Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis: A randomized controlled trial

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BACKGROUND: Recent investigations noted noninferiority in short-course antimicrobial treatments following source control in abdominal infections. We set out to investigate noninferiority of a short and fixed (24 hours) antibiotic administration compared to extended treatment after source control in complicated appendicitis in a prospective single-center open-label randomized controlled trial.

METHODS: After Institutional Review Board (IRB) approval, all consecutive adult patients (age, ≥ 18 years) with complicated appendicitis including gangrenous appendicitis, perforated appendicitis, and appendicitis with periappendicular abscess between May 2016 and February 2018 were randomly allocated to antibacterial therapy limited to 24 hours (short) vs. >24 hours (extended) administration after appendectomy. Primary outcomes included composite postoperative complications and Comprehensive Complication Index (CCI). Secondary outcome was hospital length of stay (HLOS). Follow-up analysis at 1 month was conducted per intention and per protocol.

RESULTS: A total of 80 patients were enrolled with 39 and 41 cases allocated to the short and the extended therapy group, respectively. Demographic profile and disease severity was similar between the study groups. Overall rate of complications was 17.9% and 29.3% in the short and extended group, respectively ($p = 0.23$). Mean CCI did not differ between the study groups ($p = 0.29$). Hospital length of stay was significantly reduced in the short therapy group (61 ± 34 hours vs. 81 ± 40 hours, $p = 0.005$).

CONCLUSION: In the current prospective randomized investigation, the short (24 hours) antibiotic administration following appendectomy did not result in a worse primary outcome in complicated appendicitis. The short interval administration resulted in a significant reduction in HLOS with a major cost-saving and antibacterial stewardship perspective. (*J Trauma Acute Care Surg.* 2019;86: 36–42. Copyright © 2018 American Association for the Surgery of Trauma. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic Level IV.

KEY WORDS: Acute appendicitis; complicated appendicitis; antibiotics; duration.

Appropriate perioperative antimicrobial administration is a basic tenet in gastrointestinal surgery to prevent surgical site infections (SSI).[1] In noncomplicated appendicitis including catarrhal or phlegmonous appendicitis, antimicrobial therapy following surgery is not indicated and may result in higher incidence of adverse events.[2,3] However, in complicated appendicitis including gangrenous appendicitis, perforated appendicitis, or appendicitis with periappendicular abscess, antibiotic administration is recommended following source control in a minimum of 3 days to 5 days according to the recent evidence-based guideline.[4] Similar to investigations that observed noninferiority of abbreviated antimicrobial therapy in abdominal infections overall, a recent prospective investigation suggested that a three-day antimicrobial administration following appendectomy in complicated appendicitis was noninferior to a 5-day therapy.[5–7] Furthermore, another small retrospective investigation by Kimbrell et al.[8] observed that 24-hour antibiotic therapy was noninferior to extended administration in complicated appendicitis. Based on the safety of the previous data on abbreviated antimicrobial therapy in these instances, we set out to investigate noninferiority of a short and fixed (24 hours), versus extended postoperative antimicrobial treatment after surgical source control in complicated appendicitis in a prospective open-labeled randomized controlled trial. We hypothesized that complication rates are similar between the study groups.

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METHODS

After IRB approval, all consecutive patients with an age 18 years or older with acute appendicitis based on clinical diagnosis supported by laboratory markers, ultrasound and/or computed tomography per treating physician were eligible for enrollment and were consented prior to appendectomy for postoperative randomization when complicated appendicitis was encountered at surgery between May 2016 and February 2018. Randomization to intravenous antibacterial therapy limited to 24 hours (short) vs. >24 hours (extended) administration after appendectomy was performed with a computerized software within 24-hour period following surgery when both study groups received intravenous antimicrobial treatment per the study protocol. In patients allocated to short treatment, the antibiotic administration was terminated at 24 hours after surgery and those allocated to extended treatment interval were managed at the discretion of the treating physician. Per the study protocol, likewise, the treating physician was allowed to extend the antibiotic treatment when clinically indicated in the short-treatment group. Appendicitis disease severity was classified using the disease severity score (DSS) dividing acute appendicitis into five grades: grade 1, inflamed; grade 2, gangrenous; grade 3, perforated with localized free fluid; grade 4, perforated with a regional abscess; and grade 5, perforated with diffuse peritonitis.[9] For randomization we included grade 2, 3, and 4 constituting an entity of complicated appendicitis. The DSS grade was assessed during appendectomy by surgeon performing the operation per the DSS grading protocol. A decision to perform laparoscopic vs. open appendectomy was at the discretion of the treating physician. Exclusion criteria included age < 18 years, pregnancy, cognitive impairment, diabetes, immunodeficiency (primary or secondary), ongoing chemo- or radiotherapy for any oncological disease, radical treatment of a oncological disease within 5 years, penicillin allergy, presence of a mechanical heart valve or a synthetic vascular implants or grafts. Also, patients with grade 1 or grade 5 appendicitis per DSS were excluded.

Only aminopenicillins (amoxicillin with clavulanic acid or ampicillin with sulbactam) were administered. Antibiotic

therapy was administered intravenously only in the short treatment group and in the extended group the intravenous administration was provided in 48 hours followed by a continued intravenous or an oral administration per the treating physician's assessment. The decision for the length of antibiotic therapy in the extended therapy group was also made by the treating physician. The dosage of intravenous amoxicillin/clavulanic acid and ampicillin/sulbactam was 1.2 g and 3 g every 8 hours, respectively.

Data collection included demographics, laboratory markers (white blood cell count and C-reactive protein [CRP]), antibiotic therapy, surgical treatment, complications per Clavien-Dindo (CD), Comprehensive Complication Index (CCI), and hospital length of stay (HLOS). Comprehensive Complication Index is a postoperative morbidity assessment scale based on CD classification, however, while CD classification includes only one most severe complication, the CCI includes all complications in a scale ranging from 0 (no complications) to 100 (complication resulting in patient's demise).[10,11] Higher CCI score depicts higher burden of complications.

Follow-up phone-call survey was performed 30 days after appendectomy and all the readmissions were documented. When patient indicated any adverse event on the phone-call survey, the adverse event and the respective treatment was confirmed in the Estonian National Health Information System records containing health data submitted from all national hospitals and general practitioners.

Surgical site infection including superficial and deep incisional and organ/space SSI (intra-abdominal abscess) was defined per Centers for Disease Control and Prevention guideline.[12]

Primary outcomes were postoperative complications per CD and CCI. Secondary outcome was HLOS.

The outcome analysis was performed per intention to treat (ITT) and per protocol (PP) follow-up. The p values for continuous variables were derived from the Student's t test or Mann-Whitney tests and for categorical values χ^2 or 2-sided Fisher's exact test were used. p Values less than 0.05 were considered statistically significant. Values are reported as a percentage for categorical variables and as mean ± standard deviation (SD) for continuous variables. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Mac) version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

During the study period, a total of 80 patients were enrolled with 39 and 41 cases in the short and the extended therapy group, respectively (Fig. 1). The average length of antibiotic therapy in the extended group was 6 ± 3 days. Thirty-day follow-up by phone-call survey was available in all patients. All demographic

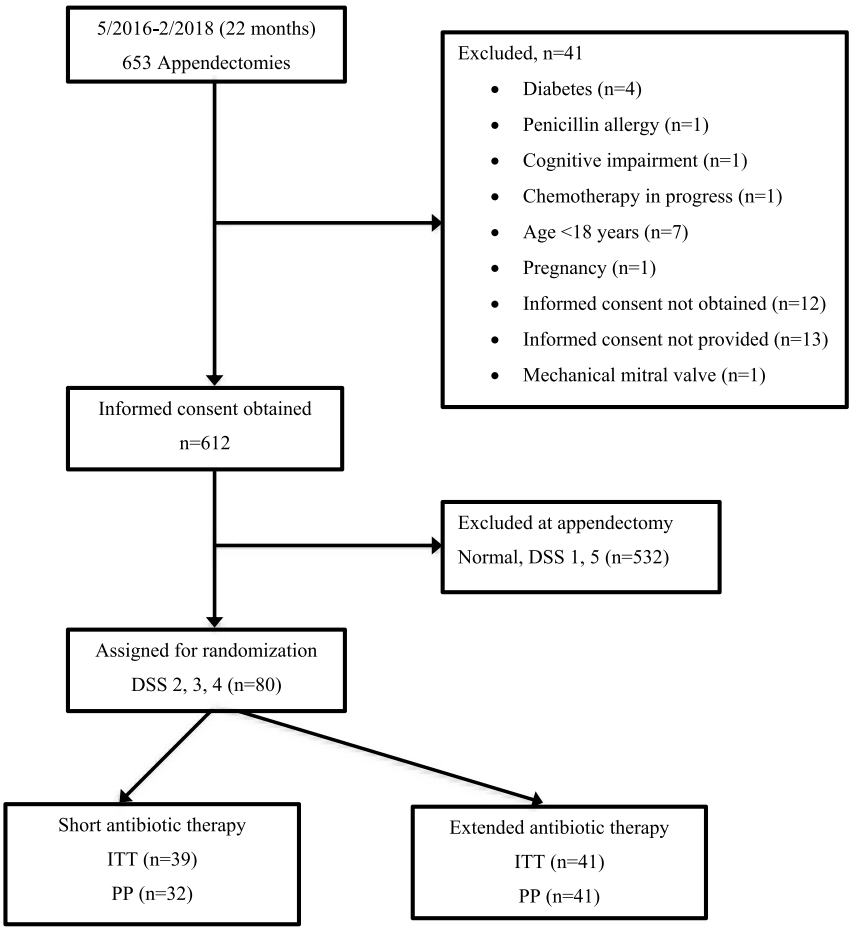

Figure 1. Flowchart of all included patients.

TABLE 1. Demographic Profile, Laboratory Values, Surgical Interventions, and Classification of Appendicitis Severity per DSS of All Patients

	ITT			PP		
n	**Short n = 39**	**Extended n = 41**	***p* value**	**Short n = 32**	**Extended n = 41**	***p* value**
Age, y	44.2 ± 15.2	45.8 ± 15.3	0.627	42.8 ± 14.4	45.8 ± 15.3	0.384
Gender (male)	56.4%	63.4%	0.523	59.4%	63.4%	0.913
Charlson's Comorbidity Index >0	38.5%	39.0%	0.959	34.4%	39.0%	0.870
Time from onset of symptoms to surgery, h	43.2 ± 31.2	48.4 ± 44.3	0.832	45.2 ± 32.8	48.4 ± 44.3	0.623
Time from ED admission to surgery, h	9.7 ± 6.9	9.1 ± 5.1	0.675	10.3 ± 7.2	9.1 ± 5.1	0.446
Mean admission WBC × 10^9/L	14.7 ± 4.4	14.3 ± 3.7	0.641	14.4 ± 4.5	14.3 ± 3.7	0.901
Mean admission CRP, mg/L	92 ± 99	87 ± 101	0.829	82 ± 93	87 ± 101	0.408
Laparoscopic appendectomy	89.7%	95.1%	0.426	87.5%	95.1%	0.455
Open appendectomy	10.3%	4.9%	0.426	12.5%	4.9%	0.394
Conversion to open appendectomy	2.6%	0	0.488	3.1%	0	0.438
Length of operation, min	52 ± 19	54 ± 20	0.680	51 ± 19	54 ± 20	0.433
DSS grade 2	71.8%	61.0%	0.306	75.0%	61.0%	0.310
DSS grade 3	20.5%	22.0%	0.875	15.6%	22.0%	0.561
DSS grade 4	7.7%	17.1%	0.313	9.4%	17.1%	0.499

ED, emergency department; WBC, white blood cell count; ITT, Intention to Treat; PP, Per Protocol; CRP, C-reactive Protein; DSS, Disease Severity Score.

and laboratory variables were similar between the study groups depicted in the Table 1. Majority of the cases had laparoscopic appendectomy with similar rates in both study groups per ITT and PP analyses. Overall, grades 2, 3, and 4 appendicitis per DSS constituted 66.3%, 21.3%, and 12.5% of the cases, respectively, and did not differ significantly between the study groups (Table 1).

Computed tomography investigation was obtained in 52.5% (n = 42) of the patients allocated to randomization. In 21.4% (n = 9) of those studies, the CT indicated a complicated appendicitis.

Hospital length of stay and detailed description of surgical complications per CD and CCI are listed in Table 2. Hospital length of stay was significantly reduced in the short therapy group (61 ± 34 hours vs. 81 ± 40 hours, $p = 0.005$ per ITT and 51 ± 21 hours vs. 81 ± 40 hours, $p < 0.001$ per PP analysis). Mean CCI and complication rate per CD did not differ significantly between the study groups and the respective follow-up analyses. Grade II complications predominated in both study groups. None of the patients had higher than grade IIIa complication. No mortalities were encountered.

When only gangrenous perforated appendicitis cases (grades 3 and 4) were stratified and compared between the study arms, the mean CCI was 5.86 and 7.14 ($p = 0.72$) and the rate of complications was 27.2% and 37.5% ($p = 0.69$) in the short and extended treatment groups, respectively.

TABLE 2. HLOS, Complications per CD classification, CCI, and Interventions in All Readmitted Patients

	ITT			PP		
n	**Short n = 39**	**Extended n = 41**	***p* value**	**Short n = 32**	**Extended n = 41**	***p* value**
HLOS, h	61 ± 34	81 ± 40	**0.005**	51 ± 21	81 ± 40	**<0.001**
Any CD complication	17.9%	29.3%	0.234	21.9%	29.3%	0.475
Grade I per CD	2.6%	9.8%	0.360	3.1%	9.8%	0.377
Grade II	10.3%	14.6%	0.738	12.5%	14.6%	1.000
Grade IIIa	5.1%	4.9%	1.000	6.3%	4.9%	1.000
Grade IIIb-V	0	0	-	0	0	-
Superficial/deep SSI	12.8%	7.3%	0.476	15.6%	7.3%	0.287
Organ/space SSI	7.7%	12.2%	0.713	9.4%	12.2%	1.000
Diarrhea	0	2.4%	1.000	0	2.4%	1.000
Pneumonia	0	2.4%	1.000	0	2.4%	1.000
Postoperative ileus	0	9.8%	0.116	0	9.8%	0.126
Mean CCI	3.93 ± 8.93	5.46 ± 9.57	0.298	4.79 ± 9.67	5.46 ± 9.57	0.579
Readmitted patients	7.7%	7.3%	1.000	9.4%	7.3%	1.000
Interventions in all readmitted patients						
Antimicrobial therapy	2.6% (1)	2.4% (1)	1.000	3.1% (1)	2.4% (1)	1.000
Percutaneous drainage + antimicrobial therapy	5.1% (2)	4.9% (2)	1.000	6.3% (2)	4.9% (2)	1.000

HLOS, Hospital Length of Stay; CD, Clavien-Dindo; SSI, Surgical Site Infections; CCI, Comprehensive Complications Index; ITT, Intention to Treat; PP, Per Protocol.

Allocation to the short treatment group was violated in seven (17.9%) cases where antibiotic therapy was extended by the treating physician. The most frequent causes for protocol violation were persistent fever in five patients and elevated postoperative CRP (250 mg/L) in two patients after 24 hours of antibiotic treatment. None of the patients had complications during the 30-day follow-up. Thus, PP analysis included 32 patients in the short interval group and 41 in the extended interval group, respectively.

Overall, a morning temperature greater than 37.3°C was measured in 41% and 44% of the patients in the extended and short duration groups at 24 hours after surgery, respectively ($p = 1.000$).

T > 37.3°C occurred in 12.2% of the cases at the time of antimicrobial administration cessation in the extended group.

Overall, superficial and deep SSIs occurred in 12.8% (n = 5) and 7.3% (n = 3) in the short and extended treatment groups, respectively ($p = 0.47$). Organ/space SSI rate was likewise similar, at 7.7% (n = 3) and 12.2% (n = 5) in the 24-hour and extended treatment groups, respectively ($p = 0.71$). No difference in SSI was noted per ITT and PP analyses. Postoperative diarrhea occurred only in one patient in the extended treatment group with a negative *Clostridium difficile* PCR test. Other complications included one pneumonia and four postoperative ileus cases in the extended group (Table 2).

The overall readmission rates were similar at 7.7% (n = 3) and 7.3% (n = 3) in fixed and extended treatment groups, respectively ($p = 1.00$). Readmissions did not differ in ITT and PP analyses. Organ/space SSIs caused all rehospitalizations and interventions included percutaneous drain placement in four and antimicrobial therapy in two patients (Table 2).

DISCUSSION

The current prospective randomized controlled trial supported our hypothesis of noninferiority of a short and fixed, 24-hour therapy, compared to an extended treatment with antibiotics after source control in complicated appendicitis. Likewise, the study demonstrated significantly reduced HLOS in the short therapy group providing a significant cost-saving perspective and an antimicrobial stewardship potential in patients suffering a common surgical emergency, that is, complicated acute appendicitis.

The interval of postoperative antimicrobial therapy is a subject of a lively debate; however, multiple well-designed recent investigations have observed noninferiority in mixed groups of patients with intraabdominal infections.[5,6] Nevertheless, prospective randomized studies specific to complicated appendicitis are scarce. According to the recent evidence, postoperative antimicrobial therapy in noncomplicated appendicitis is not recommended and may result in worse outcomes including higher rate of Clostridium difficile infections and urinary tract infections.[2] Also, HLOS and cost of care is significantly increased with the inappropriate administration of antimicrobials following surgery.[2,13] Nevertheless, postoperative administration is indicated per the guidelines in complicated appendicitis, however, randomized controlled trials are lacking to guide the best practice.[4] A large prospective observational study by van Rossem et al.[7] comparing 3-day antibiotic treatment with five-day therapy in complicated appendicitis observed no benefit on infectious complications in extended administration. Also, a small retrospective study by Kimbrell et al.[8] reported similar rate of postoperative abscess incidence among patients receiving antibiotics for 24 hours or less compared with extended administration after appendectomy for complicated appendicitis, however, the number of patients included in the study was limited to only eight patients in the 24-hour subgroup.[8]

The current investigation allocating randomly patients to receive antibiotics per fixed 24-hour interval versus extended interval observed no difference in the rate of postoperative complications or readmissions. Time from onset of symptoms to surgery and in-hospital delay being a known independent risk factors for postoperative complications were, likewise, similar.[14–16] The only significantly different outcome across all analyses was the HLOS with a significant global cost saving perspective. Also, antibiotics used in the current study are rather inexpensive and widely available providing opportunities for a wide implementation of our results.

Our analysis included both ITT and PP follow-up with no significant difference in outcomes. The short therapy group treatment was violated per treating physicians in seven cases with most frequent cause being fever, however, none of the patients developed complications. A fever in the postoperative period is a common entity and may be related with noninfectious etiology including respiratory complications, drug fever, endocrine abnormalities or surgical insult with no indications for antimicrobial therapy.[17]

The ITT analysis including all patients allocated to the respective study arms resulted in no differences in primary outcomes. The PP analysis excluded seven (17.2%) patients from the short therapy group outcome analyses due to treating physicians' extention of the antibiotic therapy. Similar to many clinical trials, treating physicians rely on previously established clinical practices involving extended therapy in complicated appendicitis. The seven cases subjected to extended therapy were excluded from the PP analysis resulting, however, in no significant differences in primary outcomes. The secondary outcome, that is, HLOS was significantly abbreviated in both follow-up analyses among patients allocated to the short therapy group.

The current study is limited by a low number of patients and inclusion of adult patients only. Nevertheless, to the best of our knowledge this is the very first randomized study to compare postoperative short antimicrobial therapy interval with extended treatment in complicated appendicitis. Thus, our study has a potential to modify postoperative management of acute complicated appendicitis in the era of rising antimicrobial resistance and to initiate large multi-center investigations to confirm our findings.

CONCLUSION

In the current prospective randomized investigation, the short (24 hours) antibiotic administration following appendectomy did not result in a worse primary outcome in complicated appendicitis. The short interval administration resulted in a significant reduction in HLOS with a major cost-saving and antibacterial stewardship perspective.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

AUTHORSHIP

S.S. participated in the literature search, study design, data collection, data analysis, data interpretation, writing, critical revision. V.M. participated in the study design, data collection, critical revision. T.L. participated in the study design, data analysis, critical revision. M.R. participated in the study design, data collection, critical revision. E.-H.N. participated in the study design, data collection, critical revision. E.L. participated in the study design, data collection, critical revision. K.-G.I. participated in the study design, data collection, critical revision. J.L. participated in the study design, data collection, critical revision. A.L. participated in the study design, data collection, critical revision. U.L. participated in the study design, data collection, critical revision. P.T. participated in the literature search, study design, data collection, data interpretation, writing, critical revision.

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DISCUSSION

Dr. Robert G. Sawyer (Kalamazoo, Michigan): Thank you to the AAST and Dr. Knudson, Dr. May for allowing me to discuss this paper which I think is very well done. Anyone who has done a randomized controlled trial realizes it's hard to do.

When you end up screening hundreds and hundreds and hundreds and hundreds of patients and end up with 80 who get randomized you understand that the amount of work is a lot more than just looking after those 80 patients who are randomized.

Dr. Saar, thank you for coming from Estonia to present a paper. I think that's fantastic on your part and welcome to our country. I hope you enjoy yourself here.

There are a couple of things I'd like to point out before I go ahead and ask some questions which I think are important to keep in mind.

Number 1 is if you look at this and you want to integrate it to your own management of patients with appendicitis you have to remember that patients with diffuse peritonitis were excluded so we're looking at group of patients who had either gangrenous peritonitis or a local infection related to the appendix but, also at the other end excluding patients who just had run-of-the-mill appendicitis without any, with just Grade I appendicitis. That's Number 1.

Number 2. You also have to remember that the complication rate is still very high for patients who have intraabdominal infections. It's 20 to 25 percent in this.

And, therefore, if you go ahead and embark it will only give you 24 hour of therapy for these patients with intraabdominal infections and you have a complication do not feel bad about yourself; it's the nature of the disease, it's not the nature of the antibiotic use.

The only – the real question I have for this is if – and I believe the data are true. You can argue that it's a slightly underpowered study, they did not enroll as many patients as they thought they really wanted to. The data is probably valid and I can't imagine enrolling twice as many patients is really going to change the actual outcomes of the study.

And when you get around to it, it comes down to implementation. And now you have data and you have surgeons in your own hospital who you are going to talk to about this. And you're going to say here is our data, why are you giving these patients five days' worth of antibiotics when we've shown the 24-hours works.

And what I really want to know is what your plans are to convince the surgeons, both in your hospital in your country and in your surgical groups with whom you work, that 24 hours is going to be okay, particularly in the patient population who you were very knowledgeable about pointing out the ones who at the end of 24 hours still had an elevated white blood cell count or still had a fever or still had an elevated CPR?

Those are the ones that are really hard to get people to still stop the antibiotics, even though many people, including myself, believe that what you are looking at is just the inflammatory

response, which is the residual and not something that can be treated with antibiotics because all the bacteria are either dead or in the process of dying when that happens.

I'm sorry. I had one more question. And that is what did you do in the circumstance when you had patients who had a perforation and you sent a culture and the culture comes back after you have stopped antibiotics and you find out that some of those organisms are resistant to the antibiotics that you had used for 24 hours, in your case based on amoxicillin or ampicillin? Did you reinitiate antibiotics or did you just follow the patient clinically?

Once again, I thank the AAST for the privilege of discussing this excellent paper.

Dr. Joseph V. Sakran (Baltimore, Maryland): Joseph Sakran from Baltimore, Maryland. Thank you for presenting that very interesting study. I had a couple of questions for you.

The first is what was the preoperative workup for these patients? Because I'm surprised that the 13 percent of Grade IV patients were taken to the operating room because many of those patients with complicated appendicitis that had abscesses we in the U.S. typically, manage non-operatively with antibiotics and drainage of abscess if present.

My second question is the length of stay that I saw was listed in hours. How does it differ if you actually compare the groups by days? And is it still significant?

And then my last question is in regards to the power of the study. It seems like it might be underpowered. Can you comment on that aspect?

Thank you so much for being here and presenting this interesting work.

Dr. Samir M. Fakhry (Mclean, Virginia): Samir Fakhry, Mclean, Virginia. Enjoyed your presentation very much and congratulations on having your work presented at the AAST.

Out of curiosity can you tell us what types of antibiotics are used in the patients that you presented? Are there any particular kinds of antibiotics that are being used by category of antibiotic? Thank you.

Dr. Lucia Chou (Seattle, Washington): Hi, Lucia Chou from Seattle. My specific topic, thanks for studying it. My main question was whether or not you had any details about the intraoperative treatment, meaning did they do any irrigation? Did they place any drains at the end of the procedure?

Dr. Sten Saar (Tallinn, Estonia): Thank you Dr. Sawyer for the discussion and thank you for all the excellent questions from the audience.

We are utilizing 24-hour therapy since the study at our institution, however, during the first months of study, surgeons were little sceptic. Nevertheless, during the course of the study short therapy became a routine as we are confident that it is safe. Also I think our study opens door for large multi-center studies which could convince the surgical community around the world.

We obtained cultures if patients were readmitted, however, in the index operation we did not take cultures routinely and only study antibiotics per protocol were administered.

Alvarado Score was calculated for all patients and most of the patients had ultrasound investigation also at the emergency department. Computed tomography was obtained in 52% of patients.

The comparison of HLOS between the study groups was calculated in hours, not in days. Nevertheless, the difference will remain significant when days were used instead.

Certainly, our study is limited by a low number of recruited patients, however, our pilot study on this subject provides a significant signal to the community.

There were many questions about antibiotics used. We administered aminopenicillins only – amoxicillin with clavulanic acid or ampicillin with sulbactam as a study antibiotics per protocol. Thank you again for the opportunity of podium!