

**PARADIGM SHIFT IN THE DIAGNOSIS AND THERAPY OF ACUTE
APPENDICITIS**

Mán Eszter M.D.

Ph.D. Thesis

UNIVERSITY OF SZEGED FACULTY OF MEDICINE

DEPARTMENT OF SURGERY

SUPERVISOR

Prof. Lázár György M.D., Ph.D., DSC

2017

Szeged

LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. Man E, Simonka Z, Varga A, Rarosi F, Lazar G

Impact of the Alvarado score on the diagnosis of acute appendicitis: comparing clinical judgment, Alvarado score, and a new modified score in suspected appendicitis: a prospective, randomized clinical trial.

SURGICAL ENDOSCOPY AND OTHER INTERVENTIONAL TECHNIQUES 28: pp. 2398–2405. (2014)

IF: 3.256

II. Mán E, Németh T, Géczi T, Simonka Z, Lázár G

Learning curve after rapid introduction of laparoscopic appendectomy: Are there any risks in surgical resident participation?

WORLD JOURNAL OF EMERGENCY SURGERY 11:(1) Paper 17. 8 p. (2016)

IF: 2.82

LIST OF ABSTRACTS RELATED TO THE SUBJECT OF THE THESIS

I. Mán E, Markóth C

Szemléletváltás az akut appendicitis kezelésében: nyitott versus laparoscopos appendectomy

In: SZTE Tudományos Diákköri Konferenciája. Konferencia helye, ideje: Szeged, Magyarország, 2009.04.16-2009.04.18. Szeged: p. 172.

II. Németh T, Gécsi T, Markóth C, Mán E, Lázár G

Laparoscopos és nyitott appendectomy.

MAGYAR SEBÉSZET 62:(6) p. 365. (2009)

III. Mán E, Németh T, Markóth C, Gécsi T, Lázár G

Szemléletváltás az akut appendicitis diagnózisában és kezelésében

In: Fiatal onkológusok és fiatal sebészek fóruma. Programfüzet, absztraktok. Konferencia helye, ideje: Kecskemét, Magyarország, 2011.04.08-2011.04.09. Budapest: p. 6.

IV. Mán E, Gécsi T, Németh T, Markóth C, Lázár G

A laparoscopos appendectomy gyors bevezetésének kockázata – előnyök, hátrányok a hagyományos technikával szemben, MAGYAR SEBÉSZET 65:(4) p. 259. 1 p. (2012)

V. Mán E, Lázár G

Comparison of Alvarado score and clinical judgement in the diagnoses of acute appendicitis: – prospective, randomized trial. In: 21st International Congress of the EAES. Vienna, Austria, 2013.06.19-2013.06.21. Vienna: Paper O121.

VI. Mán E

Learning curve after rapid introduction of laparoscopic appendectomy: Are there any risks of surgical resident participation? MAGYAR SEBÉSZET 67:(4) p. 278. (2014), 14th World Congress of the European Association of Endoscopic Surgery. Paris: 2014.06.25 -2014.06.28.

VII. Mán E, Németh T, Géczi T, Simonka Z, Lázár G

Learning curve a laparoscopos appendectomia gyors bevezetése után: vannak-e a rizikófaktorai a rezidensek által végzett beavatkozásoknak? In: MAGYAR SEBÉSZ TÁRSASÁG SEBÉSZETI ENDOSZKÓPOS SZEKCIÓ XVI. KONGRESSZUSA SEBÉSZETI TOVÁBBKÉPZŐ TANFOLYAM: Eger, Hungary, 2015.11.12-2015.11.14. Eger: p. 29.

CONTENTS

LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS.....	1
LIST OF ABSTRACTS RELATED TO THE SUBJECT OF THE THESIS	2
ABBREVIATIONS.....	6
1. INTRODUCTION	7
1.1. ACUTE APPENDICITIS: PATHOGENESIS, ETIOLOGY, AND EPIDEMIOLOGY	7
1.2. DIAGNOSING ACUTE APPENDICITIS	8
1.3. THERAPY OF ACUTE APPENDICITIS.....	9
1.3.1. NON-SURGICAL TREATMENT.....	9
1.3.2. SURGICAL TREATMENT.....	9
2. OBJECTIVES.....	10
3. PATIENTS AND METHODS.....	10
3.1. The impact of the Alvarado score on the diagnosis of acute appendicitis as determined through a comparison of clinical judgment, Alvarado score, and a new modified score for suspected appendicitis (Study 1) - prospective, randomized study.....	10
3.2. Efficient surgical treatment of acute appendicitis, open vs. laparoscopic appendectomy (Study 2) - retrospective study	11
3.2.1. Clinical data on open vs. laparoscopic appendectomy groups	11
3.2.2.1. Surgical technique for open appendectomy.....	11
3.2.2.2. Surgical technique for laparoscopic appendectomy	12
3.3. Learning curve after rapid introduction of laparoscopic appendectomy, considering the risks of surgical resident participation in the procedure (Study 3) - retrospective study.....	12
4. RESULTS.....	13
4.1. The impact of the Alvarado score on the diagnosis of acute appendicitis as determined through a comparison of clinical judgment, Alvarado score, and a new modified score for suspected appendicitis (Study 1).....	13
4.1.1. Patient characteristics	13
4.1.2. Specificity and sensitivity of Alvarado score vs. clinical judgment based on post-operative pathological findings	13
4.1.3 Creation of a new modified Alvarado score with linear regression	14
4.2. Efficient surgical treatment of acute appendicitis, open vs. laparoscopic appendectomy (Study 2).....	15
4.2.1. Patient characteristics	15
4.2.2. Surgical procedures: open vs. laparoscopic appendectomy – rapid introduction of laparoscopic appendectomy (number of procedures and operation time).....	15

4.2.3. Histological findings	16
4.2.4. Clinical data in open vs. laparoscopic groups: intraoperative blood loss, duration of antibiotic therapy, length of hospital stay, time to first bowel movement, and fever.....	17
4.2.5. Surgical complications in the open vs. laparoscopic groups	17
4.3. Learning curve period after rapid introduction of laparoscopic appendectomy, considering the risks of surgical resident participation in the procedure (Study 3).....	18
4.3.1. Patient characteristics	18
4.3.2. Surgical procedures in Group A (residents) and Group B (consultants) in the learning curve and routine use periods: number of surgeries and operation time	18
4.3.3. Clinical data in Group A (residents) and Group B (consultants) in the learning curve and routine use periods: intraoperative blood loss, conversion rate, length of hospital stay, and negative appendectomy rate	19
4.3.4. Surgical complications in Group A (residents) and Group B (consultants) in the learning curve and routine use periods	19
5. DISCUSSION	20
5.1. CHALLENGES IN DIAGNOSING ACUTE APPENDICITIS WITH THE GROWING NUMBER OF A&E UNITS	20
5.2. THE ROLE OF THE ALVARADO SCORE IN DIAGNOSING ACUTE APPENDICITIS	20
5.3. THE ROLE OF LAPAROSCOPIC APPENDECTOMY IN TREATING ACUTE APENDICITIS	21
5.4. RESIDENT PARTICIPATION IN LAPAROSCOPIC APPENDECTOMY – ARE THERE ANY DISADVANTAGES?	22
5.5. LAPAROSCOPY TRAINING IN THE RESIDENCY YEARS.....	23
SUMMARY AND KEY RESULTS	25
Acknowledgements	26

ABBREVIATIONS

AA - Acute Appendicitis

APPAC - Antibiotic Therapy vs. Appendectomy for Treatment of Uncomplicated Acute Appendicitis

ASA - Adult Appendicitis Score

AIR - the Appendicitis Inflammatory Response Score

CT - Computed Tomography

IAA - Intra-Abdominal Abscess

LA - Laparoscopic Appendectomy

NAR - Negative Appendectomy Rate

OA - Open Appendectomy

PAS - Paediatric Appendicitis Score

RIPASA - Raja Isteri Pengiran Anak Saleha Appendicitis Score

RLQ Pain - Right Lower Quadrant Pain

US - Ultrasound

1. INTRODUCTION

Acute appendicitis is the most common urgent surgical condition. The first accurate description of appendicitis was made by Fitz in 1886, and the first appendectomy was performed by Claudius Amyand in England in 1735. In New York in 1889, Charles McBurney described the pathogenesis of appendicitis, Kurt Semm performed the first laparoscopic appendectomy in 1980, which became the new gold standard in the treatment of acute appendicitis. Nowadays almost 7% of the population is being affected, which constitutes a huge financial burden. This is why cost-effectiveness has become very important nowadays in health care as well. In cases of acute appendicitis, correct diagnosis with new imaging technologies and scoring systems can reduce the negative appendectomy rate, lower the number of inadequate surgical procedures, and cut down needless health care costs. Furthermore, with the spread of minimal invasive procedures, hospital stay can be reduced, while earlier return to work represents an extra saving for the health care system.

1.1. ACUTE APPENDICITIS: PATHOGENESIS, ETIOLOGY, AND EPIDEMIOLOGY

According to the leading theory, the initial event in the pathogenesis of acute appendicitis is obstruction of the lumen caused by fecaliths, foreign bodies, intestinal parasites, tumors, or lymphoid follicular enlargement due to viral infections. Risk factors for acute appendicitis are age, sex, and ethnic group/race. The most common symptom of appendicitis is abdominal pain, or epigastric pain migrating to the right lower quadrant (RLQ) of the abdomen, this sign is the most typical feature of the patient's history, with a sensitivity and specificity of approximately 80%. Vomiting, nausea, anorexia, diarrhoea or constipation, and fever can also occur. A differential diagnosis is extremely difficult. A clinical classification is used to stratify management based on simple (non-perforated) and complex (gangrenous or perforated) inflammation. The current incidence of appendicitis is about 100 per 100,000 person-years in Europe/America. In Hungary, the approximate rate of appendectomy is 100/1,000,000 inhabitants a year, of which rate of laparoscopic appendectomy is 30/1,000,000 inhabitants. The lethality of the condition is about 0.7%, which means that it causes the death of almost 100 patients in Hungary each year.

1.2. DIAGNOSING ACUTE APPENDICITIS

It is challenging to diagnose acute appendicitis. It is based on a medical history, a physical examination and a laboratory analysis (white blood cell count and CRP), but imaging techniques (ultrasound and CT scan) may also be helpful. US is non-invasive, inexpensive, and easy to perform, the ultrasound scan also avoids radiation, but its results are examiner- and patient-dependent. Its sensitivity rate is between 71 and 94% with a specificity rate of 81 and 94%. The number of negative appendectomies can be decreased by 10% with US. A CT scan provides an even more accurate picture of the lesion and reduces the number of negative appendectomies, but it is expensive and involves exposure to radiation. Its specificity rates are between 76 and 100%, and its sensitivity is between 81 and 98%. In past years, numerous clinical scoring systems have been created to make diagnosing the condition easier. The best known is the Alvarado score (MANTRELS score) (*Table 1*). The Paediatric Appendicitis Score (PAS), the Appendicitis Inflammatory Response Score (AIR), the Raja Isteri Pengiran Anak Saleha Appendicitis Score (RIPASA), and the Adult Appendicitis Score (ASA) are also well-known scoring systems. These scores can be used as a diagnostic aid and can aid young surgeons and emergency physicians, but they are inferior when compared to the diagnostic accuracy of experienced specialist surgeons.

Symptoms	Score
Migratory right iliac fossa pain	1
Anorexia	1
Nausea / Vomiting	1
Signs	
Tenderness in right iliac fossa	2
Rebound tenderness	1
Elevated temperature	1
Laboratory findings	
Leukocytosis	2
Shift of neutrophils to the left	1
Total score	10

Table 1. Alvarado score

1.3. THERAPY OF ACUTE APPENDICITIS

The treatment of acute appendicitis has undergone a paradigm shift in the last decade. There was a change in the gold standard for operative treatment. Nowadays laparoscopic appendectomy is the first choice in surgical therapy instead of the conventional open appendectomy. In the past decade, non-operative treatment of early appendicitis has become an alternative to surgery.

1.3.1. NON-SURGICAL TREATMENT

Clinically, AA has two main presentations: uncomplicated and complicated appendicitis. Anderson showed that not all patients with uncomplicated appendicitis will progress to perforation; spontaneous progression and resolution may occur. An APPAC (Antibiotic Therapy vs. Appendectomy for Treatment of Uncomplicated Acute Appendicitis) randomized trial and meta-analysis by Varadhan et al have shown that early appendicitis can be successfully treated with antibiotics. According to these studies, antibiotic therapy (initial intravenous then conversion to oral antibiotics) may be an optional treatment for non-complicated appendicitis, but only in a tight and strictly selected patient group.

1.3.2. SURGICAL TREATMENT

Two main approaches exist to remove the inflamed appendix: the open approach (OA) and the laparoscopic approach (LA). In recent years, the minimally invasive technique has been used in emergency surgery in ever increasing numbers. LA has been proved to have numerous advantages over open surgery (more rapid recovery, less postoperative pain, a decrease in the need for medications and in complications from wound infections, reduced incidence of postoperative bowel obstruction, better cosmetic results, shorter hospital stay, and earlier return to work). On the other hand, disadvantages are: a possible higher incidence of intraabdominal abscess, longer operation time, and increased operation cost due to special devices needed for laparoscopy. LA is therefore the first type of laparoscopic surgery residents learn; they thus learn the basics of the minimally invasive surgical technique and may develop the basic skills they can use in later, more complex surgeries.

2. OBJECTIVES

In our clinical study, we intended to investigate the most important and up-to-date questions of this widely-debated condition: the use of scoring systems in diagnosing acute appendicitis, the question of open vs. laparoscopic appendectomies, and the learning curve of the surgical procedure in residency training.

- I. One objective of our work was to investigate the impact of the Alvarado score on the diagnosis of acute appendicitis through a comparison of clinical judgment, Alvarado score, and a new modified score in suspected appendicitis (Study 1).
- II. A further objective was to study the efficacy of surgical treatment through a comparison of open and laparoscopic appendectomies (Study 2).
- III. Furthermore, we investigated the learning curve period after the rapid introduction of laparoscopic appendectomy, considering the risks of surgical residents' participation in the procedure (Study 3).

3. PATIENTS AND METHODS

3.1. The impact of the Alvarado score on the diagnosis of acute appendicitis as determined through a comparison of clinical judgment, Alvarado score, and a new modified score for suspected appendicitis (Study 1) - prospective, randomized study

233 patients presenting with suspected appendicitis between September 1, 2011, and September 31, 2012, at the outpatient clinic of the Department of Surgery of the University of Szeged were enrolled in our prospective, randomized study. In Group A, the treatment decision was based on the Alvarado score (1 to 4 points: discharge; 5 to 6 points: observation and repeated scoring in 12 hours; 7 to 10 points: urgent surgery) (*Table 1*). Further treatment of patients in Group B was based on the decision made by the head surgeon on duty. In Week A, the head surgeon on duty had the opportunity to override the score. These patients were

excluded from our study. The groups were alternated on a weekly basis. Following a surgery, the accuracy of the methods was assessed by evaluating the final histological results. With a statistical method, logistic regression, we first attempted to refine the score by weighting certain data, and then, after analyzing our own experience and the efficiency of the ultrasound scan, we amended the score with new aspects and discarded older ones. The new score was tested retrospectively on 131 patients outside the study. The data were analyzed with SPSS 20, with a significance level of $p < 0.005$. (The study was approved by the Ethics Committee of the University of Szeged and was registered under Current Controlled Trials under number ISRCTN56471.)

3.2. Efficient surgical treatment of acute appendicitis, open vs. laparoscopic appendectomy (Study 2) - retrospective study

3.2.1. Clinical data on open vs. laparoscopic appendectomy groups

The data on patients operated on at our institution using the traditional technique (Group I, $n=298$) and the laparoscopic procedure (Group II, $n=430$) over a seven-year period (between January 1, 2003, and December 31, 2009) were compared retrospectively. The two surgical techniques were compared based on the following clinical data: patient gender and age, surgical picture (including any other intraoperative diagnoses), duration of the procedure, blood loss during the procedure, presence of fever, time to first bowel movement, duration of the antibiotic treatment in days, length of hospital stay, histological results, short (major and minor) and long-term complications. Four groups were formed based on the laparoscopic and surgical experience of the surgeons who performed the procedures: residents (Group 1), candidate consultants (Group 2), young consultants (Group 3), and head surgeons on duty/consultants with at least 10 years of practice (Group 4). During the surgeries, a condition other than acute appendicitis was found in 45 cases; these patients were excluded from the study. The statistical analysis was performed using SigmaStat 3.1 and the Kruskal–Wallis test. The significance level was $p < 0.05$.

3.2.2.1. Surgical technique for open appendectomy

Open appendectomy is usually performed from a transverse incision in the right lower quadrant, through the so-called McBurney incision. Vertical incisions (median laparotomy or pararectal incision) are rarely performed (e.g., in the case of peritonitis or if the diagnosis is

not sufficiently certain for an exploration of the abdominal cavity). After reaching the appendix, the mesoappendix is held between clamps, divided, and ligated. Then the appendix is clamped proximally, cut down, and then ligated. The appendix may be inverted into the cecum with a Z-stitch. The cecum is placed back into the abdomen, and the abdomen is irrigated. It is not necessary to place a tube; it depends on the severity of the inflammation.

3.2.2.2. Surgical technique for laparoscopic appendectomy

A Veress needle is placed into the abdominal cavity through an umbilical incision to perform a pneumoperitoneum with up to 10–14 mm Hg insufflation with carbon dioxide. After inserting the laparoscope to view the abdomen cavity, a 10 mm trocar is inserted in the left lower quadrant and another 5 mm trocar is inserted above the pubic symphysis. The appendix is grasped and transected with a linear endostapler, haemoclip, or endoloop, or, alternately, the base of the appendix may be suture-ligated. In the case of severe inflammation, it is packed into a laparoscopic pouch to prevent wound contamination. Peritoneal irrigation is performed to avoid formation of an intraabdominal abscess.

3.3. Learning curve after rapid introduction of laparoscopic appendectomy, considering the risks of surgical resident participation in the procedure (Study 3) - retrospective study

Laparoscopic appendectomy was introduced at our clinic in 2006 over a mere six months. In our retrospective study, we evaluated the results of surgeries performed by 5 residents (Group A – young resident colleagues with 2 to 3 years of surgical experience at the beginning of the study) and 5 consultants (Group B – consultant group, colleagues with 8 to 9 years of surgical experience) in the learning curve period (20 surgeries as recommended by the EAES) and in the period after that (up to December 31, 2009) during routine use. Therefore, subgroups were formed within Groups A and B: A1 – residents in the learning curve period, A2 – residents in the period of routine use, B1 – consultants in the learning curve period and B2 – consultants in the period of routine use. In both groups, the assistant was an older consultant on duty, who had the most experience in both conventional and laparoscopic procedures. Results were evaluated for a total of 600 patients (Group A, n=319 – A1: n=100, A2: n=219; Group B, n=281 – B1: n=100, B2: n=181). Patient selection and data collection occurred retrospectively through an analysis of our computer database (Medsolution System) and the documentation for the patients. The groups were compared based on general patient demographics, duration of surgery, operation time depending on the severity of inflammation, intraoperative blood

loss, conversion rate, hospital stay in days, negative appendectomy rate, and number of complications (early or late). SPSS 20 was used for the statistical analysis—the durations of surgery were compared with a two-sample t-test, the complications were compared with Fisher's exact test, and the effect of inflammation on the duration of surgery was determined by analysis of variance. A significance level of $p < 0.05$ was used.

4. RESULTS

4.1. The impact of the Alvarado score on the diagnosis of acute appendicitis as determined through a comparison of clinical judgment, Alvarado score, and a new modified score for suspected appendicitis (Study 1)

4.1.1. Patient characteristics

Over a period of one year, 233 patients were enrolled in our study (Group A, $n=95$; Group B, $n=138$). Their mean age was 34.6 years (17–87) (Group A: 33.3; Group B: 35.52; $p=0.069$). Gender distribution: women: Group A, $n=67$; Group B, $n=88$; men: Group A, $n=28$; Group B, $n=50$; $p=0.326$. The mean BMI was 24.6 (Group A: 23.7; Group B: 25.8; $p=0.240$), and the mean ASA score was 1.6 (1.7 in Group A and 1.5 in Group B). Thus, the demographics of the two groups can be considered homogeneous.

4.1.2. Specificity and sensitivity of Alvarado score vs. clinical judgment based on post-operative pathological findings

After surgery, the histological results were evaluated in both Groups A and B. Based on the cross-tabulation of the post-surgery histological results, the specificity of the Alvarado score and that of the conventional clinical judgment were calculated: Group A: 88.9%; Group B: 94.8% ($p=0.320$). In Group A, 8 (8.42%) negative appendectomies were performed, whereas this number was 5 (3.62%) in Group B ($p=0.160$). Spearman's rank correlation was used to assess how true it was that a higher score is accompanied by more severe inflammation. Having assessed this in both groups, we can say that the correlation point is on the border, i.e., the correlation is not too close in this regard.

Based on the ROC analysis, the clinical judgment shows a better discriminating capacity than the Alvarado scoring system: 0.933 vs. 0.749, $p=0.120$.

By estimating Youden’s index, it can be established that the cut-off values produced by the scoring system as 5 to 6 are correct; for a score below 4, appendicitis is unlikely in the patient, whereas if the score is above 7, the inflammation is highly probable. Therefore, in the so-called “grey zone,” between scores 5 and 6, it is necessary to observe the patients and, possibly, use another imaging procedure (urgent CT scan).

4.1.3 Creation of a new modified Alvarado score with linear regression

We attempted to create a new score using linear regression by weighting certain parameters. Parameters that had not been part of the score before but are important based on our clinical experience were included in the criteria system (rectal-axillary temperature difference, indirect signs). The AUC (area under curve) by ROC analysis increased (0.849); therefore, the original scoring system was successfully refined (**Table 2**).

Symptoms	Modified score
RLQ pain	0.149
Nausea/vomiting	0.503
Anorexia	-4.927
Tenderness in right iliac fossa	1.788
Indirect sign positivity (1–2)	1.393
Indirect sign positivity (2 or more)	1.298
Elevated temperature	0.57
Rectal-axillar temp. difference >1°C	0.17
Leukocytosis >10G/l	-18.423
Leukocytosis >15G/l	1.888

Table 2. New score calculated by logistic regression, ROC analysis

To further refine the score, certain predictors that had proved to be less significant were removed from the scoring system, and the result of the ultrasound scan was included instead. This resulted in a further increase in the AUC (0.899), and the score was successfully refined even further. The new modified scoring system is shown in **Table 3**.

Symptoms	Modified score
Nausea/vomiting	0.645
RLQ tenderness	1.636
Indirect sign positivity (1–2)	1.059
Indirect sign positivity (2 or more)	0.985
Leukocytosis >10G/l	-17.841
Leukocytosis >15G/l	1.455
US examination	2.239

Table 3. New modified score containing US examination and ROC analysis

4.2. Efficient surgical treatment of acute appendicitis, open vs. laparoscopic appendectomy (Study 2)

4.2.1. Patient characteristics

The data on patients operated on at our institution using the traditional technique (Group I, n=298) and the laparoscopic procedure (Group II, n=430) over a seven-year period (between January 1, 2003, and December 31, 2009) were compared retrospectively. 46.1% of the patients were female (n=140) and 53.9% were male (n=158) in the open group, whereas the laparoscopic group consisted of 190 female (44.1%) and 232 male (55.9%) patients. The mean age was 41.1 (18–72) years in Group I and 32.9 (19–68) years in Group II. The mean BMI was 24.98 (20.02–33.1) in Group I and 23.87 (19.97–31.72) in Group II. The comorbidities and the distribution of the patients based on their ASA score were assessed in the groups.

4.2.2. Surgical procedures: open vs. laparoscopic appendectomy – rapid introduction of laparoscopic appendectomy (number of procedures and operation time)

A total of 728 appendectomies were performed over the 7-year period. Whereas the number of laparoscopic appendectomies was minimal compared to that of open surgeries in 2003 (n=93) and 2004 (n=96), the number of minimally invasive surgeries reached that of the

traditional ones in 2005 thanks to the quick introduction of the laparoscopic technique, and, from 2006, the number of open appendectomies decreased to a minimum (**Figure 1**).

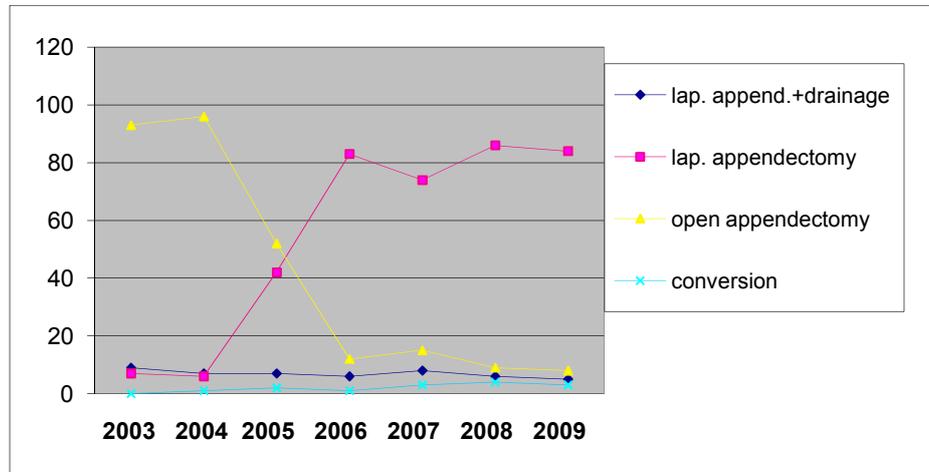


Figure 1. Changes in operation technique between 2003 and 2009

After the introduction of the laparoscopic technique, the indication for open surgery became limited. Conversion was performed in 14 cases, thus representing an average conversion rate of 3%.

The surgeons performing the procedures were divided into four groups based on their surgical experience (1 – resident, 2 – candidate consultant, 3 – young consultant, 4 – head surgeon on duty). The number of open vs. laparoscopic surgeries were the following in the main groups: Group 1- 48 vs. 29, Group- 2 115 vs. 72, Group- 3 168 vs. 128 and Group 4- 69 vs. 99.

We assessed the mean duration of the procedure for each surgical technique. The mean duration of the procedure was 62.41 (25–200) minutes in the laparoscopic group and 60.81 (20–160) minutes in the open group, and there was no significant difference between the groups in this regard ($p=0.405$).

4.2.3. Histological findings

A histological result was available after every intervention. Based on the histological examination, the number of mild cases (simple/superficial acute appendicitis) was 84 (11.5%) in the open group and 107 (14.6%) in the laparoscopic group ($p=0.72$). Severe inflammation (ulcero-phlegmonous, gangrenous or perforated appendicitis) was found in 195 cases (26.7%)

in the OA group, and 249 cases (34.2%) in the LA group ($p=0.32$). The histological examination revealed a non-inflamed appendix in 64 cases. In the laparoscopic group, two-thirds of the positive histological results showed severe inflammation on histological examination. Perforation and peritonitis was found in 51 cases (7%) in the open group and in 43 cases (6%) in the laparoscopic group. In these cases, conversion from laparoscopy was required on 12 occasions (1.6%).

4.2.4. Clinical data in open vs. laparoscopic groups: intraoperative blood loss, duration of antibiotic therapy, length of hospital stay, time to first bowel movement, and fever

With regard to clinical data, we evaluated intraoperative blood loss, duration of antibiotic treatment, presence of fever, time to first bowel movement, and length of hospital stay in the two surgical groups. Intraoperative blood loss was 45 (20–150) mL for the open technique and 55 (25–145) mL in the laparoscopic group ($p=0.505$). In the open group, the patients were given antibiotics for an average of 3.96 (1–10) days, whereas the same parameter was 2.6 (1–6) days for the laparoscopic surgeries ($p=0.01$). Time to first bowel movement was 2.52 (1–5) days in the open group and 1.74 (1–4) days in the group that received the minimally invasive technique ($p=0.02$). The length of hospital stay was 5.64 (3–18) days in the OA group and 3.25 (2–7) days in the LA group ($p=0.04$).

4.2.5. Surgical complications in the open vs. laparoscopic groups

The surgical complications were classified into major and minor ones. The number of major complications that required reoperation was 20 (2.1%) in the open group and 8 (0.8%) in the laparoscopic group. Minor complications were observed in 20 patients (2.7%) in the OA group and in 8 patients (1.1%) in the LA group. On the whole, there was a significant difference between the two procedures with regard to the number of complications ($p=0.034$). With regard to minor complications, wound infection should be noted. It occurred in 15 cases in the open group, and in 6 cases in the laparoscopic group ($p=0.025$).

4.3. Learning curve period after rapid introduction of laparoscopic appendectomy, considering the risks of surgical resident participation in the procedure (Study 3)

4.3.1. Patient characteristics

Data was evaluated for 600 patients in total between 2006 and 2009. The mean age of the patients was 38.4 years (A1: 39.6, A2: 39.3, $p=0.321$; B1: 39.1, B2: 35.9, $p=0.273$). Gender distribution: A1 – female: $n=53$, male: $n=47$; A2 – female: $n=119$, male: $n=100$; B1 – female: $n=65$, male: $n=35$; B2 – female: $n=98$, male: $n=83$. With regard to comorbidities (ASA score III to IV, severe cardiac disease, COPD, DM, underlying tumor disease, and chronic renal failure): A1: $n=10$, A2: $n=16$, $p=0.393$; B1: $n=12$, B2: $n=16$, $p=0.281$. We may thus consider these patient groups homogeneous.

4.3.2. Surgical procedures in Group A (residents) and Group B (consultants) in the learning curve and routine use periods: number of surgeries and operation time

The mean duration of surgery was 74.6 min in Group A1 57.3 min in Group A2, 64.13 min in Group B1 and 53.38 min in Group B2. When comparing the mean duration of surgery between residents and consultants in the learning curve period, we found a significant difference between the groups (A1 – residents: 74.6 min vs. B1 – consultants: 64.13 min, $p<0.05$). The same was observed when we compared the groups after the learning curve period (A2 – residents: 57.3 min vs. B2 – consultants: 53.38 min, $p<0.05$).

In the two main groups, we compared the change in duration of surgery, the learning “dynamic”: in Group A, the duration of surgery decreased from 74.6 minutes to 57.3 minutes ($p<0.05$), while a drop from 64.13 minutes to 53.38 minutes was observed in Group B ($p<0.05$). When investigating the effect of the severity of inflammation on operation time, we found a significant difference between the subgroups. In Group A (residents), operation time was 61.4 min for early appendicitis with less severe inflammation (catarrhal, phlegmonous) vs. 74.8 min for severe inflammation (gangrenous, perforated) ($p<0.05$). This value was 53.4 min vs. 68.5 min for Group B (consultants) ($p<0.05$). In the learning curve period, operation time was 58.49 min for early appendicitis and 70.12 min with severe inflammation; in the routine use period, it was 56.13min vs. 63.34 min. We found that the severity of the

inflammation significantly affected the duration of the operation when comparing Groups A and B in the LC period vs. the routine use period.

4.3.3. Clinical data in Group A (residents) and Group B (consultants) in the learning curve and routine use periods: intraoperative blood loss, conversion rate, length of hospital stay, and negative appendectomy rate

We evaluated intraoperative blood loss in the two main groups: it was 55 mL in Group A and 45 mL in Group B, and there was no significant difference ($p=0.664$). In Group A, conversion was required in 18 cases (5.6%) (adhesions due to prior surgeries [$n=6$], perforated, gangrenous appendix, the stump of which could not be treated safely with laparoscopy [$n=12$]), while this number was 21 (7.4%) in Group B (adhesions [$n=13$], the stump could not be treated safely due to severe inflammation [$n=6$], extreme obesity [$n=1$], and mesenteric injury during insufflation [$n=1$]; $p=0.321$). We also assessed whether the conversion rate was higher in the learning curve period: conversion was required in 14 out of 200 surgeries (7%) in LC period subgroups A1 and B1, while this number was 25 out of 400 (6.25%) in routine use subgroups A2 and B2, without a significant difference between the early and late periods ($p=0.522$). In addition, there was no significant difference in hospital stay between the groups (3.21 vs. 3.84 days, $p=0.391$, non-perforated group: Group A: 2.34 days; Group B: 2.13 days. Perforated group: Group A: 4.78 days; Group B: 4.98 days). The two groups did not differ in negative appendectomy rate (NAR, 8.5% vs. 7.8%, $p=0.835$) either.

4.3.4. Surgical complications in Group A (residents) and Group B (consultants) in the learning curve and routine use periods

The groups were also compared in terms of complications during and after the learning curve period. Early (within 30 days) major complications (bleeding, ileus, abscess, and thermal injury, which require reoperation), minor complications (wound infection), and late (after 30 days) complications (postoperative hernia) were assessed. There were no mortalities. The numbers of total complications were 5 in A1 (5%), 10 in A2 (4.6%), 9 in B1 (9%) and 17 in B2 (9.3%). In comparing the frequency of complications between subgroups A1 vs. B1 (5 vs. 9; 5% vs. 9%), it can be concluded that the occurrence of complications in the learning curve period was independent of surgical experience ($p=0.238$).

5. DISCUSSION

5.1. CHALLENGES IN DIAGNOSING ACUTE APPENDICITIS WITH THE GROWING NUMBER OF A&E UNITS

Despite advances in imaging procedures and laboratory analyses, diagnosing appendicitis is still a very difficult task, especially for candidate consultants and young colleagues. The failure of the initial examining physician to refer the patient for a surgical evaluation can lead to a delay in the treatment of acute appendicitis, which increases the risk of perforation and other complications. It would be necessary to assist these young colleagues in knowing when to request consultation from a specialist surgeon for patients with suspected appendicitis. In past years, numerous clinical scoring systems have been created to make it easier to diagnose the condition. The best known is the Alvarado score (MANTRELS) score. Of course, imaging procedures may also assist us. Ultrasound scan is a quick, inexpensive, repeatable procedure. An abdominal ultrasound scan is also routinely performed at our clinic for suspected appendicitis. A CT scan provides an even more accurate picture of the lesion and reduces the number of negative appendectomies, but it is expensive and involves exposure to radiation. Its specificity rates between 76 and 100%, and its sensitivity is between 81 and 98%.

5.2. THE ROLE OF THE ALVARADO SCORE IN DIAGNOSING ACUTE APPENDICITIS

In past years, numerous clinical scoring systems have been created to facilitate the diagnosis of the condition. The best known is the Alvarado score (MANTRELS score). Numerous studies by Sooriakumaran et al., Sanjon B et al. and Pouget-Baudry et al. have confirmed the reliability of both the Alvarado score and the modified Alvarado score (MAS) in the diagnosis of appendicitis. According to a recent review, a cut-off value of 5 points in the scoring system is an excellent tool for deciding whether the patient should be discharged or provided with further treatment (observation and/or surgery). When our sensitivity-specificity values were plotted with Youden's index, a similar result was reached. The so-called grey zone was between 5 and 6 points. In these cases, further observation or an imaging procedure (CT) is needed to confirm the diagnosis. According to some studies by Owen et al., Arian et al. and Khan et al., a value above 7 points is the diagnostic criterion for an urgent surgery and the

number of negative appendectomies decreases below 16%. According to other studies by Singh et al., Al-Quahtani et al. and Adeldaim et al the conventional clinical judgment is more reliable with regard to the indication for surgery, and the number of negative appendectomies in these cases is about 12% . In our study, the specificity of the conventional clinical judgment was higher than that of the Alvarado scoring system, but the difference was not significant (94.8% vs. 88.9%, $p=0.32$). In Group A, 8 (8.42%) negative appendectomies were performed, whereas this number was 5 (3.62%) in Group B ($p=0.16$). We have found the score to be reliable in the diagnosis of the condition and that it assists the staff at the emergency outpatient clinic, primarily in the decision on admission/discharge and on consulting a specialist. By further refining the Alvarado score based on our own clinical experience, we created a new score using linear regression which has become easier to use and has a better diagnostic accuracy.

5.3. THE ROLE OF LAPAROSCOPIC APPENDECTOMY IN TREATING ACUTE APENDICITIS

Appendicitis is the most common urgent surgical condition. Although 30 years have now passed since the introduction of the laparoscopic technique, numerous studies are still being conducted on the advantages and disadvantages of the procedure, compared with open appendectomy. Based on the studies published to date by Gullet et al., Milewczyk et al., Olmi et al laparoscopy has numerous advantages over the traditional procedure with regard to length of hospital stay, postoperative pain, and infectious complications. According to another author, Ignacio et al., the minimally invasive technique has no advantages over the open method, and its costs are higher than those of conventional appendectomy. According to the most recent meta-analyses from B. Wei et al and from Li X et al, oral feeding can be introduced earlier, the hospital stay is shorter, and there were fewer postoperative complications after a laparoscopic procedure. The duration of the procedure, however, is longer in the case of the minimally invasive technique.

When reviewing the clinical data in our practice, we found that there was a significant difference between the two surgical techniques with regard to the length of hospital stay, the duration of antibiotic treatment, time to first bowel movement and number of complications (OA: 40;, LA: 13;, $p=0.001$) as well. When assessing the duration of the procedure and the surgical complications in relation to surgical experience, we found no difference between the

data from 2005 and those from 2008 and 2009. Another great advantage of laparoscopy is the possibility of exploration. Laparoscopy, though invasive, can be both diagnostic and therapeutic as well.

The question is frequently raised whether cases with severe inflammation and perforation can be treated safely with the minimally invasive technique. When assessing the data on our patients we found that two-thirds of the positive histological results showed severe inflammation on histological examination. Significantly fewer complications were observed when the cases with severe inflammation were treated with the minimally invasive technique (compared to the open group). Perforation and peritonitis were found in 51 cases (7%) in the open group, and in 43 cases (6%) in the laparoscopic group. In these cases, conversion from laparoscopy was required on 12 occasions (1.6%). It must be noted that 57% of all wound infections occurred in those open surgeries where perforation of the appendix and peritonitis were observed.

5.4. RESIDENT PARTICIPATION IN LAPAROSCOPIC APPENDECTOMY – ARE THERE ANY DISADVANTAGES?

The minimally invasive technique was also introduced rapidly at our clinic, over a period of six months in 2006, and it completely superseded the open method. The laparoscopic-to-open ratio in Group A (residents) was 0.22 before 2006 and 10.21 between 2006 and 2009. In Group B (consultants), the same ratio was 0.37 before 2006 and 4.8 after 2006. Therefore, it is also increasingly important to develop laparoscopic skills and learn basic minimally invasive procedures in training young surgeons at our clinic. This trend can be observed in the training program at foreign universities as well. Many studies have investigated the effect of resident participation in laparoscopic surgeries (Noble et al., Perry et al., Shabtai et al.). However, there is still no clear evidence for the minimum number of laparoscopic cases to achieve proficiency. The EAES consensus guideline recommends a minimum of 20 operations. Some other retrospective studies by Sanfey et al., Kim et al., Jaffer et al. also recommend 20–30 operations during the learning curve. Based on our own experience, this number of surgeries is necessary for a resident to be able to perform appendectomy independently. After the learning curve period (20 surgeries), there was a significant difference in mean duration of surgery both in the consultant group and the resident group (64.13 vs. 53.38 min and 74.6 vs.

57.3 min, respectively, $p < 0.05$). According to our results, the severity of the inflammation affected operation time significantly.

The mean hospital stay in days and conversion rate are good measures of laparoscopic experience, as this period is longer in the case of a prolonged, complicated surgery. In our study, there was no significant difference between the learning curve period and the period after that either in hospital stay or conversion rate, nor was there any difference when comparing young surgeons with consultants. It was determined by the severity of the inflammation.

Since, according to our results, there was no significant difference in the frequency of complications between subgroups A1 and B1 (5 vs. 9; 5% vs. 9%, $p = 0.238$) and subgroups A2 and B2 (10 vs. 17; 4.5% vs. 9.3%). We only observed a difference between the groups in duration of surgery: 74.6 min in subgroup A1 and 64.13 min in subgroup B1 ($p < 0.05$), while it was 57.3 min in subgroup A2 and 53.38 min in B2 ($p < 0.05$). It is interesting that the decrease in duration of surgery after the learning curve period was greater among residents. As they performed an increasing number of surgeries, they used the laparoscopic instruments with ever greater confidence, and both the surgeon performing the surgery and the surgical staff felt more confident in the laparoscopic situation.

5.5. LAPAROSCOPY TRAINING IN THE RESIDENCY YEARS

In Hungary, residents must complete a two-week “Basic laparoscopic skills course”, where they learn the basics of laparoscopy in training boxes and have the opportunity to practice on live animals (splenectomy, appendectomy, cholecystectomy, and bowel sutures). However, the real training starts when they assist in basic (cholecystectomy, laparoscopic hernia repair, and appendectomy) and advanced (colorectal surgery, hiatal hernia repair, splenectomy, etc.) laparoscopic surgeries. The first laparoscopic procedure that they perform individually with the help of a supervisor (consultant) is mostly laparoscopic appendectomy. Through the six years of surgical residency training, each candidate must perform a fixed number of basic laparoscopic procedures (25 appendectomies and 20 cholecystectomies).

According to some studies by Sanfey et al, simulator and animal model training decreases subsequent intraoperative complications. Others suggest that real procedures performed in the OR are required for the actual development of skills and for the resident to become a skilled

surgeon (McFadden et al.). According to a U.S. surveys by Park et al. and Unawana et al., a large proportion of residents feel that they did not perform a sufficient number of laparoscopic procedures during their residency and therefore do not feel secure when they have to perform surgery independently.

With the spread of laparoscopy, increased attention must be paid to the training of residents, and there is a need to implement standardized training models, as it is clear that, in our case, laparoscopic appendectomy is a technique that can also be used safely by residents in the learning curve period—naturally under the supervision of a consultant. Learning this technique provides residents with a valuable opportunity to perform more difficult, more complex laparoscopic surgeries with adequate safety in the future.

SUMMARY AND KEY RESULTS

1. *Based on our prospective, randomized clinical trial, the Alvarado score is a reliable tool in diagnosing acute appendicitis, and it aids the staff at the emergency outpatient clinic, primarily in the decision on admission/discharge and on consulting a specialist.*
2. *Furthermore, in our prospective randomized clinical trial, we created a new score using linear regression, by weighting certain parameters from the conventional Alvarado score and opting in new parameters we have found important based on our clinical experience (rectal-axillary temperature difference, indirect signs, and US investigation). It has become easier to use the new scoring system, as it involves fewer criteria.*
3. *Our results confirm that the quick introduction of laparoscopic appendectomy poses no risks. We have shown numerous advantages of the method compared to the traditional, open technique, such as shorter hospital stay, less need for antibiotics, shorter time to first bowel movement, and fewer major and minor complications. This surgical technique can also be used by young surgeons, since better results were achieved in this group than with the traditional method with regard to the duration of the procedure and the number of complications as well.*
4. *Laparoscopic appendectomy is a technique that can also be used safely by residents in the learning curve period—naturally under the supervision of a consultant. Learning this technique provides residents with a valuable opportunity to perform more difficult, more complex laparoscopic surgeries with adequate safety in the future.*

Acknowledgements

First and foremost, I wish to express my gratitude to Prof. Dr. György Lázár for having offered me the opportunity and for the ongoing support, constant help and inspiration in my work.

I would like to offer my special thanks to Dr. Géczi Tibor for giving a great support at the beginning of my Scientific Students' Associations work, to Dr. Varga Ákos for his help in planning, organizing and evaluating our prospective, randomised study and to Dr. Krisztina Boda and Ferenc Rárosi for their assistance in doing the statistics.

And I am obliged to all my colleagues for their support in my everyday work in the Department of Surgery. Without them this work would have never been completed.

Last but not least, I would like to express my gratitude to my family for their support and understanding.