (n = 13), the decision was based exclusively on clinical symptoms or laboratory findings. A similar result was found for escalations in the UA group (n = 4). The decision to escalate the therapy was based on antibiograms in two cases (50.0%) and exclusively on clinical symptoms or laboratory findings in the remaining two cases (50.0%).

A similar pattern was found for de-escalations, as the antibiogram played a role in 61.1% of the CA and 60.0% of the UA cases that underwent de-escalation. Overall, this corresponds to a proportion of 56.8% of escalations or de-escalations for UA and CA cases for which the antibiogram was considered by the treating surgeon. However, when considering the total number of UA and CA cases for which antibiograms were available (n = 659), the proportion of UA and CA cases in which the postoperative antibiotic therapy was adjusted according to the antibiogram (i.e., escalation or de-escalation) decreases to 8.7%.

In a total of n = 9 cases (UA: n = 4; CA: n = 5; NA: n = 0; NC: n = 0) in which initially no primary postoperative empirical antibiotic therapy was prescribed, during the course of hospitalization, a decision was made to initiate antibiotic treatment. The reasons for this decision included one newly occurring complicated urinary tract infection, a prolonged postoperative course with ongoing drainage and ileus, atypical microbial profiles with unusual resistance patterns observed in a patient following prior international travel, unusual microbial profiles in a patient originating from a non-European region, and a case involving postoperative fever. Postoperative revision surgeries and the antibiotic therapies administered in such cases are discussed in the following chapter.

3.8 Postoperative Complications

This chapter addresses postoperative complications that occurred either during the initial hospital stay or led to an emergency return visit at the University Hospital Tübingen within 90 days after surgery. Complications are assessed according to the Dindo-Clavien classification, and comparisons are drawn among the patient groups.

3.8.1 Overview of All Postoperative Complications

A comparison of UA and CA shows that all postoperative complications specified in Table 28 occurred significantly more frequently in the CA group. Among the most common complications occurring outside of the surgical site are ileus and fever (for definitions, see section 2.6). Postoperative intraabdominal abscesses represent the most common complication located at the surgical site and occur significantly more often in the CA group than in the UA group (Odds Ratio: 23.09; 95% CI: 8.20 – 65.00). To account for the slightly varying rates of missing data for each complication, Table 28 shows the number of cases for which data were available in a separate column labeled "*valid n*".

Table 28. Postoperative Complications.

	Uncomplicated appendicitis			Complicated appendicitis			Statistic	
Postoperative complication	*valid n*	*n*	*% of valid n*	*valid n*	*n*	*% of valid n*	*Odds Ratio (95% CI)*	*p**
Acute kidney injury	843	2	0.2%	402	10	2.5%	10.73 (2.34 – 49.19)	<.001
Constipation	842	20	2.4%	402	101	25.1%	13.79 (8.39 – 22.68)	<.001
Body temperature > 37.0 °C	838	99	11.8%	402	194	48.3%	6.96 (5.23 – 9.28)	<.001
Sepsis	843	2	0.2%	403	5	1.2%	5.28 (1.02 – 27.35)	.039
Impaired wound healing	843	9	1.1%	402	17	4.2%	4.09 (1.81 – 9.26)	<.001
Intraabdominal abscess	842	4	0.5%	403	40	9.9%	23.09 (8.20 – 65.00)	<.001
Appendix stump leak	843	0	0.0%	403	5	1.2%	-	.003
Peritonitis	843	2	0.2%	403	24	6.0%	26.63 (6.26 – 113.24)	<.001

Note that rates of missing data for specific complications vary slightly for different complications. Percentage values, therefore, represent the proportion of available (valid) cases.
*All p-values derived from two-sided, non-directional χ^2 test of independence or Fisher's exact test for cases in which expected frequencies of n < 5 per cell.

The Dindo-Clavien classification of complication severity was applied to the subgroup of patients (UA: n = 148; CA: n = 223; NA: n = 20) in which either 1. one of the complications listed in Table 28 was documented, 2. a revision procedure was performed during the hospital stay, or 3. an emergency return visit and re-consultation within a 90-day period after surgery was documented.

The severity grades across cases can be categorized as follows: Grade 0 (29.6%), Grade I (35.9%), Grade II (19.7%), and greater than Grade 2 (14.8%). Figure 26 provides a breakdown of the distribution of postoperative complication severity for the mentioned subgroup, segmented by UA, CA, and NA.

The majority of cases in all three groups can be assigned to Grade 0 or Grade 1 complications (UA: 79.1%, CA: 56.7%, NA: 95.0%). In both, the UA and CA group, one patient had a Grade V complication. For all other complications of Grade 2 or greater, CA cases show higher proportions, than UA or NA cases. Grades IIIa and IVa were only present in CA (6.5% and 2.1%), but not in UA or NA cases.

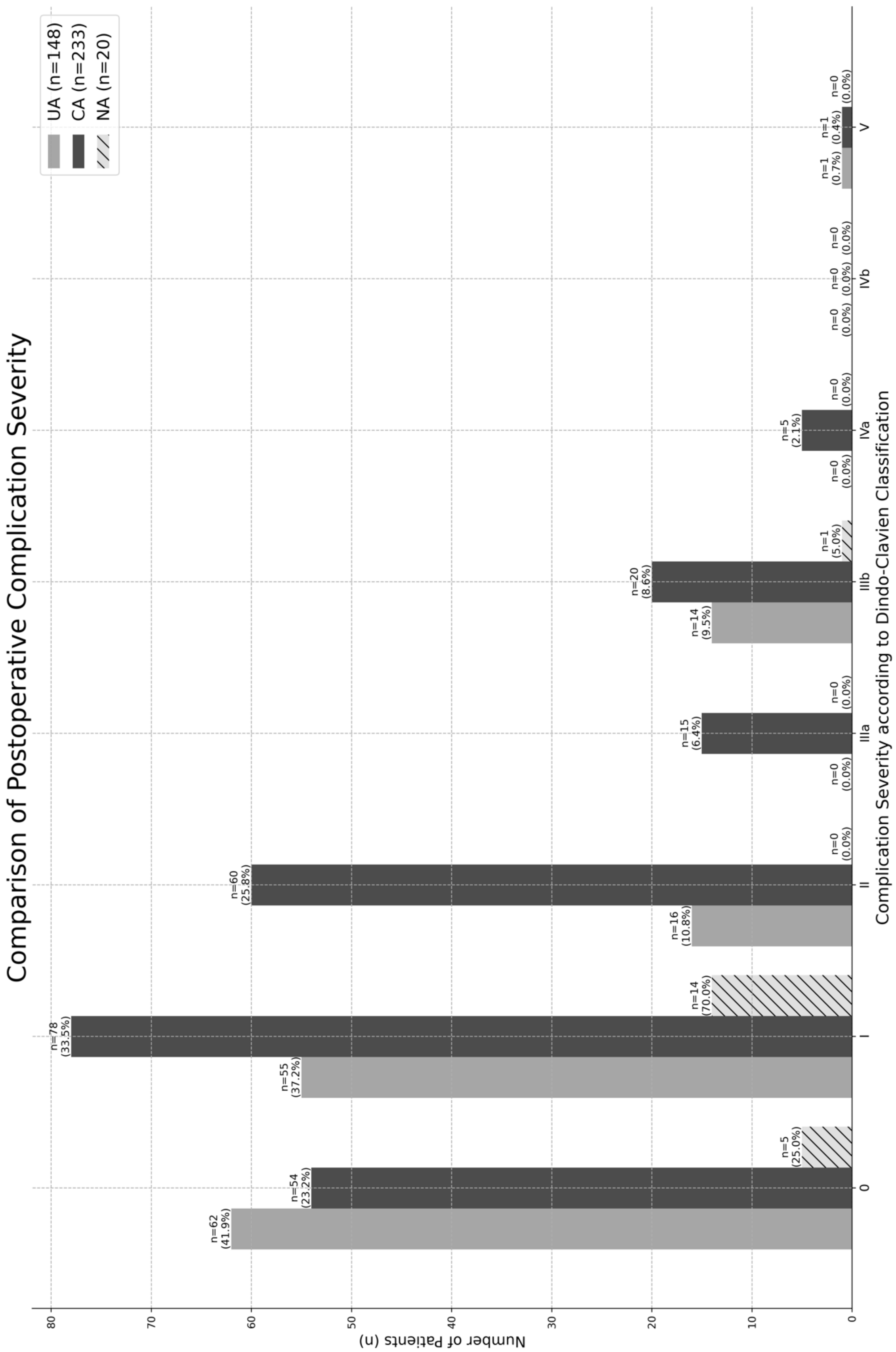

Figure 26. Severity of Postoperative Complications.

Mortality rates, corresponding to grade V complications were low in UA (0.7%) and CA (0.4%). However, when considering not only the subset of cases that was reported to have any postoperative complication but all patients undergoing appendectomy, these proportions decrease even more to 0.12% for UA (n = 1 / 843), and 0.25% for CA (n = 1 / 403).

3.8.2 Surgical Site Infections

Surgical site infections (SSIs) following appendectomy occurred in n = 73 cases (UA: n = 12, CA: n = 55, NA: n = 2, NC: n = 4), corresponding to a rate of 5.4% for all cases. These infections can further be classified into superficial (involving the cutis and subcutis of the surgical incisions), deep incisional (involving tissue from below the subcutis up to muscle fasciae), and organ or space surgical site infections (involving any other organ or space between organs of the body that was involved in the surgery).

The distribution of SSIs in UA and CA is presented in Table 29. The most common SSIs were organ and space infections for the CA (11.2%), and superficial infections for the UA group (0.8%). There was no significant difference in the frequency of deep incisional SSIs between the groups (p = .148), as there was only one such case in the CA and no case in the UA group.

Table 29. Postoperative Surgical Site Infections.

	UA *(n=843)*			CA (*n=403*)			Statistic
Surgical site infection	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Superficial incisional	7	0.8%	0.8%	9	2.2%	2.2%	.040^{Z}
Deep incisional	0	0.0%	0.0%	1	0.3%	0.3%	.148^{Z}
Organ or space between organs	5	0.6%	0.6%	45	11.2%	11.2%	<.001^{Z}
No surgical site infection	831	98.6%	98.6%	348	86.3%	86.3%	<.001^{Z}
Not specified	0	0.0%	-	0	0.0%	-	-

^{Z} Two-proportion Z-test

Overall, SSIs occurred significantly more often in the CA group (n = 55, 13.7%), compared to UA (n = 12, 1.4%). The odds of any surgical site infection were over 10 times higher for CA cases (χ^2 = 77.69, OR = 10.95, 5.79 – 20.69, p < .001), compared to UA. This result is in line with the observations regarding revision rates during the initial hospital stay, as well as, revisit, readmission and revision surgery rates, all of which are higher in the CA compared to the UA group, as presented in the following sections.

3.8.3 Revision Procedures During the Initial Hospital Stay

A reoperation or abscess drainage was performed in n = 21 cases during the initial hospital stay (UA: n = 3; CA: n = 18; NA: n = 0; NC: n = 0). The timing for this procedure ranged from one to 10 days (4.81 ± 3.01 days) after the appendectomy. The main symptoms reported by the patients included abdominal pain (n = 16), fever or chills (n = 8), constipation (n = 2), or vomiting (n = 1). As a result, radiological diagnostic procedures were conducted in a large proportion of these patients to investigate their symptoms (n = 19; 90%). The primary radiological diagnoses were: intraabdominal abscess or fluid collection in n = 9 cases, perforation or leakage of the staple line, suture or GI-tract anastomosis in n = 4 cases, ileus in n = 2 cases, and other unclassified diagnoses in n = 4 cases.

3.8.4 Return Visits, Readmissions and Revision Surgeries

Among all patients discharged who did not undergo a revision procedure during the initial hospital stay, n = 116 (8.62%) presented emergently with symptoms potentially related to the appendectomy (e.g., including any gastrointestinal symptoms, nausea and vomiting, fever and chills, superficial or deep pain in the area of surgery, or impaired wound healing, but excluding emergency visits due to injuries or elective consultations) within a 90-day postoperative period. In 37.9% of these emergent re-consultations, patients were readmitted for the management of postoperative complications (n = 44). Among these readmitted patients, n = 27 subsequently underwent surgical intervention (or abscess drainage) to treat a complication of the prior appendectomy (Figure 27).

Out of all n = 1346 emergency appendectomies performed, n = 48 (3.57%) of the patients required reoperation or abscess drainage postoperatively. Among them, n = 21 (abscess drainage: n = 4; reoperation: n = 17) occurred during the initial hospital stay, and n = 27 (abscess drainage: n = 8; reoperation: n = 19) followed an emergency readmission.

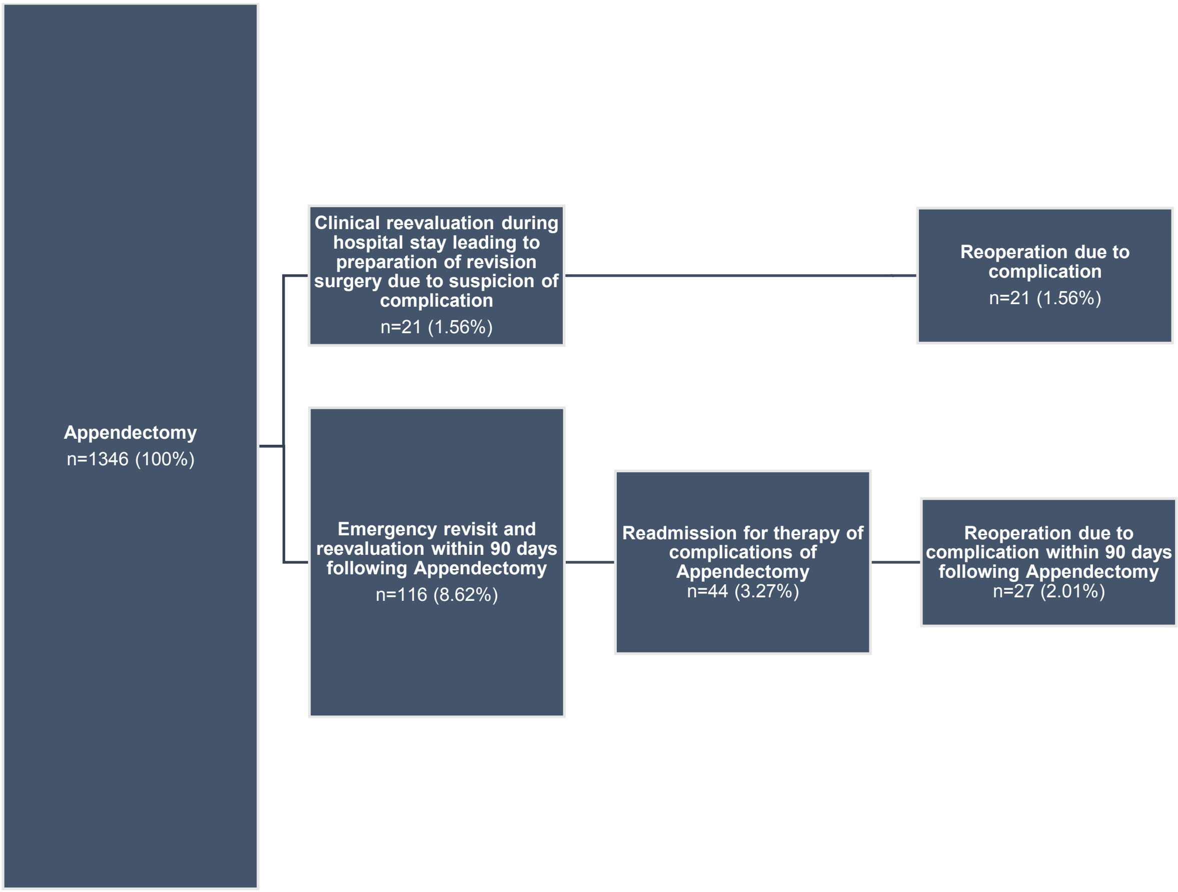

Figure 27. Patient Emergency Revisits, Readmissions, and Reoperations within a 90-Day Timeframe Following Appendectomy.

3.8.4.1 Emergency and Elective Hospital Return Revisits and Re-consultations

In the 90-day postoperative course, among all patients discharged, who did not already undergo a revision procedure during their hospital stay (n = 1325; UA: n = 840; CA: n = 385; NA: n = 79; NC: n = 21), patients from the CA group returned to the emergency department significantly more often with symptoms, which are possibly related to appendicitis or appendectomy (CA: n = 56; 14.55%), than those from the UA group (UA: n = 49; 5.84%) ($\chi^2 = 24.47$, $p < .001$). This result indicates that the odds of such an emergency revisit are 2.75 times higher for cases of CA, compared to UA (95% CI: 1.83 – 4.12). There was no group difference regarding the time interval between the appendectomy and emergency revisit (UA: 17.2 ± 17.5 days; CA: 15.7 ± 13.7 days; $t = 0.492$, $p = .624$).

From the NA group, n = 6 patients (7.60%), and from the NC group, n = 5 patients (23.81%), presented to the emergency department with symptoms which were documented as possibly related to the appendectomy. In another n = 22 cases that presented again within 90 days, the symptoms were considered as unrelated to the preceding appendectomy. Therefore, these cases are not discussed in further detail. Additionally, n = 28 patients returned for elective follow-up concerning conditions identified during the appendectomy. The most common reason for elective follow-up visits was oncological surveillance and related elective surgery due to incidental findings of neoplasms of the appendix.

No significant difference in the distribution of symptoms at emergency revisits (Table 30) was found between UA and CA cases (χ^2 = 7.50, p = .186). Therefore, no post-hoc tests were calculated for this variable. Abdominal pain was the most common main symptom in both groups (UA: 57.1%, CA: 41.5%).

Table 30. Main Symptoms Leading to Emergency Revisits.

	UA *(n=49)*			CA (*n=56)*		
Main symptom	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*
Abdominal pain	28	57.1%	57.1%	22	39.3%	41.5%
Fever or chills	8	16.3%	16.3%	19	33.9%	35.9%
Nausea or vomiting	2	4.1%	4.1%	1	1.8%	1.9%
Superficial wound pain	3	6.1%	6.1%	6	10.7%	11.3%
Gastrointestinal complaints	3	6.1%	6.1%	1	1.8%	1.9%
Wound infection	5	10.2%	10.2%	4	7.1%	7.6%
Not specified	0	0.0%	-	3	5.4%	-

Imaging studies were performed in 91.8% of UA, and 85.7% of CA cases during the emergency revisit (Table 31). The distribution of main radiological findings differed significantly across the UA and CA groups (χ^2 = 28.20, p < .001). Normal postoperative findings were significantly more frequent in the UA group (UA: n = 31, 68.9%) compared to CA cases (n = 13, 27.1%; Z = 4.04, p < .001).

Table 31. Main Radiological Findings in Emergency Revisits.

	UA *(n=49)*			CA (*n=56)*			Statistic
Main radiographic finding	*n*	*% of total n*	*% of valid n*	*n*	*% of total n*	*% of valid n*	*p*
Normal postoperative findings	31	63.3%	68.9%	13	23.2%	27.1%	<.001^Z
Intraabdominal abscess or fluid collection	3	6.1%	6.7%	26	46.4%	52.2%	<.001^Z
GI-tract perforation or staple line leak	1	2.0%	2.2%	2	3.6%	4.2%	.596^Z
Hernia	1	2.0%	2.2%	1	1.8%	2.1%	.963^Z
Ileus	4	8.2%	8.9%	2	3.6%	4.2%	.354^Z
Pathology of (sub-)cutaneous scar tissue	2	4.1%	4.4%	1	1.8%	2.1%	.520^Z
Gynecologic pathology	1	2.0%	2.2%	1	1.8%	2.1%	.963^Z
Thrombotic event	0	0.0%	0.0%	1	1.8%	2.1%	.330^Z
Other pathology	2	4.1%	4.4%	1	1.8%	2.1%	.520^Z
No imaging study	4	8.2%	-	8	14.3%	-	-

^{Z} Two-proportion Z-test

The most prevalent main radiological findings were intraabdominal abscesses or fluid collections occurring in more than half of all CA revisit cases in which imaging studies were performed (n = 26, 52.2%) compared to less than 10% in the UA group (n = 3, 6.7%; Z = -4.94, p < .001). For all the other categories of main radiographic findings, no significant difference in proportions could be found between UA and CA. However, it is important to note the smaller sample sizes for those categories.

3.8.4.2 Indications for Patient Readmissions

Among the n = 116 patients, who presented emergently with symptoms possibly related to appendectomy within 90 days following the procedure, most (n = 67; 57.8%) were either discharged or treated as outpatient cases. Five patients, who were readmitted, were not classified as emergency readmissions for treatment of symptoms causally related to appendicitis or appendectomy.

In total, n = 44 patients were readmitted for the treatment of symptoms which were found to be causally related to appendicitis or appendectomy (UA: n = 11; CA: n = 29; NA: n = 0; NC: n = 4). Patients in the CA group (n = 29; 7.5%) were readmitted significantly more often than those from the UA group (n = 11; 1.3%) (χ^2 = 30.43, p < .001). This result indicates that the odds of readmission for CA cases were 6.14 times higher, than for UA cases (95% CI: 3.03 – 12.43).

The most common reason (n = 23) for readmission was suspicion of intraabdominal abscesses or intraabdominal fluid collections. Another frequent reason (n = 5) was the suspicion of bowel obstruction. In n = 4 cases each, patients were admitted for the surgical treatment of incisional hernias, surgical treatment of cutaneous or subcutaneous scarring tissue inflammation, or for non-operative inpatient antibiotic therapy. Additional reasons for readmissions included one case of severe pain requiring inpatient analgesic therapy, one thrombotic event, one paracolic hematoma extending into the lesser pelvis, and one case of a right-sided hydrosalpinx (blockage of the fallopian tube), resulting from spreading of the infection from the appendix to the right salpinx.

3.8.4.3 Antibiotic Therapy in Cases of Readmissions and Revision Procedures

Readmitted patients with symptoms classified as causally related to the appendectomy or appendicitis, received antibiotic therapy in 77.3% (n = 34 / 44).

The average duration of post-revision-surgery antibiotic therapy was 6.36 ± 2.27 days (range 4 – 16 days) with no significant differences between the UA and CA groups (UA: 6.20 ± 1.10 days; CA: 6.39 ± 2.44 days; $t = -0.174$; $p = .863$). Patients with CA received a higher number of different antibiotic agents compared to cases with UA (Mann-Whitney-U test: $Z = 3.355$; $p < .001$).

When only a single antibiotic drug was administered (n = 12), Piperacillin/Tazobactam was the most commonly prescribed (n = 5), followed by Meropenem (n = 2). Amoxicillin/Clavulanic Acid, Ampicillin/Sulbactam, Ciprofloxacin, and Metronidazole were each prescribed in one case each. In one case the type of antibiotic agent was not documented.

The most frequently administered combinations of antibiotics for cases in which a combination of two antibiotic agents was administered after the revision procedure (n = 17) are presented in Table 32.

Table 32. Combinations of Antibiotic Agents in Revision Procedures.

Combinations of two antibiotic agents			*n (%)*
Ciprofloxacin	+	Metronidazole	5 (29.4%)
Piperacillin/Tazobactam	+	Metronidazole	4 (23.5%)
Piperacillin/Tazobactam	+	Amoxicillin/Clavulanic Acid	2 (11.8%)
Piperacillin/Tazobactam	+	Fluconazole	2 (11.8%)
Piperacillin/Tazobactam	+	Ceftriaxone	1 (5.9%)
Piperacillin/Tazobactam	+	Erythromycin	1 (5.9%)
Cefotaxime	+	Metronidazole	1 (5.9%)
Ciprofloxacin	+	Cefotaxime	1 (5.9%)

Note that this table exclusively contains cases in which a combination of two antibiotic agents was administered following the revision procedure (n = 17). Cases in which one antibiotic agent (n = 12), or ≥3 antibiotic agents (n = 10) were prescribed are not presented in this table.

The following flow chart (Figure 28) provides an overview of the antibiotic therapy administration at different stages of the patient journey. The figure illustrates the proportion of patients receiving antibiotic therapy at various stages observed in this study, including perioperative treatment, hospitalization, patient discharge, emergency return hospital revisits, readmissions and revision procedures. Note that the shading intensity of the rectangular objects corresponds to the proportion of cases receiving antibiotic therapy at a particular stage. For the timepoints "No Emergency Hospital Revisit" and "Emergency Hospital Revisit" no shading is applied, as patients typically did not receive antibiotics during this timeframe.

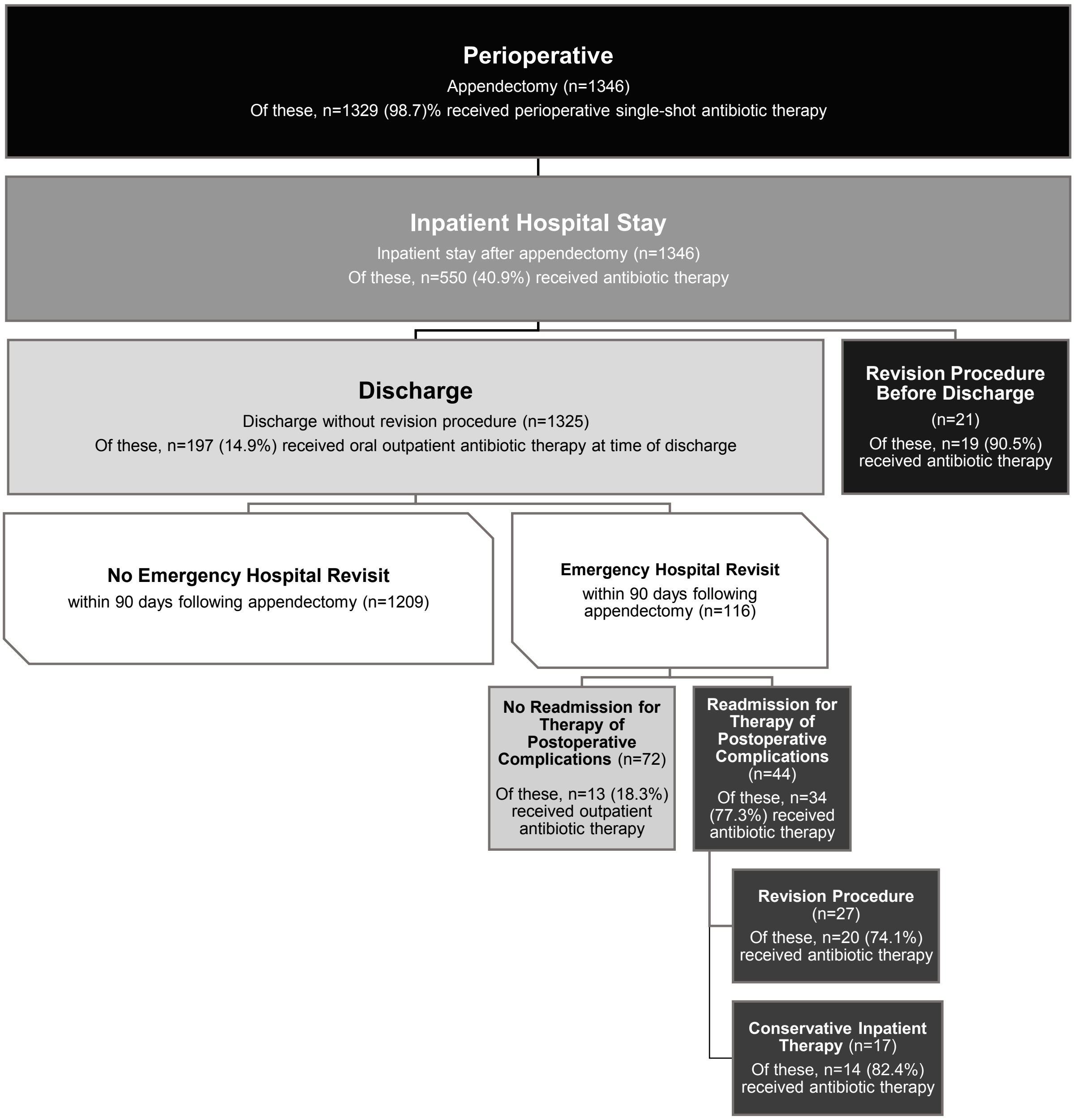

Figure 28. Overview of Antibiotic Therapy Administration at Different Stages of the Patient Journey.

Considering all timepoints, it can be observed that the maximum frequency of antibiotic therapy administration is at the perioperative time period when 98.7% of cases had antibiotic therapy documented. Less than half (40.9%) of the patients received an antibiotic therapy during their following hospital stay. Patients who underwent a revision procedure during their hospital stay (n = 21) received antibiotic therapy in 90.5% of cases following the revision procedure. Of the n = 1325 patients discharged without having to undergo a revision procedure, 14.9% received oral out-patient antibiotic therapy at discharge. Out of the n = 44 patients, who were readmitted for postoperative complication treatment, antibiotic therapy was restarted in 77.3% of cases. While some of the readmitted patients underwent non-operative management of complications including in-patient antibiotic therapy in 82.4% of cases, the majority of patients underwent a revision procedure such as a reoperation or abscess drainage. The frequency of antibiotic therapy in these patients was 74.1% and thereby comparable to the non-operative management group.

3.8.4.4 Emergency Revision Procedures upon Readmission

In a total of n = 27 cases who revisited the hospital's emergency department (UA: n = 8; CA: n = 16; NA: n = 0; NC: n = 3), revision surgery (n = 19) or abscess drainage (n = 8) was conducted to treat complications of appendicitis or appendectomy. The average time difference from appendectomy to emergency revision procedure was 16 days and ranged from 2 to 88 days (16.1 ± 19.3 days) for this group of patients (excluding revision procedure during the initial hospital stay).

The main symptoms experienced by these patients following appendectomy were: abdominal pain (n = 12), fever or chills (n = 10), gastrointestinal complaints (n = 2), superficial wound infections (n = 2) or superficial wound discomfort without signs of infection (n = 1). Radiological diagnostic assessments were performed for n = 25 (92.6%) of these patients (ultrasound: n = 6, CT: n = 18, MRI: n = 1). The main radiological diagnoses included: intraabdominal adhesions (n = 15), GI-tract perforation, leak of staple line or anastomosis (n = 3), impaired bowel passage (n = 3), hernias (n = 2), and hematoma (n = 1). One case showed normal postoperative findings on sonography, but still underwent surgery in which an adhesive ileus due to duodenal torsion was later diagnosed intraoperatively.

3.8.4.5 Diagnoses in Emergency Revision Procedures

Revision procedures following appendectomy, either during hospitalization or upon readmission, can be categorized into surgical and radiological interventions. In this study, radiological intervention exclusively refers to CT-guided abscess drainage. Surgical interventions include minimally invasive and open surgeries, such as surgical management of subacute gastrointestinal bleeding or adhesiolysis in cases of ileus. In some cases of postoperative acute abdomen, surgical interventions were performed also for diagnostic purposes, as the diagnosis was unclear on imaging or symptoms were severe enough to skip imaging and directly proceed with diagnostic surgery. To ensure comparability, the following table focuses on the final diagnosis rather than the indication for the revision procedure.

The primary diagnoses differed significantly across the UA and CA groups (χ^2 = 15.94, p = .026). Among the most common diagnoses in the CA group were intraabdominal abscesses (61.8%). These were treated approximately equally often by CT-guided drainage (n = 11) or surgery (n = 10). Comparing the distribution of postoperative diagnoses during revision procedures between UA and CA, a statistically significant effect is observed only for the surgical treatment of intraabdominal adhesions. These occurred more frequently in the UA group (n = 4; 36.4%) than in the CA group (n = 2; 5.9%) relative to the total number of postoperative revision procedures (p = .010). However, it should be noted that sample sizes for most diagnoses are low.

Table 33. Surgical Diagnoses in Emergency Revision Procedures.

	UA *(n=11)*		CA (*n=34)*		Statistic
Surgical diagnosis	*n*	*% of n*	*n*	*% of n*	*p*
Intraabdominal abscess (CT-drainage)	1	9.1%	11	32.4%	.129^Z
Intraabdominal abscess (surgery)	1	9.1%	10	29.4%	.173^Z
GI-tract perforation or staple line leak*	1	9.1%	7	20.6%	.386^Z
GI-tract bleeding	2	18.2%	1	2.9%	.078^Z
Intraabdominal adhesions (including ileus)	4	36.4%	2	5.9%	.010^Z
Abdominal hernia	0	0.0%	1	2.9%	.565^Z
Gynecologic diagnosis	1	9.1%	0	0.0%	.075^Z
Other diagnosis	1	9.1%	2	5.9%	.711^Z

^{Z} Two-proportion Z-test
* Also includes anastomotic leaks for cases of ileocoecal resections
Note that the “% of total n” and “% of valid n” columns are omitted as there were no missing values.

In the NC group n = 3 cases underwent a revision procedure. These included two cases with cutaneous or subcutaneous abscess formation and one case of an abdominal hernia. In the NA group no emergency revision procedures were performed.

3.9 Postoperative Sampling for Microbiological Analysis

In the postoperative course, microbiological samples were obtained and analyzed in 4.7% of all cases (n = 63). However, in some cases microbiological samples were collected for reasons unrelated to appendicitis/appendectomy, such as catheter-associated urinary tract infections. For the following analyses, only patients with samples directly related to appendectomy or its postoperative complications are considered (n = 55, 4.1%). The most common location of swab collection was intraabdominal, however, depending on postoperative complications, it also included extraabdominal locations, such as in cases of subcutaneous or cutaneous wound infections. The following chapter focuses on variations in microbiological results (swab collection site, amount of different species per culture, presence of anaerobes) between UA and CA.

In six cases, post-appendectomy microbiological samples were not analyzed together with the other swabs due to special features of each individual case. These include n = 4 cases of blood cultures, n = 1 cerebrospinal fluid (CSF) sample, and n = 1 Quantiferon test. The CSF sample was taken 2 days following appendectomy in a patient with a pre-existing ventriculoperitoneal shunt to rule out an infection of the central nervous system. The Quantiferon test was conducted 20 days postoperatively in a patient with histologically suspected intestinal tuberculosis of the appendix. Regarding the four cases in which blood cultures were taken, collection took place in the intensive care unit due to suspicion of sepsis.

3.9.1 Collection Sites of Post-Appendectomy Swabs

Microbiological samples obtained postoperatively and directly linked to appendectomy or its postoperative complications were available in n = 55 cases (UA: n = 4; CA: n = 44; NA: n = 2; NC: n = 5). These swabs were taken intraabdominally in n = 46, and extraabdominally in n = 9 cases. This is in line with the distribution of SSI locations including n = 53 organ or space between organs, and n = 19 superficial incisional locations (for details, see section 3.8.2 Surgical Site Infections). The average time interval from appendectomy to the first related postoperative swab did not significantly differ between UA and CA cases (UA: 34.75 ± 38.47 days; CA: 7.30 ± 8.29 days; t = 1.42; p = .124). However, it can be noted that the variance in the UA group is large due to the small number of UA patients who underwent post-appendectomy swab sampling (n = 4). Table 34 illustrates the sampling sites of post-appendectomy swabs. Due to the small sample size in the UA group, no statistical tests are performed.

Table 34. Location of Post-Appendectomy Swab Sampling.

	UA *(n=4)*		CA (*n=44)*	
Location of swab sampling	*n*	*% of n*	*n*	*% of n*
Intraabdominal (during revision surgery)	4	100.0%	25	56.8%
Intraabdominal (at patients' bedside*)	0	0.0%	12	27.3%
Cutaneous or subcutaneous at surgical incision site	0	0.0%	6	13.6%
Other	0	0.0%	1[§]	2.3%

* Sampling from a drain placed during appendectomy
[§] Notable sampling site in severe course of disease: pleural drainage. Initially, multiple liver abscesses originating from a covered perforated appendicitis involving the sigmoid colon and small intestine were observed. Subsequently, multiple abscesses originating from the liver spread per continuitatem and resulted in pleural empyema.
Note that the "% of total n" and "% of valid n" columns are omitted as there were no missing values.

Swabs from intraabdominal abscesses (UA: n = 1, CA: n = 9), from the peritoneum (UA: n = 2, CA: n = 7), or from intraabdominal fluid collections (UA: n = 0, CA: n = 3) were the most common locations for intraabdominal swabs taken during revision surgeries.

3.9.2 Overview of Post-Appendectomy Culture Results

In total, positive microbiological culture results were detected in n = 34 (UA: n = 2 / 4; CA: n = 28 / 44; NA: n = 1 / 2; NC: n = 3 / 5) out of the considered n = 55 patients who underwent post-appendectomy swab collection, accounting for 61.8%.

Overall, n = 18 of the n = 55 patients with post-appendectomy cultures, had two valid swabs taken. Therefore, in total n = 73 cultures were available for analysis. Figure 29 presents the distribution of the number of distinct species per cultures for all valid postoperative swabs for UA and CA cases:

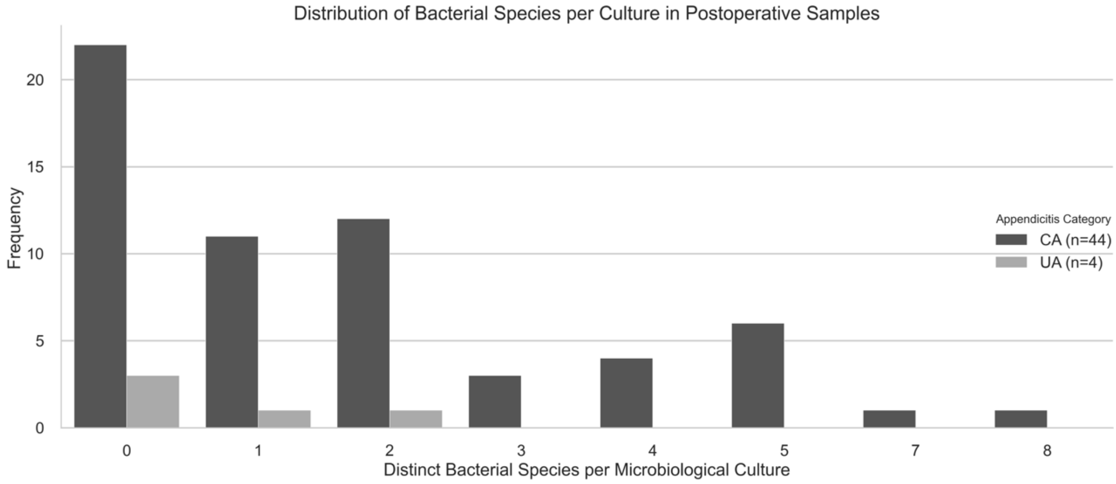

Figure 29. Distribution of Bacterial Species in Postoperative Cultures.

Regarding all categories (UA, CA, NA, and NC), it can be noted that n = 28 cultures showed no growth of bacteria (38.6%), n = 13 cultures showed single species infections (17.8%), and n = 32 of the cultures showed mixed infections (43.8%).

Considering only positive culture results, the average number of different species identified in post-appendectomy swabs was 1.5 ± 0.71 for UA and 2.64 ± 1.97 for CA ($t = -0.807$; $p = 0.213$). Anaerobes were identified in n = 15 cases (UA: n = 1/4; CA: n = 12/44; NA: n = 0/2; NC: n = 2/5), corresponding to a proportion of 44.1% of anaerobe presence in cases of positive cultures.

For CA, the number of different species was significantly higher in cultures containing at least one anaerobe (n = 12, 4.0 ± 2.13), compared to cultures with exclusive evidence of aerobes (n = 16, 1.63 ± 1.02; $t = 3.56$, $p = .003$). Due to the limited number of only two culture-positive post-appendectomy swabs in the UA group, no statistical tests are performed for this group.

3.9.3 Bacterial Genera and Species in Post-Appendectomy Cultures

While intraoperative swab samples from appendectomy were only considered valid if taken intraabdominally, valid postoperative swabs consist of n = 46 intraabdominal, and n = 9 extraabdominal samples.

In the n = 55 patients with valid postoperative swabs the genera Escherichia (n = 19, 34.55%, of which n = 3 MDRGN), and Enterococcus (n = 14, 25.46%, of which n = 2 VRE faecium) were the most commonly present in cultures. They were followed by the genera Bacteroides (n = 11, 20.0%), Streptococcus (n = 11, 20.0%), Staphylococcus (n = 6, 10.91 %), and Pseudomonas (n = 4, 7.27%). In this section, the distributions of genera are provided separately for UA and CA cases. Special attention is given to culture results from intraabdominal abscess samples. A comparison with the bacterial spectrum found during appendectomies is presented in section 3.9.4.

3.9.3.1 Bacterial Genera and Species in Post-Appendectomy Cultures from Uncomplicated Appendicitis

As only four patients of the UA group underwent postoperative sampling, and, of those, two patients had positive microbiological culture results, these cases will be presented individually:

The first patient was a 64-year-old female (ASA 2, BMI 27.3) who underwent laparoscopic appendectomy of a non-perforated phlegmonous appendicitis. During revision surgery for treatment of an intraabdominal abscess (7 days after appendectomy), two swabs were obtained from an intraabdominal abscess. One showed growth of Escherichia Coli, the other showed negative cultures.

The second patient was a 30-year-old female (ASA 2, BMI 36.8) who also underwent laparoscopic appendectomy of a non-perforated phlegmonous appendicitis during which an iatrogenic perforation of the jejunum occurred. During revision surgery (resection of a part of the injured jejunum), five days after appendectomy, one intraabdominal swab of the visceral peritoneum of the jejunum was obtained. Cultures showed growth of Prevotella nanciensis and Streptococcus oralis.

3.9.3.2 Bacterial Genera and Species in Post-Appendectomy Cultures from Complicated Appendicitis

Forty-four out of the n = 55 patients who underwent post-appendectomy sampling belong in the CA group (80.0%), and CA patients accounted for 82.3% of patients with positive post-appendectomy culture results. Therefore, CA culture results are similar to the overall results for all groups.

Sixteen CA patients had two post-appendectomy swabs obtained, so that n = 60 culture results are available for analysis. Cultures from n = 22 swabs were negative (36.7%). Single species infections were detected in n = 11 cultures (18.3%), and mixed species infections were detected in n = 27 cultures (45.0%). For a visualization and comparison with UA, see Figure 29. Distribution of Bacterial Species in Postoperative Cultures.

Regarding the n = 44 CA cases with post-appendectomy swabs, the order of the most common genera is equal to all post-appendectomy swabs, with the most common genera being Escherichia (n = 16, 36.36%, of which n = 2 MDRGN), Enterococcus (n = 13, 29.55%, of which n = 2 VRE faecium), and Bacteroides (n = 10, 22.73%). They were followed by the genera Streptococcus (n = 9, 20.46%), Staphylococcus (n = 5, 11.36%), and Pseudomonas (n = 4, 9.09%).

3.9.3.3 Bacterial Genera and Species in Microbiological Culture Results from Intraabdominal Abscesses in Surgical Site Infections

In this section, the bacterial genera and species detected in cultures, which were obtained from intraabdominal abscesses during treatment of SSIs, are presented. SSIs of the intraabdominal space surgery were documented in n = 53 patients (see section 3.8.2). Of those, n = 31 patients received post-appendectomy intraabdominal swabs. However, only n = 11 of these patients had swabs for which was clearly documented that they were taken directly from intraabdominal abscesses. In n = 3 patients, two samples were obtained, whereas for the other patients only one sample was obtained from the intraabdominal abscess. Therefore, n = 14 culture results were available for analysis. In all of the n = 3 patients who had two samples, culture results were identical for both samples (two negative cultures and one culture positive for two species: Citrobacter koseri and Aggregatibacter aphrophilus).

Overall, cultures were positive in n = 9 out of the n = 11 patients (81.8%). Single species growth was observed in n = 1 patient (n = 9.1%), and mixed positive cultures in n = 8 patients (81.8%). Mixed cultures included n = 2 distinct bacterial species in four patients, n = 3 and n = 4 species in two patients each.

The most common genera included Streptococcus spp. (n = 5), Escherichia spp. (n = 4, of which n = 1 MDRGN), Bacteroides spp. (n = 3, of which no VRE), and Aggregatibacter spp. (n = 2).

Anaerobes were present in five patients, whereas exclusively aerobic infections were detected in four patients. The average number of bacterial species was higher in infections with presence of anaerobes (mean = 2.67 species per culture) compared to exclusively aerobic infections (mean = 1.75 species per culture). Due to the small sample size no statistical tests are performed for this analysis.

3.9.4 Comparison of Intra- and Postoperative Culture Results

In this section, the microbiological culture results from intraoperative and post-appendectomy swabs are compared regarding frequency of the most common genera, as well as frequency of particular species.

In cultures from intraoperative intraabdominal swabs, the genera Bacteroides (42.57%), Escherichia (33.29%, of which 3.1% MDRGN), and Streptococcus (15.71%), followed by Enterococcus (14.29%, of which 2.0% VRE), Bilophila (9.71%), Pseudomonas (9.43%), Parabacteroides (5.29%), Klebsiella (4.71%), Eggerthella (4.29%) and Staphylococcus (3.29%), were the most commonly identified. In cultures from postoperative swabs (intra- and extraabdominal) the genera Escherichia (34.55%, of which 15.79% MDRGN), and Enterococcus (25.46%, of which 14.29% VRE faecium) were the most commonly present. They were followed by the genera Bacteroides (20.0%), Streptococcus (20.0%), Staphylococcus (10.91 %), and Pseudomonas (7.27%).

The list of the most common genera is, therefore, comparable between cultures from intraoperative and postoperative swabs, however, the order is not the same. In both, the intraoperative intraabdominal, as well as, the postoperative swabs (intra- and extraabdominal), the four most commonly detected species in cultures were Bacteroides (intra: 42.57%, post: 20.0%), Escherichia (intra: 33.29%, post: 34.55%), Streptococcus (intra: 15.71%, post: 20.0%) and Enterococcus (intra: 14.29%, post: 25.46%).

A comparison of the most commonly detected genera in culture results from intraoperatively and postoperatively obtained swabs is presented in Figure 30.

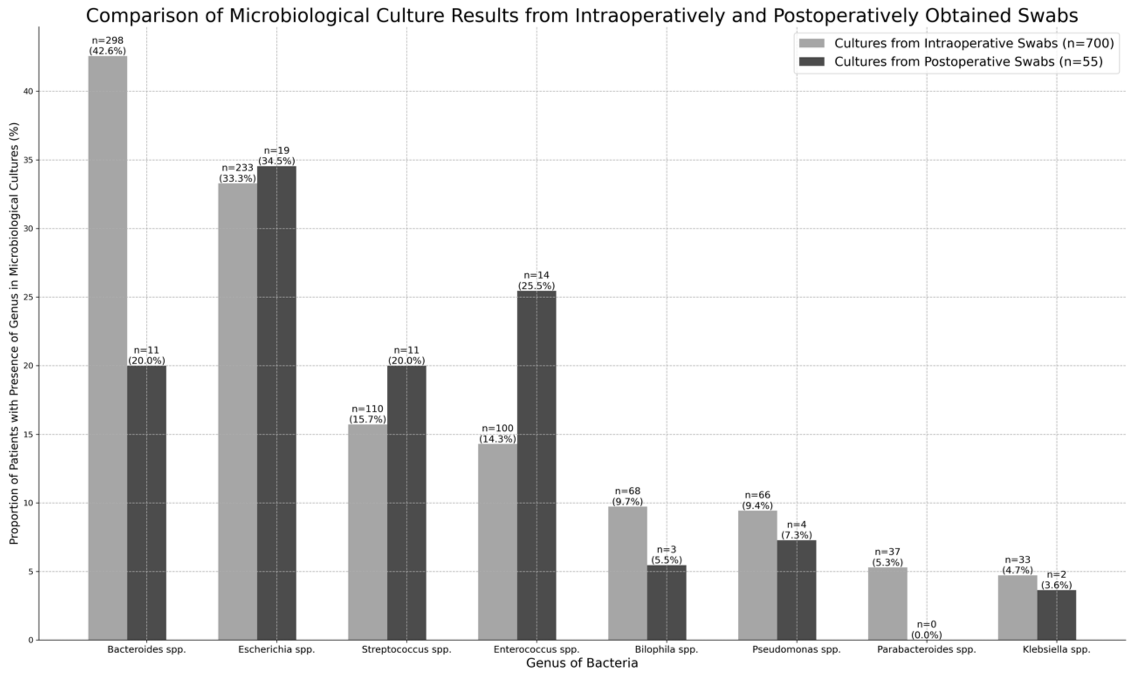

Figure 30. Comparison of Microbiological Culture Results from Intraoperatively and Postoperatively Obtained Swabs.

While it is important to consider the smaller sample size of postoperative swabs, and the associated increase in variance, on visual inspection of the figure above, it is particularly notable that the proportions of Bacteroides spp. ($Z = -3.28$, $p = .001$) and Enterococcus spp. ($Z = 2.23$, $p = .026$) differ significantly from intra- to postoperatively obtained swabs. For the other genera, such as Escherichia, Streptococcus, Bilophila etc. no statistically significant difference in proportions could be found (all $p > .05$; see Table 35).

The following table (Table 35) provides a detailed comparison for proportions of presence of bacterial genera in intraoperatively- and postoperatively obtained cultures. The genera are divided into groups sorted by gram stain and metabolic characteristics. For each group the order of genera is based on the number of patients with positive cultures for a given genus for intraoperative samples. Note that due to limited fulfillment of the assumptions for the Pairwise-Z-Test, p-values are marked with an asterisk if calculated for genera with frequencies of $n < 5$ in one of the two groups, as they should be interpreted with caution.

Table 35. Bacterial Genera in Intra- and Postoperative Cultures.

Gram Stain	Metabolic Characteristics	Genus of Bacteria	Intraoperative†	Postoperative§	p
+	Anaerobic	Eggerthella spp.	31 (4.43%)	4 (7.27%)	.334*
+	Anaerobic	Parvimonas spp.	20 (2.86%)	2 (3.64%)	.741*
+	Anaerobic	Clostridium spp.	13 (1.86%)	1 (1.82%)	.984*
+	Anaerobic	Actinomyces spp.	9 (1.29%)	-	.398*
+	Anaerobic	Peptostreptococcus spp.	4 (0.57%)	2 (3.64%)	.014*
+	Anaerobic	Clostridioides spp.	1 (0.14%)	-	.779*
+	Anaerobic	Eubacterium spp.	-	1 (1.82%)	<.001*
+	Facultative anaerobic	Streptococcus spp.	110 (15.71%)	11 (20.0%)	.404
+	Facultative anaerobic	Enterococcus spp.	100 (14.29%)	14 (25.46%)	.026
+	Facultative anaerobic	Staphylococcus spp.	23 (3.29%)	6 (10.91%)	.005
+	Facultative anaerobic	Corynebacterium spp.	7 (1.0%)	-	.456*
+	Facultative anaerobic	Propionibacterium spp.	3 (0.43%)	1 (1.82%)	.172*
-	Anaerobic	Bacteroides spp.	298 (42.57%)	11 (20.0%)	.001
-	Anaerobic	Bilophila spp.	68 (9.71%)	3 (5.45%)	.297*
-	Anaerobic	Parabacteroides spp.	37 (5.29%)	-	.080*
-	Anaerobic	Prevotella spp.	22 (3.14%)	3 (5.45%)	.356*
-	Anaerobic	Fusobacterium spp.	14 (2.0%)	-	.290*
-	Anaerobic	Odoribacter spp.	12 (1.71%)	1 (1.82%)	.955*
-	Anaerobic	Alistipes spp.	8 (1.14%)	1 (1.82%)	.657*
-	Anaerobic	Veillonella spp.	1 (0.14%)	1 (1.82%)	.020*
-	Anaerobic	Dialister spp.	-	1 (1.82%)	<.001*
-	Facultative anaerobic	Escherichia Coli	233 (33.29%)	19 (34.55%)	.849
-	Facultative anaerobic	Klebsiella spp.	33 (4.71%)	2 (3.64%)	.714*
-	Facultative anaerobic	Citrobacter spp.	22 (3.14%)	3 (5.45%)	.356*
-	Facultative anaerobic	Eikenella spp.	7 (1.0%)	1 (1.82%)	.568*
-	Facultative anaerobic	Enterobacter spp.	9 (1.29%)	1 (1.82%)	.739*
-	Facultative anaerobic	Proteus spp.	9 (1.29%)	-	.398*
-	Facultative anaerobic	Aggregatibacter spp.	8 (1.14%)	2 (3.64%)	.119*
-	Facultative anaerobic	Haemophilus spp	2 (0.29%)	1 (1.82%)	.082*
-	Aerobic	Pseudomonas spp.	66 (9.43%)	4 (7.27%)	.596*
-	Aerobic	Acinetobacter spp.	4 (0.57%)	1 (1.82%)	.272*

†n=700 cases with valid samples, §n=55 cases with valid samples, *p-values of Two-proportion Z-tests calculated for genera with frequencies of n < 5 in one of the two groups

It is notable that for cases with n ≥ 5 in both groups, statistically significant differences in proportions can be found for the genera Enterococcus spp., Staphylococcus spp., and Bacteroides spp., which is in line with the results from the figure above (Figure 30). Staphylococcus spp., however, were not presented in the graph, as this genus was not among the most common in intra- and postoperative swabs. The frequency of Staphylococcus spp. is approximately three times higher in post-appendectomy swabs, compared to intraoperative swabs (intra: 3.29%, post: 10.91%). It is important to mention that intraoperative samples consist of only intraabdominally obtained swabs, whereas postoperative samples also include n = 9 extraabdominal swabs.

3.10 Summary of Results

While the gender distribution was balanced for male and female patients in UA and CA, the age distribution differed significantly across the groups. The median age of the CA group was significantly higher compared to UA. UA affected patients from all age groups, however predominantly young patients, whereas CA was broadly distributed across all age ranges. The percentage of CA patients with pre-existing conditions and regular medication use, and consequently, preoperative ASA scores were also higher compared to UA.

All preoperative symptoms were more frequent or severe in the CA group, which also showed a higher variability in pain localization, so that in preoperative clinical diagnostics, perforated acute appendicitis was more frequently suspected in this group. Cross-sectional imaging was also ordered more often in this group. Preoperative CRP levels and leukocyte counts were significantly higher in CA.

Extended procedures, including coecectomy or ileocoecal resection, and open surgical approaches or conversions from laparoscopic to open surgery, were more common in the CA group. Periappendicular abscesses were described in approximately three-quarters of CA cases. Among CA cases, gangrenous appendicitis represented the majority of diagnoses in surgical operation reports However, only one-third of the surgical diagnoses of gangrene were confirmed by histopathology. For UA, phlegmonous and catarrhal appendicitis were the most prevalent diagnoses. Appendicoliths were described in approximately one-quarter of CA patients compared to one-eighth of UA patients.

Perioperative antimicrobial prophylaxis can be considered the standard for this procedure, with the most common combination of agents being Cefotaxime + Metronidazole. Valid intraabdominal swab samples for microbiological cultures were collected almost twice as frequently in the CA group compared to UA. Cultures were positive in 56% of cases, with a significantly higher proportion in the CA group. However, the distribution of bacterial genera was similar in UA and CA. Most positive cultures showed mixed species infections with the presence of anaerobes. The genera Bacteroides, Escherichia, and Streptococcus, followed by Enterococcus, Bilophila, Pseudomonas, Parabacteroides, Klebsiella, Eggerthella, and Staphylococcus, were the most commonly identified.

The average postoperative hospital stay duration was more than twice as long for CA (4.8 days) compared to UA (2.0 days). An empirical postoperative antibiotic therapy with an average duration of 3.0 days in CA, compared to 0.3 days in UA, was administered in 82% of CA and 21% of UA patients. The most common single-drug regimen was Piperacillin-Tazobactam. Common prescriptions of two agents included Ciprofloxacin + Metronidazole or Cefotaxime + Metronidazole. Coverage of the microbial spectrum by the primary empirical postoperative antibiotic therapy was observed for half of the CA and one-fifth of the UA cases with positive culture results. The regimen was continued until termination without any change of agents for most patients. Antibiograms were rarely considered for escalations or deescalations. The most common reason for adjustment was oralization.

Postoperative complications occurred significantly more frequently in the CA group. SSIs, of which most were intraabdominal, were documented in 5% of patients and occurred approximately ten times more often in CA. Postoperative revision procedures or abscess drainages were more commonly required in CA and overall in 3.6% of patients. Half of the revision procedures were performed during the initial hospital stay, whereas the other half of the procedures were performed after an emergency revisit. Intraabdominal abscesses occurred in 5.2% of all CA patients (0.24% in UA) and were the leading diagnosis in revision procedures for the CA group. These were treated equally often by CT-guided drainage as by surgery. The second most common diagnosis for the CA group was GI-tract perforation or staple line leak. For the UA group, the most common diagnosis was intraabdominal adhesion, including bowel obstruction, followed by intraabdominal abscesses and GI-tract bleedings.

Post-appendectomy microbiological samples were available for 4.1% of all patients (UA: 0.5%, CA: 10.9%). Cultures were positive in 61%, mostly showing mixed species infections. Anaerobes were present in 44% of positive cultures. The microbial spectrum from post-appendectomy cultures was similar to the culture results from appendectomies, with the four most commonly detected species being Escherichia, Enterococcus, Streptococcus, and Bacteroides. The proportion of Bacteroides spp. was significantly lower in post-appendectomy cultures, whereas the proportion of Enterococcus spp. was significantly higher, when compared to intra-appendectomy cultures.

4 Discussion

The primary objective of this study was to characterize the clinical course of acute appendicitis in adults, identify risk factors for complications, and analyze the local microbial spectrum associated with this disease. To achieve this, data from EHRs at the University Hospital of Tübingen from 2015 to 2021 were analyzed.

The aim of this chapter is to discuss the implications of the study's results and to contextualize them in the current scientific literature of appendicitis research while carefully considering their limitations.

4.1 Results in the Context of Current Scientific Literature

The following section aims to contextualize patient demographics, preoperative diagnostics, surgical technique, intraoperative findings, postoperative course and complications, microbiological culture results, and antiinfective therapy investigated in this study within the current scientific literature and puts special attention to recent developments in the field.

4.1.1 Patient Cohort

The gender distribution in the patient cohort was balanced, showing only a slightly higher proportion of male patients (UA: 51.6%; CA: 53.5%). Multiple studies have also described a slight predominance in males (rate ratio 1.4:1, overall rate of 53.1%) (Addiss et al., 1990; Lin et al., 2015) or near to equal incidence (Stöß et al., 2021).

The age distribution was similar to findings from a German nationwide analysis for the years 2010 – 2017 (Stöß et al., 2021), which showed that the majority of adult patients had an age up to 35 years. The median age of the CA group was significantly higher compared to UA (52 vs 28 years). In line with that, Stöß et al.

(2021) described CA rates of 11% for the age group 15-35, compared to higher rates of 36% in patients older than 35 years. Similarly, Lasek et al. (2018) described increased rates of CA in older patients (21% in patients < 40 years of age, 38% in patients between 40 and 64 years of age, 44% in patients between 65 and 74 years of age and 57% in patients older than 75 years of age) in a multicenter observational study across surgical centers in Poland and Germany. The authors also found increased patient age to be associated with increased risk of perioperative complications and prolonged length of hospital stay.

As the percentage of CA patients with pre-existing conditions such as oncological disease, chronic kidney disease, or diabetes mellitus type II and regular medication use was also higher, compared to UA, there is a possibility for a confounding effect of age on the postoperative outcomes, which needs to be considered. For example, the distribution of preoperatively measured creatinine levels showed significantly higher values in CA. These values remained with no significant changes over the postoperative course in both groups. The significantly higher proportion of postoperatively occurring AKIs in the CA group may, therefore, present an effect of increased age and corresponding impaired kidney function rather than a pathophysiological relationship with CA.

4.1.2 Preoperative Diagnostics

The median time interval between the onset of symptoms and surgery was two days in the CA group compared to one day in the UA group. When considering that the course of acute appendicitis has been described as progressive, leading to local edema, hypoperfusion, and ischemia, followed by necrosis and perforation (see section 1.2), this finding suggests that perforations were associated with a delayed patient presentation to the ER. The finding that the CA group also showed higher variability in pain localization, with fewer patients reporting pain restricted to the right lower abdomen, supports this assumption.

The primary imaging modality for appendicitis differs significantly across different healthcare systems. As reported in a previous publication, nearly all patients in countries that are prone to medical litigation suits undergo CT scans during the diagnostic process. For example, in a large US-American trial, 90% of patients who were diagnosed with appendicitis had preoperative CT scans (Strohäker et al., 2023; Yeh et al., 2021). This is in line with the American College of Radiology recommendation which considers CT scans an appropriate tool to diagnose appendicitis (Garcia et al., 2018; Strohäker et al., 2023). In Europe, where most countries are less prone to medical litigation suits, considerations of cancerogenicity risks associated with ionizing radiation make focused ultrasound the primary imaging modality (Bolmers et al., 2022; Strohäker et al., 2023; Téoule et al., 2020). Consequently, the German appendicitis treatment guideline (Andric et al., 2021) suggests sonography as a standard radiographic diagnostic procedure before the initiation of therapy. Therefore, while appendicitis may still be considered a predominantly clinical diagnosis, pre-therapeutic patient risk stratification today requires a combination of clinical examination and radiographic studies. In line with that suggestion, sonography was performed in 96% of the UA and 79% of the CA cases, whereas cross-sectional imaging was performed in 14% of UA and 54% of CA cases in this study. The most common reason for performing cross-sectional imaging were inconclusive findings from ultrasound, or, especially in the CA group, skipping of the ultrasound and primary use of CT due to suspicion of severe disease such as perforated appendicitis.

Preoperative CRP levels and leukocyte counts were significantly higher in CA and showed high to moderate ROC-AUCs of 0.82 and 0.59 for classifying CA vs UA. In line with other classification systems, such as the Alvarado score (Alvarado, 1986), our group also included these variables in a model for pre-therapeutic UA vs CA classification (Strohäker et al., 2023). Significant differences in preoperative creatinine and bilirubin levels, both higher in the CA group, may be due to the confounding factor of patient age and overall health status rather than a consequence of appendicitis.

4.1.3 Surgical Technique

In line with the continuous increase in the proportion of laparoscopic appendectomies, Stöß et al. (2021) described an increase in laparoscopic approaches for appendectomy between 2010 (76%) and 2017 (93%). In our study, the procedure was planned as a laparoscopic surgery in 95.4% of patients. Therefore, a continued increase of laparoscopic procedures can be noted.

Similar to results from the MUSTANG Trial (Yeh et al., 2021) which reported average procedure durations of 80 minutes for perforated, 68 minutes for gangrenous and 59 minutes for UA, the average procedure duration in our study was significantly longer in CA (79 minutes) compared to UA (51 minutes). Surgeries involved coecectomy or ileocoecal resections more frequently in CA (CA: 21.8% and 6.0%; UA: 3.7% and 0.1%). It is important to note that in a comparison of studies, it is necessary to consider whether only appendectomies or also extended procedures were included in the analysis. For example, some studies, such as Stöß et al. (2021), consider cases based on ICD codes, while other studies (Leeser et al., 2022) consider cases based on surgical procedure codes.

4.1.4 Intraoperative Findings

According to Andric et al. (2021), in Europe, appendicitis is considered mainly a clinical diagnosis, resulting in high NA rates of up to 32%, in contrast to rates below 5% in the US (Yeh et al., 2021). The aforementioned medicolegal considerations significantly influence the use of CT scans for preoperative diagnostics and are an important factor influencing NA rates (see section 4.1.2). In our cohort, excluding NC cases, the NA rate was 6.0%. This rate is higher than would be expected with standard use of preoperative CT scans but lower than typically observed in European hospitals. Previous literature has highlighted the operator-dependent variability in diagnostic accuracy of ultrasound for appendicitis (Cho & Oh, 2023; Pohl et al., 1998). The low NA rates in our study may be partially attributed to the availability of experienced ultrasonographers at our university hospital.

In line with findings from previous trials (Davidson et al., 2021; Vons et al., 2011) which suggested increased risk of CA in patients with appendicolith, appendicoliths were significantly more common in CA (24.1%) compared to UA (11.9%) in our study. In the literature, the presence of appendicoliths during episodes of appendicitis was described at higher rates between 27% (Davidson et al., 2021; Flum et al., 2020) 39% (Ranieri et al., 2021) and 41% (Kaewlai et al., 2023). During our observation period, the reporting of appendicoliths lacked standardization. As a result, it remains uncertain whether the comparatively lower appendicolith rate observed in our study is an underestimation due to incomplete documentation or represents a genuine difference from other study populations.

Appendix perforation was documented in n = 310 cases, corresponding to an overall rate of 24.9% for all acute appendicitis cases (including those with missing values regarding perforation status). Perforation rates in acute appendicitis in adults were reported at 15.8% (Drake et al., 2014), 16% (Davidson et al., 2021; Flum et al., 2020), and 19% (Körner et al., 1997) in prospective trials. The 2020 WSES Jerusalem guidelines (Di Saverio et al., 2020) described perforation rates ranging from 16 to 40% depending on patient age groups.

Periappendicular abscesses in acute appendicitis (UA or CA) were documented in n = 155 cases, representing 12.4% of all UA and CA cases. However, data on this variable were missing in approximately half of these cases. When we consider only the cases with complete data, where the presence or absence of a periappendicular abscess was explicitly mentioned in the surgical reports, the rate increases to 25.3%. This higher rate contrasts with previous studies, which have reported periappendicular abscess rates of 2-10% in acute appendicitis (Cheng et al., 2017; Suzuki et al., 2023). This discrepancy suggests that our calculation based on complete (i.e. valid) cases may overestimate the true prevalence in our cohort due to the exclusion of cases with missing data, which could differ systematically from those with complete data. Therefore, it is crucial to specify whether rates are calculated based on total cases or only on complete (i.e. valid) cases, as was performed wherever appropriate in chapter 3. This distinction affects the interpretation of the results and their comparability with other studies. For a detailed discussion regarding the topic of incomplete data, refer to section 4.2.2.

4.1.5 Intraoperative Sampling for Microbiological Analysis

The microbial spectrum from intraoperative sampling was shown to be similar in UA and CA. As culture results are typically only available after the termination of postoperative empirical antibiotic therapy, over 90% of antibiograms available in our study cohort were not used to adjust the postoperative antibiotic therapy.

It was surprising to see that some patients underwent intraoperative intraabdominal sampling for microbiological cultures but did not receive postoperative empirical antibiotic therapy. The indication for swab sampling and the usefulness of culture results is unclear in these cases. The value of intra-peritoneal pus sampling was also questioned in a prospective cohort study by Akingboye et al. (2018) in which microbiological culture results from pus samples did not lead to any adjustments of postoperative antibiotic therapies in patients with CA.

While overall, intraoperative and post-appendectomy culture results were found to be similar regarding the microbial spectrum, the overlap of cultures from intraoperative and post-appendectomy SSI sampling in individual patients was rather low, thereby making intraoperative culture results poor predictors of pathogens associated with infectious postoperative complications. Similar results of poor overlap have been previously described for the adult (Foo et al., 2008) and pediatric population (Dahlberg et al., 2019). Therefore, the regular sampling during appendectomies, while useful for population-based studies and the assessment of locoregional microbial spectra, is of questionable value on the individual patient level and should only be performed in selected cases. Consequently, we suggest standardizing indications for the collection of microbiological cultures and postoperative empirical antibiotic therapies for avoiding unnecessary costs and optimizing treatment.

4.1.6 Microbiological Culture Results

Most of the common pathogens isolated from peritoneal fluid during appendectomies in the POSAW Trial by Sartelli et al. (2018), which were presented in Figure 2, were also identified in intraoperative cultures from this patient cohort, however at differing frequencies for many genera, especially Escherichia coli, E. faecalis, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Valid intraabdominal swab samples for microbiological cultures were collected almost twice as frequently in the CA group (79%) compared to the

UA group (41%). In comparison, only 19.6% of patients underwent intraabdominal swab sampling in the POSAW Trial. Cultures were positive in 56% of cases compared to 34% in the POSAW Trial.

Regarding all positive cultures from intraoperative intraabdominal sampling, the genera Bacteroides (our study: 43%, POSAW: 38%), Escherichia (our study: 33%, POSAW: 58%) and Streptococcus (our study: 16%, POSAW: 8.7%) followed by, Enterococcus (our study: E. faecalis 4.6%, E. faecium 4.2%; POSAW: E. faecalis in 15.3% and E. faecium in 4.0%) Bilophila (our study: 10%, POSAW: not mentioned), Pseudomonas aeruginosa (our study: 8.4%; POSAW: 1.8%), Parabacteroides (our study: 5%, POSAW: not mentioned), Klebsiella (our study: Klebsiella pneumoniae: 2.6%, Klebsiella oxytoca 1.3%; POSAW: Klebsiella pneumoniae 6.9%, Klebsiella oxytoca 1.5%,), Eggerthella (our study: 4%, POSAW not mentioned) and Staphylococcus (our study: Staph. aureus: 0.4%; POSAW: Staph. aureus 2.2%), were the most commonly identified.

Other bacteria mentioned in the POSAW Trial but not among the ten most common in this study were: Enterobacter spp. (1.9%, POSAW: 1.8%), Proteus spp. (1.3%, POSAW: 0.4%), and Clostridium spp. (1.8%, POSAW: 1.5%).

In a Korean study by Song et al. (2018) which investigated microbial cultures in appendicitis from swabs obtained from luminal contents of the appendix or fluid from periappendiceal abscesses between 2006 and 2015, the most common microorganisms were E. coli (our study 33%, POSAW: 58%, Song et al.: 64.6%) and Pseudomonas aeruginosa (our study 8.4%; POSAW: 1.8%, Song et al.: 16.4%). The results demonstrate the value of studying the locoregional variances in the microbial spectrum and support the consideration of such variances for empirical antibiotic therapy of both, non-operative management, as well as, surgical management of appendicitis.

4.1.7 Antibiotic Therapy

In line with recommendations suggesting perioperative antimicrobial prophylaxis for appendicitis (Andersen et al., 2001; Daskalakis et al., 2014; Di Saverio et al., 2020), this strategy can be considered the standard for appendectomies in our patient cohort as it was documented for over 99% of patients. Approximately 80%

of patients received a combination of two antibiotic agents. The most common combination of agents was Cefotaxime + Metronidazole, which also corresponds to the most common regimen used in a Cochrane meta-analysis (Andersen et al., 2001) and can still be recommended.

An empirical postoperative antibiotic therapy was administered in 82% of CA and surprisingly also in 21% of UA patients. This finding for UA was not in line with recommendations from a systematic review by Daskalakis et al. (2014) and the Centers for Disease Control SSI Prevention Guideline (Berríos-Torres et al., 2017), which both suggest a prescription of postoperative antibiotic therapy only in cases of perforated appendicitis. However, it is notable that the average duration of postoperative antibiotic therapy in UA was only 1.7 days.

The minimum duration of postoperative IV antibiotic regimen recommended for CA by Daskalakis et al. (2014) is 3 days of treatment. This corresponds to the results from an observational cohort study by van Rossem et al. (2014) which investigated a 3-day course of IV Cefuroxime + Metronidazole and found it to be equally effective to a 5-day course in preventing postoperative occurrence of intraabdominal abscesses or wound infections. In line with that, the average duration of the primary postoperative antibiotic regimen was 3.7 days in CA.

Oral administration of antibiotics can reduce the length of stay and reduce costs in postoperative acute appendicitis treatment (Kleif et al., 2017). McCarthy and Avent (2020) suggested that, in general, “after adequate control of the source of infection the benefits of intravenous antibiotics are limited to the first few days of treatment”. According to Andric et al. (2021), switching from IV to PO antibiotics is a common strategy following appendectomies. In line with that, antibiotics were oralized in approximately 20% of CA cases. However, Daskalakis et al. (2014) suggested that there was not enough evidence for the use of oral antibiotics after the initial IV treatment following surgical treatment of acute appendicitis. In a retrospective multicenter study comparing IV and PO routes of antibiotic administration as primary empirical treatments following appendectomy in CA (3-day regimen), non-inferiority of the enteral antibiotics group was reported (Kleif et al., 2017). Combining the finding of the PO route being as effective as the IV route in preventing intraabdominal abscesses and wound infections (Kleif et al., 2017), the finding of a 3-day course being as effective as a 5-day course, and the importance of surgical source control, a 3-day course of PO antibiotics may be considered as a possible postoperative CA treatment if surgical source control can safely be achieved. However, further research is needed to assess the safety of postoperative empirical oral antibiotic therapy in cases of CA.

As the majority of patients were not hospitalized in the pre-operative timeframe and the infection was present at hospital admission, according to Silva-Nunes and Cardoso (2019), these infections were typically caused by the patients' own flora and fell into the category of community-acquired intraabdominal infections. Anaerobes were present in 86% of CA cases with positive culture results and were associated with a higher number of distinct species per culture, supporting the use of antibiotics with anaerobic coverage, such as metronidazole, in postoperative treatment. Coverage of Enterobacteriaceae such as Escherichia coli (33.3%), Citrobacter (3.1%), or Klebsiella spp. (2.6%), and Streptococci (16%), is also recommended.

As outlined in the previous section, intraoperative cultures showed growth of Pseudomonas aeruginosa in 8.4% (7.3% in post-appendectomy cultures). While the combination of two agents most commonly used for postoperative antibiotic therapy in this study (Ciprofloxacin + Metronidazole) provides coverage, after publication of a drug safety warning letter in April 2017 in Germany regarding use of fluoroquinolone antibiotics which informed medical professionals about reports including long-lasting and potentially irreversible side effect affecting quality of life of fluoroquinolones affecting the musculoskeletal and nervous system, it was increasingly replaced with Cefotaxime + Metronidazole, which is ineffective for this species.

In cultures from intraoperative sampling, the frequency of the Enterococci species E. faecalis was comparable (4.6%), whereas the frequency of E. faecium was lower (4.2%) compared to the POSAW study (see section 4.1.3). In our patient cohort, Vancomycin resistance was 6.9% in E. faecium, and the MDR rate in

E. coli was 3.0%. The results indicate low resistance rates for the spectrum of appendicitis in our locoregional study.

As Enterococci produce a low-affinity penicillin-binding proteins, such as the low-affinity class B penicillin-binding protein 5 (PBP5), they exhibit a "high-level resistance to most cephalosporins and all semi-synthetic penicillins" (Kristich et al., 2014). In this study, metronidazole was the agent most commonly added to cephalosporins. However, metronidazole is also not effective in Enterococci. The frequency of Enterococcus spp., especially VRE, was significantly increased in cultures from SSIs compared to intra-appendectomy cultures. These results emphasize the need for appropriate coverage of Enterococcus spp. (including VRE) during postoperative infectious complications.

Varying frequencies of positive cultures from intra- to post-appendectomy swab samples were also found for Bacteroides spp. which were significantly less frequent in post-appendectomy cultures. Dahlberg et al. (2019) showed a low overlap between intraoperative cultures from appendectomy and postoperative abscesses in children. In our study we could confirm this finding (Strohäker et al., 2024) for the adult population. Therefore, the study of locoregional variances is particularly important as it may serve as a guide for postoperative empirical antibiotic therapy in CA cases, which is typically recommended by German and international guidelines (Andric et al., 2021; Di Saverio et al., 2020), but also as a guide for empirical treatment in cases of infectious complications.

4.1.8 Length of Hospital Stay

(Stöß et al., 2021) described a continuous decrease of postoperative hospital stay duration within the past years in Germany (2010: 5.1 days, 2017: 4.4 days). The mean length of hospital stay in our study was 2.90 days. This finding supports a continuing decrease for the length of hospital stay. In comparison, the median hospital stay duration following appendectomy for appendicitis was only one day for UA, and three days for perforated appendicitis in the US-American MUSTANG Trial (Yeh et al., 2021). This is in line with findings from a systematic review by de Wijkerslooth et al. (2021) which found no increased risk of adverse outcomes following same-day discharge after appendectomy, especially for patients with

UA undergoing laparoscopic surgery. Considering the overall trend of reducing length of hospital stay it is reasonable to assume that an expedited discharge after appendectomy will also be favored in German hospitals for selected patient groups in the future (Minz et al., 2023).

4.1.9 Postoperative Complications

An increasing number of researchers consider non-operative management of appendicitis (especially UA) as an alternative treatment to avoid risks and costs associated with surgery (Allievi et al., 2017; de Almeida Leite et al., 2022; Salminen et al., 2015; Vons et al., 2011). However, as recurrence rates range up to almost 50% (Flum et al., 2020) other authors question the benefit of non-operative antibiotic management and consider an early surgical removal of the appendix as the appropriate primary therapy (Rocha et al., 2015; Sceats et al., 2019). A recent Cochrane review concluded that the current evidence for avoiding appendectomy following non-operative antibiotic treatment is very uncertain and there is too few data available to assess, whether complication rates vary between conservative and operative treatment groups (Doleman et al., 2024).

In a systematic review and meta-analysis by Danwang et al. (2020), the incidence of SSIs following appendicitis was 7.0% globally and 5.8% for Europe. Similarly, in our study SSIs were documented in 5.4% of patients. SSIs occurred approximately ten times as often in the CA group (13.7%) compared to UA (1.4%). This finding is in line with the results from the MUSTANG Trial (Yeh et al., 2021) which showed significantly higher postoperative intraabdominal abscess rates in perforated, compared to non-perforated appendicitis, and a retrospective multicenter study by Giesen et al. (2017) which found CA to be a major predictor of SSIs following appendectomy.

Out of all emergency appendectomies performed, 3.6% required reoperation or abscess drainage postoperatively. Intraabdominal abscesses represented the most common SSI and diagnosis on revision procedures in CA. The timing of the revision procedure was similar to findings from a Dutch retrospective cohort study by Zamaray et al. (2022) which reported diagnosis of postoperative intraabdominal abscesses during the index hospital stay at 46% and correspondingly 54% at readmission. In our study 44% of revision procedures were performed during the index hospital stay and correspondingly 56% after readmission.

The 30-day mortality rate following appendicitis was 1.8% in a large US-American study including data from 1991 to 1999 (Margenthaler et al., 2003). A continuous mortality rate decrease could be noted for the following years. In Germany, the mortality rate of CA further decreased from 0.62% to 0.42% between 2010 and 2017 (Stöß et al., 2021). Overall, the 90-day mortality rate in our study showed a further decrease with rates of 0.12% for UA and 0.25% for CA.

4.2 Methods and Limitations

This is a study of over one thousand consecutive appendectomies performed at a large German university hospital, which fulfills a function as a local secondary care center and a function as a larger tertiary referral center. Therefore, our patient cohort consists of patients from all age groups, genders, health status levels, and socioeconomic backgrounds.

The study constitutes a retrospective analysis of partially incomplete patient data, subject to the limitations typically associated with these so-called Medical Record Review (MRR) (Worster & Haines, 2008) or Retrospective Chart Review (RCR) (Vassar & Matthew, 2013) studies. While the retrospective study design presents limitations that may compromise the robustness of the retrospective analysis, it also offers advantages, such as the analysis of data from an authentic hospital setting, indicating increased external validity.

4.2.1 Single Center Study

One limitation of the retrospective study lies in the lack of data on patient presentations before and after appendectomy outside the university hospital. However, as mentioned by our group in a previous publication, “Given that we are the only hospital providing emergency surgical care for our district, we work under the assumption that near all complications presented to our ER.” (Strohäker et al., 2024). Nevertheless, this is still an assumption, and it is possible that rates of postoperative surgical consultations are underestimated in this study compared to studies using a systematic follow-up scheme.

The single-center study design, while insufficiently representative of a general worldwide population as aimed for by other studies such as the multi-center POSAW Trial (Sartelli et al., 2018), is adequate for the assessment of the locoregional bacterial spectrum of appendicitis in the region of the University Hospital Tübingen.

4.2.2 Data Missing not at Random

Another limitation of the retrospective study design is missing data due to incomplete and partly non-standardized documentation. The proportions of missing data vary between variables and also differ significantly in the groups that are separately examined in this study. For example, the availability of data regarding clinical symptoms in the admission reports significantly differs between the UA group for fever (69% of cases) and the CA group (76% of cases). The reasons why this parameter was recorded significantly more often in the CA group cannot be definitively reconstructed from the data. According to Rubin (1976), this type of missing data can be categorized as missing not at random (MNAR), which is generally seen as the most problematic category of missing data (Kang, 2013).

These results can be attributed to the study's design, which involved retrospective analysis of patient reports created in an everyday clinical setting. What patients were asked and what surgeons documented depended on what was considered relevant from the current medical perspective at a given time.

Even though intuitively appealing, it cannot be concluded that a missing value in a particular variable corresponds to a specific variable level. Comparisons of the proportions for variables between the UA and CA groups are, therefore, limited. To account for this factor, the tables presented in the result section display the proportions of UA and CA cases in two columns, one presenting all cases including missing values and another presenting the subset excluding missing or unspecific values. According to Kang (2013), this technique corresponds to the listwise deletion approach or available case analysis, which was described as potentially biasing in the estimates of model parameters. Due to this limiting factor, no predictive modeling for postoperative complications was performed. Instead, factors were presented in primarily descriptive statistical analysis.

4.2.3 Selection Bias and Non-Standardized Treatment

As this RCR did not observe a sample of appendectomy cases but covered all patients who underwent appendectomy, there is no risk of a case sampling bias, which is typically a concern in medical literature and considered a form of selection bias (Cortes et al., 2008). However, the previously mentioned retrospective documentation bias leading to data MNAR can be considered a form of selection bias as non-standardized documentation is more likely to omit less severe than more severe findings.

It is reasonable to assume that the surgeon's individual judgment of appendicitis severity lead to differences in preoperative, intraoperative, and postoperative care for UA and CA patients. In a large-scale retrospective observational study, Agniel et al. (2018) showed that the "presence of a laboratory test order, regardless of any other information about the test result" was significantly associated with the odds of patient survival in 86% of tests ordered by clinicians. The authors concluded that the context of EHR data must be carefully considered. One example of such careful consideration is the availability of culture results. As intraoperative intraabdominal swab sampling was not standardized, culture results were not available in the form of a representative but rather a real-life convenience sample. In a previous publication, we observed that the mere availability of culture results, which corresponds to the surgeon's decision to take intraabdominal samples at surgery, was a predictor of the continuation of antibiotic therapy even after controlling for variables strongly associated with CA, such as age, ASA score, leukocyte counts, and CRP levels, but also gangrene, abscess, peritonitis, and perforation of the appendix (Strohäker et al., 2024).

4.3 Conclusions

Overall, acute appendicitis is a common procedure associated with low risks. However, the risk is increased in CA, which in turn is associated with increased patient age and later consultation of hospital emergency departments. The standard procedure is laparoscopic appendectomy with adjunct perioperative antimicrobial prophylaxis for all patients.

The microbial spectrum of UA and CA at Tübingen University Hospital has been similar and stable throughout recent years. As culture results are typically only available after the termination of postoperative empirical antibiotic therapy and have a low overlap with cultures from post-appendectomy SSI sampling, the benefit of regular sampling during appendectomies is questionable.

Comparison of the frequencies of bacterial species showed significant differences from findings in other studies, such as worldwide multi-center (POSAW by Sartelli et al., 2018) and local studies (Song et al., 2018), supporting the importance of the consideration of locoregional bacterial spectra for guiding empirical postoperative therapy in CA.

Anaerobes were typically present in CA and were associated with mixed-species infection, supporting the use of antibiotics with anaerobic coverage in postoperative treatment. Coverage of Enterobacteriaceae is also recommended. Coverage of Pseudomonas aeruginosa was shown to be limited as after issuing of a severe side-effect warning for fluoroquinolones, this group was increasingly replaced with Cefotaxime + Metronidazole, which are ineffective for this species.

Post-appendectomy culture results showed limited effectiveness of cephalosporins in postoperative infectious complications due to increased rates of Enterococci compared to intra-appendectomy samples. Resistance rates in this patient cohort are low but increase in postoperative complications, especially for VRE. These results suggest that a stronger broad-spectrum antibiotic treatment that warrants coverage of Enterococci and especially VRE faecium is necessary for empirical treatment of postoperative complications.

The administration of postoperative antibiotic therapy in UA was unnecessarily high. Therefore, antibiotic stewardship guidelines need to be promoted more actively. In-house guidelines should emphasize that postoperative antibiotic therapy is necessary exclusively for CA cases, which should receive a three-day course of antibiotics.

In the NA group, no emergency revision procedures were performed. Therefore, even though the benefit of NA is questionable on an individual patient level, it can still be considered safe.

5 Summary

Appendicitis, first described in 1886, remains a condition with only partially understood pathophysiology. While appendectomy is the worldwide gold standard treatment, the paradigm of surgery is increasingly challenged as non-operative antibiotic management is being studied as an alternative to surgery. The first German guideline for the treatment of appendicitis in adults was published in 2021.

This retrospective medical chart review study described a cohort of 1346 consecutive patients undergoing emergency appendectomy at a German university hospital within a six-year time frame and investigated preoperative symptoms, surgical treatment, postoperative course, and especially infectious complications following the procedure. Special attention was given to the microbial spectrum from intraoperatively obtained intraabdominal swabs and post-appendectomy culture results. Cases were classified as CA, UA, NA, or NC according to an algorithm that followed suggestions of several international guidelines. CA was defined by the presence of appendix inflammation plus either one or a combination of the following: gangrene of the appendix, perforation of the appendix, or periappendicular abscess.

We were able to show that UA affected predominantly young patients, whereas CA patients were significantly older, had more pre-existing conditions, higher ASA scores, and more severe symptoms, as well as a higher variability in abdominal pain localization before admission. Hospital stay duration was more than twice as long for CA (4.8 days) compared to UA (2.0 days). CA patients had higher preoperative leukocyte counts and CRP levels, and surgeries involved extended resection of the coecum or ileocoecal resection more often than in UA. Histopathological evaluation was not always equal to surgical assessment of

appendix perforation and often suggested milder stages of inflammation than indicated by operation reports.

The most common combination of agents for perioperative antimicrobial prophylaxis was Cefotaxime + Metronidazole, and antibiotic treatment was continued in more than 80% of CA patients for an average duration of 3.7 days compared to 21% and 1.7 days in the UA group.

Microbiological sampling performed during appendectomy was dependent on the surgeon’s choice and performed almost twice as frequently in CA (79%) compared to the UA (41%). Post-appendectomy microbiological sampling was performed in 4.1% of all patients (UA: 0.5%, CA: 10.9%). Culture results showed no growth of bacteria in 43% (post-appendectomy: 39%), single species infections in 9% (post-appendectomy: 18%), and mixed infections in 48% (post-appendectomy: 44%) of cases. The average number of different species identified for UA was 2.8 (post: 1.5) and for CA 3.7 (post: 2.6). Anaerobes were present in 80% of intraoperatively obtained positive cultures and in 44% of post-appendectomy positive cultures.

The microbial spectrum from post-appendectomy cultures was similar to the culture results from appendectomies, with the four most commonly detected species being Bacteroides (intra: 43%, post: 20%), Escherichia (intra: 33%, post: 35%), Streptococcus (intra: 16%, post: 20%), and Enterococcus (intra: 14%, post: 25%). The proportion of Bacteroides spp. was significantly lower in post-appendectomy cultures, whereas the proportion of Enterococcus spp. was significantly higher. While the overall distribution of bacterial genera was similar between the intra and post-appendectomy culture results, the overlap for each individual patient was rather low.

A comparison of the frequencies of bacterial species showed significant differences from findings in other studies, supporting the importance of the consideration of locoregional bacterial spectra for guiding empirical postoperative therapy in CA. Given that microbiological culture results were considered for adjustments in antibiotic therapy in only a small fraction of cases and were poor predictors of pathogens found in post-appendectomy cultures, we recommend standardizing the indications for collecting cultures.

Postoperative complications were more common in the CA group. SSIs were documented in 5% of patients, most commonly intraabdominal, followed by superficial incisional infections. SSIs occurred approximately ten times as often in the CA group compared to UA (13.7% vs 1.4%). Out of all emergency appendectomies performed, 3.6% required reoperation or abscess drainage postoperatively. Almost half of the revision procedures were performed during the initial hospital stay, whereas the remaining procedures were performed after an emergency revisit and readmission of patients.

Most revision procedures were performed within ten days following appendectomy, and less than 10% were performed later than one month after appendectomy. Intraabdominal abscesses were the most common diagnosis on revision procedures in the CA group. The second most common diagnosis for the CA group was GI-tract perforation or staple line leak. For the UA group, the most common diagnosis was intraabdominal adhesion, including bowel obstruction.

Revisits were 2.5 times more frequent in CA cases, readmissions 5.8 times more frequent, and revision surgeries or abscess drainages 4.2 times more frequent compared to UA. Overall, the mortality rate was low at 0.12% for UA and 0.25% for CA. In the NA group, no emergency revision procedures were performed, suggesting the safety of the procedure and allowing for the attribution of revision procedures in UA and CA to factors inherent to the disease rather than treatment.

The results underlie the limitations and potential biases of retrospective medical chart reviews, as data was available or missing dependent on documentation in a real-world hospital setting, patients were discharged and not followed up, and data from only one hospital was considered.

6 Deutsche Zusammenfassung

Die akute Appendizitis wurde bereits 1886 beschrieben, jedoch ist die Pathophysiologie dieser Krankheit bis heute nicht vollständig geklärt. Das

Paradigma der Appendektomie als Goldstandard der Behandlung wurde in den letzten Jahren zunehmend in Frage gestellt. Als Alternative wurde die konservative, empirische antibiotische Therapie untersucht. Die erste deutsche Leitlinie zur Behandlung der Appendizitis bei Erwachsenen wurde im Jahr 2021 veröffentlicht.

Diese retrospektive Beobachtungsstudie basiert auf elektronischen Patientenakten einer Kohorte von 1346 konsekutiven Patienten, welche innerhalb eines Zeitraums von sechs Jahren in einem deutschen Universitätsklinikum einer notfallmäßigen Appendektomie unterzogen wurden. Die präoperativ auftretenden Symptome, die chirurgische Therapie, der postoperative Verlauf und insbesondere postoperativ auftretende infektiologische Komplikationen wurden untersucht. Ein besonderes Augenmerk wurde hierbei auf das lokoregionale Keimspektrum aus intraoperativ und im postoperativen Verlauf gewonnen Abstrichen gelegt.

Fälle wurden entsprechend einem Algorithmus, der Vorschlägen mehrerer internationaler Leitlinien folgte, als komplizierte Appendizitis (KA), unkomplizierte Appendizitis (UA), negative Appendektomie (NA) oder nicht klassifizierbar (NK) eingestuft. KA wurde durch das Vorhandensein einer Entzündung des Appendix sowie dem Vorhandensein mindestens einer der folgenden Faktoren: Gangrän des Appendix, Perforation des Appendix oder perityphlitischer Abszess definiert.

Wir konnten zeigen, dass UA überwiegend junge Patienten betrifft, während Patienten mit KA deutlich älter sind, mehr Vorerkrankungen, höhere ASA-Scores und ausgeprägtere Symptome haben. Im Vergleich zu UA war die Krankenhausaufenthaltsdauer bei KA als mehr als doppelt so lang (KA: 4,8 Tage, UA: 2,0 Tage). Patienten mit KA hatten präoperativ ausgeprägtere Leukozyten- und CRP-Spiegel. Die Operationen umfassten häufiger ausgedehnte Verfahren, wie Resektionen des Coceums oder ileocoecale Resektionen, als bei UA. Die histopathologische Bewertung unterschied sich von der chirurgischen Einschätzung in Bezug auf Perforation des Appendix, sowie Entzündungsstadium in einigen Fällen und deutete im Vergleich zu Operationsberichten oft auf mildere Entzündungsstadien hin.

Die häufigste Kombination von Wirkstoffen für die perioperative Antibiotikatherapie war Cefotaxim + Metronidazol. Die antibiotische Behandlung wurde bei mehr als 80% der KA Patienten für eine durchschnittliche Dauer von 3,7 Tagen fortgesetzt (UA: 21%; 1,7 Tage).

Die mikrobiologische Abstrichentnahme während der Appendektomie war nicht standardisiert und wurde je nach Einschätzung des Operateurs durchgeführt. Insgesamt wurden Abstriche bei 79% der KA, sowie 41% der UA durchgeführt und damit etwa doppelt so häufig in der KA Gruppe angeordnet. Im postoperativen Verlauf wurde bei 4,1 % aller Patienten eine Probeentnahme zur mikrobiologischen Diagnostik durchgeführt (UA: 0,5%, KA: 10,9%). Die Kulturergebnisse zeigten kein Bakterienwachstum in 43 % (Post-Appendektomie: 39%), Wachstum einer einzigen Spezies in 9 % (Post-Appendektomie: 18%) und Mischinfektionen in 48% (Post-Appendektomie: 44%) der Fälle. Bei UA wurden durchschnittlich 2,8 Spezies (Post-Appendektomie: 1,5), verglichen zu 3,7 Spezies bei KA (Post-Appendektomie: 2,6) nachgewiesen. Anaerobier konnten in 80 % der intraoperativ gewonnenen positiven Kulturen und in 44% der positiven Post-Appendektomie Kulturen nachgewiesen werden.

Das mikrobielle Spektrum der Kulturen aus Post-Appendektomie Abstrichen war vergleichbar mit jenem aus intraoperativ gewonnen Abstrichen, wobei die vier am häufigsten nachgewiesenen Bakteriengattungen Bacteroides (intra: 43%, post: 20%), Escherichia (intra: 33%, post: 35%), Streptokokken (intra: 16%, post: 20%) und Enterokokken (intra: 14%, post: 25%) waren. Der Anteil von Bacteroides spp. war in den Post-Appendektomie Kulturen im Vergleich zu den bei Appendektomie gewonnenen Abstrichen signifikant niedriger, wohingegen der Anteil von Enterococcus spp. signifikant höher war. Während das mikrobielle Spektrum der Kulturen aus Intra- und Post-Appendektomie Abstrichen über alle Patienten hinweg grundsätzlich ähnlich war, zeigte sich auf individueller Ebene eine geringe Überschneidung von Intra- und Post-Appendektomie Abstrichergebnissen.

Die Häufigkeitsverteilung verschiedener Bakteriengattungen zeigte signifikante Unterschiede zu anderen internationalen Studien. Dies bestätigt, dass lokoregionale Keimspektren für die Ausrichtung einer empirischen Therapie der KA relevant sind. Dadurch, dass mikrobiologische Abstrichergebnisse nur selten zur Anpassung der antibiotischen Therapie führten und diese unzureichende Prädiktoren für Post-Appendektomie Abstrichergebnisse bei Komplikationen waren, empfehlen wir eine Standardisierung der Indikationsstellung der intraoperativen Abstrichentnahme.

Postoperative Komplikationen wurden in der KA Gruppe häufiger berichtet. Chirurgische Wundinfektionen, welche am häufigsten intraabdominal, gefolgt von oberflächlichen Wundinfektionen auftraten, wurden bei 5% aller Patienten dokumentiert. Chirurgische Wundinfektionen traten in der KA Gruppe (13,7%) etwa zehnmal so häufig wie in der UA Gruppe (1,4%) auf. Insgesamt erforderten 3,6 % der Patienten postoperativ eine Revisionsoperation oder Abszessdrainage. Nahezu die Hälfte der Revisionseingriffe wurde während des initialen Krankenhausaufenthalts durchgeführt. Die übrigen Eingriffe erfolgten nach einer notfallmäßigen Wiedervorstellung und Wiederaufnahme der Patienten.

Die meisten Revisionseingriffe erfolgten innerhalb der ersten 10 postoperativen Tage, wohingegen weniger als 10% später als einen Monat nach Appendektomie durchgeführt wurden. Intraabdominale Abszesse stellten die häufigste Diagnose bei Revisionseingriffen in der KA Gruppe dar. Die zweithäufigste Diagnose in dieser Gruppe waren Klammernahtinsuffizienzen oder anderweitige Perforation des Gastrointestinaltrakts. In der UA Gruppe waren intraabdominale Adhäsionen einschließlich Bridenileus die häufigste Diagnose bei notfallmäßigen Revisionseingriffen.

Notfallmäßige Wiedervorstellungen bei Patienten mit KA waren 2,5-mal, ungeplante Wiederaufnahmen 5,8-mal und ungeplante Revisionsoperationen oder Abszessdrainagen 4,2-mal häufiger, als bei Patienten mit UA. Die Mortalitätsrate lag bei 0,12% in Fällen von UA bzw. 0,25% in Fällen von KA und ist damit insgesamt gering.

In der NA Gruppe wurden keine Revisionsoperationen durchgeführt. Dies deutet darauf hin, dass die nach UA und KA folgend nötigen Revisionseingriffe eher auf die Appendizitis selbst, als auf das operative Verfahren der Appendektomie zurückzuführen sind und untermauert die Sicherheit des Eingriffs.

Die in dieser Studie analysierten Daten stammen aus einem einzigen Krankenhaus und basieren auf Dokumentation, welche während des realen Krankenhausalltags erfolgte. Hierdurch, sowie aufgrund einer nicht standardisierten postoperativen Aufenthaltsdauer, als auch einem fehlenden follow-up sind die Daten teilweise unvollständig. Die Ergebnisse unterliegen den daraus resultierenden Einschränkungen und potenziellen Verzerrungen, welche sich bei retrospektiven Analysen elektronischer Patientenakten grundsätzlich ergeben.

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7 Erklärung zum Eigenanteil

Die Arbeit wurde in der Universitätsklinik für Allgemeine, Viszeral- und Transplantationschirurgie an der Universitätsklinik Tübingen unter Betreuung von Frau Prof. Dr. med. Ruth Ladurner durchgeführt.

Die Konzeption der Studie erfolgte in Zusammenarbeit mit Herrn Dr. med. Jens Strohäker.

Sämtliche Datenerhebung wurde von mir eigenständig durchgeführt. Die Listen der OPS Codes von Appendektomien mit Auflistung der Patientenfallnummern, welche für die Studie in Frage kamen, wurden von Herrn Dr. med. Jens Strohäker beantragt und mir von ihm zur Verfügung gestellt.

Die statistische Auswertung erfolgte eigenständig durch mich. Für Teile der Datenanalyse, welche ich in Python und R durchgeführt habe, habe ich den ChatGPT-3 (Stand 01.11.2023) Prompt „Shorten this code and improve readability by adding #comments“ verwendet. Mein gestalterischer Einfluss wurde hierdurch nicht beeinträchtigt. Die Auswahl der Analysen, sowie die Hypothesenerstellung- und Testung, sowie Interpretation der Ergebnisse erfolgte eigenständig durch mich.

Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Teile der Arbeit habe ich zunächst auf Deutsch verfasst und diese sowohl selbstständig unter Zuhilfenahme der online Version von www.pons.de (Stand 10.01.2024) sowie die online Übersetzungs-Software www.deepl.com (Stand 10.01.2024) ins Englische übersetzt. Ein persönliches Lektorat habe ich nicht in Anspruch genommen.

Tübingen, den 15.08.2024

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Martin Brüschke

8 Veröffentlichungen

Teile der vorliegenden Dissertationsschrift wurden bereits in den folgenden Publikationen veröffentlicht:

Strohäker, J. K. H., **Brüschke, M. J.**, Bachmann, R., Mihaljevic, A. L., Ladurner, R., & Beltzer, C. R. (2024). Intraoperative bacterial cultures fail to reliably predict the bacterial spectrum encountered during infectious complications after appendicitis. *Updates in surgery*, *76*(1), 147–154. https://doi.org/10.1007/s13304-023-01698-y

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