Lauri Viinikainen

QUALITY OF LIFE AND PATIENT SATISFACTION AT 7-YEAR FOLLOW-UP OF ANTIBIOTIC THERAPY VS APPENDECTOMY FOR UNCOMPLICATED ACUTE APPENDICITIS – SECONDARY ANALYSIS OF THE APPAC RANDOMIZED CLINICAL TRIAL

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For more than a century, appendectomy has been the standard treatment for acute appendicitis and is still one of the most common emergency operations annually worldwide. Today, appendicitis is recognized to present in two forms, complicated and uncomplicated acute appendicitis. In the light of current research, it is known that antimicrobial therapy can be applied as an effective and safe treatment for uncomplicated acute appendicitis resulting in decreased morbidity, shorter sick leave, and major cost savings for the society compared with appendectomy.

In our study, we evaluated the long-term effects of appendectomy and antibiotic therapy on quality of life and patient satisfaction in a secondary analysis of a randomized clinical trial (APPAC) comparing appendectomy and antibiotic therapy in the treatment of uncomplicated acute appendicitis. Between 2009 and 2011, 530 patients (aged 18 to 60 years) with a CT scan diagnosed uncomplicated appendicitis, were enrolled in the APPAC study and randomized to undergo appendectomy or antibiotic treatment. Antibiotic treatment consisted of intravenous ertapenem for three days, followed by per oral levofloxacin and metronidazole for seven days. In case of suspected appendicitis recurrence, antibiotic group patients underwent appendectomy without further imaging according to the study protocol.

Of the 530 patients who were enrolled in the trial, 423 (80 %) were available for a phone interview at median follow-up of seven years. The interview was conducted by using a standardized QOL (Quality of life) EQ-5D-5L -question set consisting of five questions currently measuring quality of life and satisfaction, plus two separately added questions mapping whether patients would again choose the same treatment based on their experience and the potential reasons for their treatment choice.

There was no significant difference in QOL between the patients undergoing appendectomy and the patients receiving successful antibiotic treatment. However, there was a significant difference in patient satisfaction between the treatments; patients undergoing appendectomy were more satisfied with their treatment than those in the antibiotic group who had to undergo surgery for recurrence of the disease. Patients in antibiotic group with successful antibiotic therapy without recurrence had no difference in the satisfaction rates compared with the appendectomy group.

In the treatment of uncomplicated appendicitis, long-term QOL is similar between the two treatments, but the lower patient satisfaction in the antibiotic group patients undergoing surgery indicates that predictive parameters for disease recurrence should be actively assessed. Despite the lower satisfaction rate in the antibiotic group patients undergoing surgery, a significant proportion of patients with recurring disease would still re-select antibiotic therapy to avoid surgery. As antibiotic therapy is a safe and effective treatment for uncomplicated appendicitis, the choice of the optimal therapy should be a joint decision with the patient, considering the benefits and risk of the various treatment options.

Keywords: Appendicitis, appendectomy, antibiotic treatment, quality of life

Sisällys

Umpilisäketulehduksen leikkaus- ja antibioottihoidon vaikutus potilaiden elämänlaatuun ja potilastyytyväisyyteen – satunnaistetun APPAC-monikeskustutkimuksen pitkäaikaisseuranta

Tausta

Akuutti umpilisäketulehdus on maailmanlaajuisesti yksi eniten terveydenhuoltoa kuormittava akuutin vatsakivun syy. Akuutin umpilisäketulehduksen elinikäinen sairastumisriski on 6,7–8,6 %. Vuosittain primaarivaiheessa umpilisäkkeen poistoleikkauksia tehdään esimerkiksi Yhdysvalloissa n. 250 000[1] ja Iso-Britanniassa n. 40 000[2]. Yli sadan vuoden ajan leikkaushoito on ollut ensisijainen hoitomuoto akuutissa umpilisäketulehduksessa, ja McBurney esitteli leikkaushoidon tuloksia ensimmäisen kerran vuonna 1894[3]. Ennen nykyään ymmärrettyä taudinkuvan erottelua lievempään eli komplisoitumattomaan ja vaikeampaan eli komplisoituneeseen muotoon, umpilisäketulehduksen päätetapahtuman on ajateltu olevan aina puhkeaminen ja siitä jatkumona aiheutuva yleistynyt vatsakalvon tulehdus. Kuitenkin jo vuonna 1886 patologi Fitz[4] totesi obduktiomateriaaleissaan tulehtuneen umpilisäkkeen yhteydessä myös merkkejä mahdollisesta spontaanista umpilisäketulehduksen paranemisesta. Nämä tutkimukset tehtiin ennen antibioottiaikaa ja yhdessä ne ovat sittemmin ohjanneet hoitolinjoja tähän päivään asti.

Epidemiologia ja patofysiologia

Umpilisäketulehdusta esiintyy kaikissa ikäluokissa, mutta sairastumisen todennäköisyys pienenee 30 ikävuoden jälkeen. Esiintyvyyshuippu on 10–19 vuotiaiden ikäryhmässä. Sukupuolten välillä ei esiintyvyydessä ole suurta eroa, mutta keskimäärin miehillä taudin yleisyys kaikissa ikäluokissa on noin 1,4-kertainen naisiin verrattuna. Taudin esiintyvyys on myös selkeästi pienempi tummaihoisten keskuudessa sekä heikomman hygienian maissa; vastaavasti teollistuneissa maissa esiintyvyys on suurempi[5].

Patofysiologiaa ei taudin yleisyydestä huolimatta tarkasti tunneta. Umpilisäketulehduksen aiheuttavia etiologisia syitä ovat muun muassa luumenin ahtautuminen, infektio ja näistä seuraava verenkierron häiriö ja iskemia, vierasesineet, hyvä hygienia, prosessoitu ruoka sekä ravinnon vähäkuituisuus[5,6]. Umpilisäkkeen luumenin ahtautuminen estää umpilisäkkeen tyhjentymisen, joka saa aikaan luumenin sisäisen paineen nousun. Tämän johdosta umpilisäkkeen verenkierto heikkenee ja intraluminaalinen bakteerimäärä lisääntyy johtaen seinämänekroosiin ja puhkemaan[7]. Edellä mainittu tapahtumaketju sopii etenkin komplisoituneen umpilisäketulehduksen patofysiologiaan. Puhkeaminen johtaa umpilisäkkeen sijainnin mukaan joko yleistyneeseen vatsakalvon tulehdukseen eli peritoniittiin tai vatsaontelon sisäisen paiseen muodostumiseen[8]. Komplisoituneeksi umpilisäketulehdukseksi kuvataan muotoa, jonka yhteydessä esiintyy paise, seinämän puhkeaminen, tai tuumori. Myös fekoliitin eli ulostekiven esiintymisen umpilisäkkeen luumenissa on todettu liittyvän vaikeampaan taudinkuvaan.

Komplisoitumattoman tautimuodon patofysiologiaa ei vielä tunneta hyvin. Komplisoitumatonta muotoa esiintyy yleisimmin lapsilla, ja tämän ajatellaan olevan aikuisten

komplisoitumattoman paksunsuolen umpipussitulehduksen eli divertikuliitin kanssa saman taudin kaksi eri manifestaatiota. Tämän hypoteesin esittivät Livingston ja yhteistyökumppanit epidemiologisessa tutkimuksessaan[9], jossa he totesivat lapsilla esiintyvän komplisoitumattoman umpilisäketulehduksen kehityksen olevan samansuuntainen kuin aikuisilla esiintyvän komplisoitumattoman divertikuliitin. Molempien taudinkuvien epidemiologia erosi merkityksellisesti komplisoituneista tautimuodoista tukien sitä ajatusta, että kyseessä olisi myös patofysiologiltaan kaksi erilaista tautia[9]. Vuonna 1886 Fitz[4] myös totesi obduktiolöydöksissään olevan merkkejä itsestään rajoittuvista ja parantuvista umpilisäkkeen tulehduksista.

Diagnostiikka

Akuutin umpilisäketulehduksen epäily on yksi yleisimmistä ensiapua kuormittavista sairauksista[10]. Diagnosointi on kliinisesti haastavaa[11], oirekuva voi vaihdella lievästä vatsakivusta peritoniittiseen ja septiseen tilaan. Vatsan oikean alaneljänneksen kipu ja arkuus liitettynä oksenteluun, kuumeiluun ja diffuusiin arkuuteen ovat tyypillisimmät löydökset umpilisäketulehduksen yhteydessä. Laboratoriomerkkiaineista kohonneet valkosoluarvot ja C-reaktiivinen proteiini tukevat kliinisten löydösten lisäksi diagnoosia.

Suurin osa kuvantamisesta tapahtuu nykyään tietokonetomografialla eli TT-kuvauksella, myös ultraääni- tai magneettikuvaus ovat käytössä umpilisäketulehduksen diagnostiikassa. Aikuisilla TT-kuvauksen herkkyys (sensitiivisyys) on n. 96,4 % ja tarkkuus (spesifisyys) n. 92,17 %. TT-kuvantamiseen sisältyy kuitenkin aina säteilyrasitus ja sitä voidaan vähentää matala-annoksisella TT-kuvantamisella (low-dose CT), jonka on todettu kliinisesti yhtä tehokas umpilisäketulehduksen diagnosoinnissa verrattuna normaaliannoksiseen TT-kuvantamiseen (herkkyys 96,25 % ja tarkkuus 93,22 %) [12]. Kliinisen arvioinnin avuksi on kehitetty prognostisia pisteytyskaavioita[13], joiden avulla pyritään poissulkemaan akuutti umpilisäketulehdus, mutta toistaiseksi käytössä olevilla pisteytyksillä ei pystytä erotusdiagnostiikkaan tautimuotojen välillä ilman kuvantamista.

Hoito

Leikkaushoito on ollut vallitseva hoitomuoto umpilisäketulehduksen hoidossa jo yli 100 vuoden ajan, ja se on edelleenkin ainoa hoitovaihtoehto, kun kyseessä on komplisoitunut muoto. Laparoskooppinen umpilisäkkeen poisto on nykyään leikkaushoidon kultainen standardi[14,15]. Laparoskopiaan liittyy vähemmän komplikaatioita, matalampi leikkauksenjälkeinen sairastavuus sekä lyhempi toipumisaika avoleikkaukseen verrattuna. Umpilisäketulehduksen puhkeamisen seurauksena esiintyvä paise (periappendikulaariabskessi) komplisoi noin 2–6 % umpilisäketulehduksista[16]. Hoito voidaan toteuttaa joko suonensisäisellä antibiootilla, jonka yhteydessä voidaan tarvittaessa tehdä radiologinen perkutaaninen märkäkertymän tyhjentäminen tai leikkauksella. Konservatiivisen hoidon jälkeen suositellaan elektiivistä leikkaushoitoa 6–12 viikon kuluttua uusiutumisriskin vuoksi. Yli 40-vuotiaille potilaille suositellaan elektiviistä leikkaustoimenpidettä, sillä tässä ikäryhmässä paiseen muodostumisen taustalta usein löydetään umpilisäkkeen kasvain (16 %)[17].

Vaikka umpilisäkkeen poistoleikkaus on yksi maailman eniten suoritetuista toimenpiteistä[15], se on silti yleisanestesiassa tehtävä toimenpide, johon sisältyy leikkausriskejä ja

leikkauksenjälkeistä sairastavuutta[2]. Nykytutkimusten valossa antibioottihoito on osoittautunut turvalliseksi vaihtoehdoksi leikkaushoidolle komplisoitumattomassa umpilisäketulehduksessa[18-25]. Mikäli antibioottihoidon jälkeen umpilisäketulehdus uusiutui, tauti oli vastaava lievempi tulehduksen muoto eikä antibioottihoitoon liittynyt lisääntyneitä komplikaatioita eli ensilinjan hoitona antibioottihoito oli turvallista[26]. Tehokkuuden ja turvallisuuden lisäksi antibioottihoitoon liittyi vähemmän komplikaatioita, lyhempi sairasloma ja merkittävät kustannussäästöt hoidon kokonaiskustannuksissa[27]. Tutkimusten perusteella antibioottihoito on varteenotettava ensilinjan hoito komplisoitumattomassa umpilisäketulehduksessa ja aihekokonaisuus vaatii aktiivista lisätutkimusta sekä konservatiivisen hoidon optimoimiseksi huomioiden sekä antibioottihoidon optimointi[28] että myös mahdollinen oireenmukainen hoito[29]. Pediatrisilla potilailla tehty tutkimus osoitti myös konservatiivisen hoidon olevan tehokas, turvallinen ja potilastyytyväisyydeltään vähintään vastaava hoitovaihtoehto silloin, kun vanhemmat saivat itse päättää lapsensa hoidosta[30].

Nykyään tiedetään suurimman osan (70–75 %) umpilisäketulehduksista olevan komplisoitumatonta muotoa, jotka voidaan hoitaa turvallisesti mikrobilääkkein[18-22]. Ensimmäiset tutkimukset antibiooteilla hoidetuista umpilisäkkeen tulehduksista julkaistiin jo vuonna 1956 Coldreyn toimesta[31], mutta tutkimusaihe oli myös tuolloin erittäin kiistanalainen ja tulokset jäivät vaille huomiota ennen uuden aktiivisen tutkimuksen alkamista 1990- ja 2000-luvulla.

Aineisto

Vuosina 2009-2012 APPAC-tutkimukseen[18] rekrytoitiin 530 potilasta (18-60 v.), joilla oli TT-kuvauksella diagnosoitu komplisoitumaton umpilisäketulehdus (ei ulostekiveä, paisetta, seinämän puhkeamista tai kasvainepäilyä). Potilaat satunnaistettiin kahteen ryhmään – umpilisäkkeen poistoleikkaus tai antibioottihoito (ertapeneemi 1 g kerran päivässä suonensisäisesti kolmen vuorokauden ajan, jota seurasi levofloksasiini 500 mg kerran päivässä ja metronidatsoli 500 mg kolmesti vuorokaudessa suun kautta seitsemän vuorokauden ajan). Ensisijaisena päätetapahtuma pidettiin umpilisäketulehduksen paranemista. Tämä määritettiin leikkaushoitoryhmässä onnistuneena umpilisäkkeen poistoleikkauksena ja antibioottiryhmässä taudin paranemisena edellyttäen, että taudin uusiutumista ei tapahtunut vuoden kuluessa hoidosta. Mikäli antibioottihoidon saaneilla potilailla tauti uusiutui, päädyttiin leikkaushoitoon. Tutkimus osoitti konservatiivisen hoidon olevan tehokas (73 %) ja turvallinen ensilinjan hoitovaihtoehto akuutin komplisoitumattoman umpilisäketulehduksen hoidossa. Leikkauksen mahdollinen viivästyminen ei aiheuttanut myöskään lisääntyneitä komplikaatioita. Nämä 1 vuoden tulokset vahvistuivat APPAC-tutkimuksen 5 vuoden pitkäaikaisseurannassa[26], jonka aikana taudin uusiutumisen esiintyvyys antibioottiryhmässä oli 39.1 %. Näistä 85 potilaalla, jotka ajautuivat leikkaushoitoon taudin uusiutuisen epäilyn vuoksi, 76:lla todettiin komplisoitumaton umpilisäketulehdus, 2:lla komplisoitunut tulehdus ja 7 potilaalla ei esiintynyt lainkaan tulehtunutta umpilisäkettä. Myöskin komplikaatioiden määrä oli merkitsevästi pienempi antibioottiryhmässä (6,5 %) kuin leikkausryhmässä (24,4 %) ($P < ,001$).

Tässä tutkimuksessa tarkasteltiin edellä mainittuun tutkimukseen osallistuneiden potilaiden pitkäaikaisseurannan elämänlaatua (QOL, Quality of Life) ja potilastyytyväisyyttä. Haastattelut toteutettiin puhelinhaastatteluina keväällä 2018. Potilaat haastateltiin käyttämällä

EQ-5D-5L kysymyspatteria, jonka avulla tarkasteltiin alkuperäisen hoitotapahtuman (konservatiivinen/operatiivinen) vaikutusta elämänlaatuun. Kyselykaavaketta muokattiin tutkimustarpeitamme sopivammaksi lisäämällä loppuun kysymällä tutkittavilta, olisivatko he valinneet uudestaan saman hoitotoimenpiteen kokemuksensa pohjalta, mikäli saisivat itse päättää hoidosta ja minkä vuoksi.

Umpilisäketulehduksen leikkaus- ja antibioottihoidon vaikutus potilaiden elämänlaatuun

Elämänlaatua ja potilastyytyväisyyttä on aiemmin vertailtu laparoskooppisen ja avoimen umpilisäkkeen poistoleikkauksen välillä[32], mutta seurantaa ei akuutin umpilisäketulehduksen hoidossa ole tiedettävästi aiemmin tehty vertailtaessa operatiivista ja konservatiivista hoitoa aikuisilla. Pediatrisilla potilailla suoritetussa tutkimuksessa vuoden seurannan ajan ei havaittu eroa HRQOL:ssa (health-related quality of life) operatiivisesti ja konservatiivisesti hoidettujen potilaiden välillä[30].

Tämän tutkimuksen tavoitteena oli selvittää antibiootti- sekä leikkaushoidon vaikutuksia pitkäaikaisseurannassa elämänlaatuun sekä potilastyytyväisyyteen. Seurannassa 530 potilaasta 423 potilasta (80 %) oli tavoitettavissa puhelimitse 7 vuoden mediaaniseurannassa, joista 206 (84 naista, 122 miestä, keski-ikä 43 vuotta) satunnaistettiin antibioottihoitoon ja 217 (76 naista, 141 miestä, keski-ikä 45 vuotta) leikkaushoitoon. Antibioottihoidetuista 206:sta potilaasta 81 (39 %) ajautui edelleen leikkaushoitoon uusiutuneen umpilisäketulehduksen epäilyn vuoksi. Tutkimusprotokollan mukaan niille antibioottihoidon saaneille potilaille, joille seurannassa heräsi epäilys taudin uusiutumisesta, suoritettiin umpilisäkkeen poistoleikkaus. Näistä 14 leikattiin samalla hoitojaksolla ja 67 myöhemmin seurannan aikana. Alkuperäistutkimuksen[18] 530 potilaasta 257 satunnaistettiin antibioottiryhmään, joista 15 leikattiin heti ensimmäisellä hoitojaksolla. Näistä 8:lla todettiin komplisoitumaton muoto ja 7:llä komplisoitunut muoto. Viiden vuoden aikana seurannassa 85 potilasta leikattiin uusiutuneen umpilisäketulehduksen epäilyn vuoksi. Näistä 76 todettiin komplisoitumaton tulehdus, kahdella komplisoitunut muoto ja seitsemällä terve umpilisäke[26].

Antibiootti- ja leikkausryhmien välillä ei todettu eroja elämänlaadussa. Kokonaisuudessaan 122 potilasta raportoi kokevansa jonkinasteisia vatsavaivoja, joista suurimmalla osalla (75 %) kyse oli epäspesifisestä kivusta. Antibioottiryhmässä 5,8 % ja leikkausryhmässä 7,8 % koki kokevansa vatsakipuja epäiltyjen kiinnikkeiden vuoksi.

Ryhmien välillä havaittiin merkitsevä ero, kun vertailtiin tyytyväisyyttä hoitoon. Leikkaushoidon saaneet olivat tyytyväisempiä hoitoonsa kuin potilaat, jotka saivat ensimmäiseksi antibioottihoidon ja ajautuivat tämän jälkeen leikkaushoitoon taudin uusiutuessa. Sen sijaan eroa ei havaittu leikkausryhmän ja onnistuneen antibioottihoidon välillä. Antibioottiryhmässä potilaat, joilla tauti ei uusiutunut eivätkä joutuneet leikkaukseen, olivat tyytyväisempiä kuin ne, joilla tauti uusiutui.

Samoin ryhmien välillä havaittiin merkitsevä ero hoitomuodon uudelleen valinnassa. Leikkausryhmässä 77 % valitsisi jälkeenpäin uudelleen ensisijaiseksi hoitovaihtoehdoksi leikkaushoidon, 18 % antibioottihoidon ja 6 % ei osannut valita. Koko antibioottiryhmässä 63 % valitsisi uudelleen konservatiivisen hoidon ensisijaisesti, 34 % leikkaushoidon ja 3 % ei

osannut valita hoitovaihtoehtojen väliltä. Antibioottiryhmässä niistä potilaista, jotka saivat pelkän antibioottihoidon, 83 % valitsisi uudelleen saman hoitomuodon, kun taas 14 % valitsisi leikkaushoidon ja 3 % potilaista ei osannut valita hoitomuotojen väliltä. Niistä potilaista, jotka antibioottihoidon aikana tai jälkeen joutuivat leikkaushoitoon, 33 % valitsisi edelleen ensisijaiseksi hoitovaihtoehdoksi konservatiivisen hoidon, kun taas 64 % ei valitsi uudelleen samaa hoitomuotoa ja 3 % oli epävarma valinnastaan. Hoitomuodon valinnassa ero oli potilastyytyväisyyttä vastaava eli ei eroa onnistuneen antibioottihoidon ja leikkauksen välillä, mutta leikkaushoitoon päätyneet antibioottipotilaat valitsivat saamansa hoitomuodon merkittävästi näitä kahta muuta ryhmää harvemmin.

Tyytyväisyyden suhteen tulos ei sikäli ollut yllättävä, että potilaat, jotka joutuivat epäonnistuneen antibioottihoidon jälkeen uudelleen hoitoon, olivat vähemmän tyytyväisempiä kuin kaksi muuta ryhmää. Huomioitavaa kuitenkin on, että taudin uusiutumisesta huolimatta 33 % valitsisi uudelleen konservatiivisen hoidon. Tämä kertoo siitä, että joissain tilanteissa potilaat ovat valmiita hyväksymään riskin taudin mahdollisesta uusiutumisesta välttääkseen leikkauksen. Umpilisäkkeen poistoleikkauksen jälkeistä elämänlaadun heikkenemistä ei tule aliarvioida, vaikka tämä onkin lyhyellä aikavälillä palautuvaa[33]. Komplisoitumattoman umpilisäketulehduksen optimaalisimman hoitovaihtoehdon valinta pitää tehdä yhdessä potilaan kanssa hoitomuotojen hyödyt ja haitat huomioiden. Potilaan asianmukaisen informoinnin ja oman valinnan merkityksen huomioimisen lisäksi aihekokonaisuus vaatii aktiivista lisätutkimusta sekä tarkan erotusdiagnostiikan että konservatiivisen hoidon optimoimiseksi.

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Liitteet

Liite1. Quality of Life and Patient Satisfaction at 7 Year Follow-up of Antibiotic Therapy vs Appendectomy for Uncomplicated Acute Appendicitis – A Secondary Analysis of a Randomized Clinical Trial

JAMA Surgery | Original Investigation

Quality of Life and Patient Satisfaction at 7-Year Follow-up of Antibiotic Therapy vs Appendectomy for Uncomplicated Acute Appendicitis
A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Long-term results support antibiotics for uncomplicated acute appendicitis as an alternative to appendectomy. To our knowledge, treatment-related long-term patient satisfaction and quality of life (QOL) are not known.

OBJECTIVE To determine patient satisfaction and QOL after antibiotic therapy and appendectomy for treating uncomplicated acute appendicitis.

INTERVENTIONS Open appendectomy vs antibiotics with intravenous ertapenem, 1 g once daily, for 3 days followed by 7 days of oral levofloxacin, 500 mg once daily, and metronidazole, 500 mg 3 times per day.

DESIGN, SETTING, AND PARTICIPANTS This observational follow-up of the Appendicitis Acuta (APPAC) multicenter randomized clinical trial comparing appendectomy with antibiotics included 530 patients age 18 to 60 years with computed tomography–confirmed uncomplicated acute appendicitis who were randomized to undergo appendectomy (273 [52%]) or receive antibiotics (257 [49%]). The trial was conducted from November 2009 to June 2012; the last follow-up was May 9, 2018. The data were analyzed in February 2019.

MAIN OUTCOMES AND MEASURES In this analysis, post hoc secondary end points of postintervention QOL (EQ-5D-5L) and patient satisfaction and treatment preference were evaluated.

RESULTS Of the 530 patients enrolled in the trial (appendectomy group: 273 [174 men (64%)] with a median age of 35 years; (antibiotic group: 257 [155 men (60%)] with a median age of 33 years), 423 patients (80%) were available for phone interview at a median follow-up of 7 years; 206 patients (80%) took antibiotics and 217 (79%) underwent appendectomy. Of the 206 patients taking antibiotics, 81 (39%) had undergone appendectomy. The QOL between appendectomy and antibiotic group patients was similar (median health index value, 1.0 in both groups; 95% CI, 0.86-1.0; $P = .96$). Patients who underwent appendectomy were more satisfied in the treatment than patients taking antibiotics (68% very satisfied, 21% satisfied, 6% indifferent, 4% unsatisfied, and 1% very unsatisfied in the appendectomy group and 53% very satisfied, 21% satisfied, 13% indifferent, 7% unsatisfied, and 6% very unsatisfied in the antibiotic group; $P < .001$) and in a subgroup analysis this difference was based on the antibiotic group patients undergoing appendectomy. There was no difference in patient satisfaction after successful antibiotic treatment compared with appendectomy (cumulative odds ratio [COR], 7.8; 95% CI, 0.5-1.3; $P < .36$). Patients with appendectomy or with successful antibiotic therapy were more satisfied than antibiotic group patients who later underwent appendectomy (COR, 7.7; 95% CI, 4.6-12.9; $P < .001$; COR, 9.7; 95% CI, 5.4-15.3; $P < .001$, respectively). Of the 81 patients taking antibiotics who underwent appendectomy, 27 (33%) would again choose antibiotics as their primary treatment.

CONCLUSIONS AND RELEVANCE In this analysis, long-term QOL was similar after appendectomy and antibiotic therapy for the treatment of uncomplicated acute appendicitis. Patients taking antibiotics who later underwent appendectomy were less satisfied than patients with successful antibiotics or appendectomy.

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Invited Commentary
Author Audio Interview
Supplemental content

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Appendectomy has been the standard treatment for acute appendicitis for more than a century[1] and one of the most common surgical procedures performed annually.[2] Large epidemiological studies have shown that there are 2 forms of acute appendicitis: uncomplicated and complicated, suggesting a differing pathophysiology for the 2 forms.[3] In recent years, there has been increasing evidence from randomized clinical trials[4-8] and meta-analyses[9-11] indicating that patients with uncomplicated acute appendicitis can be treated safely and efficiently with antibiotics. Our recent 5-year results further support the notion that antibiotic treatment is a safe alternative to appendectomy for uncomplicated acute appendicitis also at long-term follow-up.[12] In addition, antibiotic therapy for uncomplicated acute appendicitis is associated with substantial cost savings.[13] Nonoperative management of uncomplicated acute appendicitis is under intense research and the important aspects of patient preference and satisfaction, quality of life (QOL), and joint decision-making have only recently been recognized.[9,14] However, providing patients with unbiased information of all treatment options for uncomplicated acute appendicitis is challenging, as the manner of presenting and framing the information has a substantial influence on the answers; in survey trials, this is further complicated by an imaginary situation. To our knowledge, the assessment of postintervention QOL, patient satisfaction, and preference at long-term follow-up has not yet been conducted in randomized clinical trials in an adult patient population comparing antibiotics with appendectomy for uncomplicated acute appendicitis. The aim of this study was to compare the post hoc long-term QOL and patient satisfaction after antibiotic therapy and appendectomy for treating uncomplicated acute appendicitis for all the patients enrolled in the original Appendicitis Acuta (APPAC) trial.

Key Points

Question What is the long-term quality of life (QOL) and patient satisfaction after antibiotic treatment or appendectomy for uncomplicated acute appendicitis?

Findings In this secondary analysis of a randomized clinical trial with 7-year observational follow-up of 423 patients, there was no difference in QOL between the treatments. Patients who underwent appendectomy were more satisfied in their treatment than patients taking antibiotics based on the antibiotic group patients undergoing appendectomy; patient satisfaction after successful antibiotic treatment and appendectomy was similar.

Meaning The long-term QOL of patients with uncomplicated acute appendicitis is similar after appendectomy and antibiotics, but the lower satisfaction of patients who underwent an operation and took antibiotics calls for identifying predictive parameters for appendicitis recurrence.

Methods

The study design, rationale, and methods for the initial APPAC trial have been previously reported (Supplement 1).[4,15] Briefly, the initial APPAC trial is a multicenter, open-label, noninferiority randomized clinical trial conducted from November 2009 to June 2012 at 6 Finnish hospitals (Turku, Oulu, and Tampere university hospitals and Jyväskylä, Mikkeli, and Seinäjoki central hospitals). The trial protocol was approved by the ethics committees of all participating hospitals and all patients gave written informed consent to participate in the study. The ethics committee granted a waiver for this study. The trial involved 530 patients age 18 to 60 years with computed tomography (CT)–confirmed uncomplicated acute appendicitis. Patients were randomized to either undergo open appendectomy or receive antibiotic treatment with intravenous ertapenem (1 g, once daily) for 3 days followed by 7 days of oral levofloxacin (500 mg, once daily) and metronidazole (500 mg, 3 times per day).

The CT criteria for acute appendicitis included an appendiceal diameter exceeding 6 mm with wall thickening accompanied with at least 1 of the following features: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix. The exclusion criteria included complicated acute appendicitis (defined as the presence of an appendicolith, perforation, abscess, or suspicion of a tumor on the CT scan), age younger than 18 years or older than 60 years, contraindications for CT, peritonitis, an inability to adhere with treatment and provide informed consent, and the presence of serious systemic illness. Patients in the antibiotic group were followed up by surgeons who could use their clinical judgement to pursue appendectomy if considered necessary. Most of the treating surgeons were not part of the core study team and provided care according to their normal clinical practice. All antibiotic group patients with a clinical suspicion of recurrent appendicitis underwent appendectomy. The last follow-up date for the current report at a median follow-up of 7 years (range, 5.7-8.2 years) was May 6, 2018. The objective for the long-term follow-up study was to compare the post hoc secondary end point of QOL with patient satisfaction and treatment preference between antibiotic therapy and appendectomy for the treatment of uncomplicated acute appendicitis.

Assessment of QOL and Patient Satisfaction

Quality of life was assessed using the validated EQ-5D-5L questionnaire (version April 18, 2017; EuroQOL).[16-18] The assessment was conducted by unmasked, structured phone interviews between January and May 2018 by 3 researchers (S.S., J.H., and L.V.) who had not been involved in patient treatment. The descriptive questions cover 5 dimensions of everyday life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The answers are categorized in 5 levels ranging from no problems to extreme problems with numerical scoring from 1 to 5, respectively. These numerical scores for the 5 dimensions can be combined into a 5-digit number describing the respondent's health state. These health state scores may then be converted into a single index value[19] ranging between 0 (death) and 1 (full health) for each patient, illustrating the total QOL of the patient by country-specific validation tools. The validation specific for Finland for the EQ-5L-5D is not available. In this situation, according to the recommendations by the EuroQOL group to use a population

closely resembling ours, we used the validation for Denmark. Additionally, the questionnaire reflects the patient's self-rated health on a vertical visual analog scale (VAS) between 0 (worst health imaginable) and 100 (best health imaginable). Based on the study aim and patient population, we slightly modified the questionnaire by asking about abdominal pain and/or discomfort instead of general pain and discomfort.

Patient satisfaction with a received treatment was assessed by asking patients to score their satisfaction on a 5-point scale: very satisfied, satisfied, indifferent, unsatisfied, and very unsatisfied. The patients were also asked whether they would again choose the same treatment knowing the course and outcomes of the treatment.

In addition to the intention-to-treat analysis comparing the appendectomy and antibiotic treatment groups, we also performed a subgroup analysis by categorizing patients into 3 groups: appendectomy group, successful antibiotic treatment group (ie, no appendectomy), and antibiotic treatment group undergoing appendectomy. The primary end point of the original APPAC study was treatment success predefined to be assessed at 1-year follow-up.[4,15] Success for the appendectomy group was defined as a patient successfully undergoing an appendectomy. In the antibiotic group, treatment efficacy was defined as the resolution of acute appendicitis resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year. The need for later appendectomy after primary antibiotic treatment for this study was evaluated at the time of QOL and satisfaction assessment. In this post hoc outcome analysis of QOL and patient satisfaction, this subgroup analysis is of clinical interest as the main drawback of antibiotic treatment of uncomplicated acute appendicitis is the possibility of appendicitis recurrence.

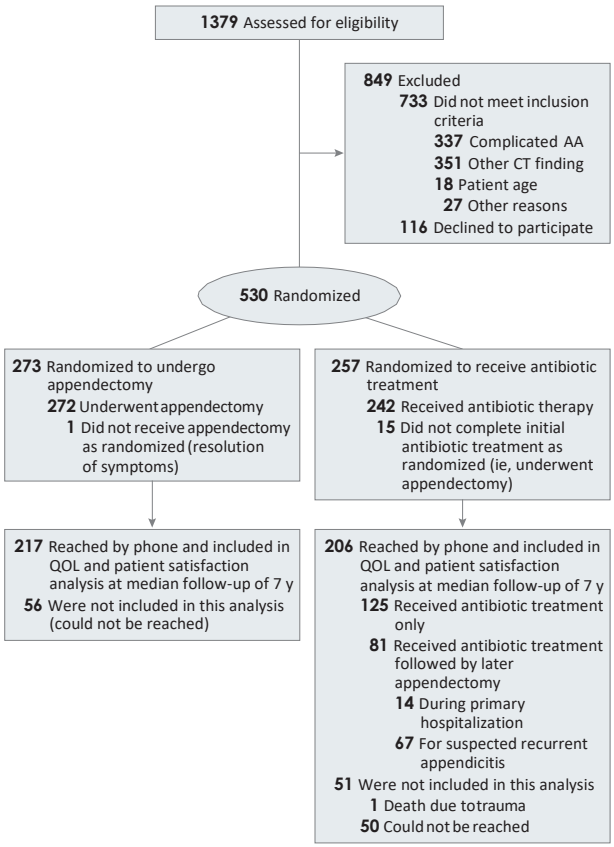
Statistical Analysis

Continuous variables were characterized using means or medians and the range of values or 95% confidence intervals of medians for nonnormally distributed variables; in the case of categorical variables, frequencies and percentages were used. The differences between groups in QOL scores and VAS values were tested using the Mann-Whitney *U* test. The satisfaction of care was analyzed using a multivariable cumulative logistic regression analysis to adjust the results for sex and age. The treatment preference in hindsight was analyzed using a multivariable multinomial logistic regression analysis to adjust the results for sex and age. The results of the logistic regression analyses were quantified using cumulative odds ratios (CORs) or odds ratios (ORs) with 95% confidence intervals. Two-sided tests were used and $P < .05$ was considered statistically significant. Statistical analyses were conducted using the SAS system for Windows, version 9.4 (SAS Institute).

Results

Figure 1 shows the trial profile. Patient baseline demographic characteristics were similar between the study groups at baseline[4] and in this QOL analysis. Of the 530 patients (201 women [38%]) enrolled in the APPAC trial, 423 (80%) were available for a phone interview at a median follow-up of 7 years (range, 5.7-8.2 years). All of the patients reached by the researchers participated in the study. Of the 423 patients available for phone interview, 206 (47%) were originally randomized to receive antibiotic treatment (84 women [41%]; mean [SD] age, 43 [12.4] years; follow-up rate, 80%) and 217 (51%) to undergo appendectomy (76 women [35%]; mean [SD] age, 45 [12.0] years; follow-up rate, 79%). Of the 206 antibiotic group patients, 81 (39%) had undergone appendectomy (36 women [44.4%]; mean [SD] age, 44 [11.4] years), 14 (17.3%) during primary hospitalization and 67 (83%) for suspected recurrent appendicitis. There were no differences in response rates by group (217 of 272 [80%]) in the appendectomy group, 80% (206 of 257) in the antibiotic group, with 125 receiving antibiotics alone and 81 antibiotics with later appendectomy (response rates 80% and 81%, respectively). Of the 81 patients who underwent appendectomy after initial antibiotic treatment, 70 patients (86%) had surgery before the 1-year follow-up, 30 patients (37%) between years 1 and 5, and 1 patient (1%) between year 5 and QOL follow-up.

Figure 1. Study Flowchart

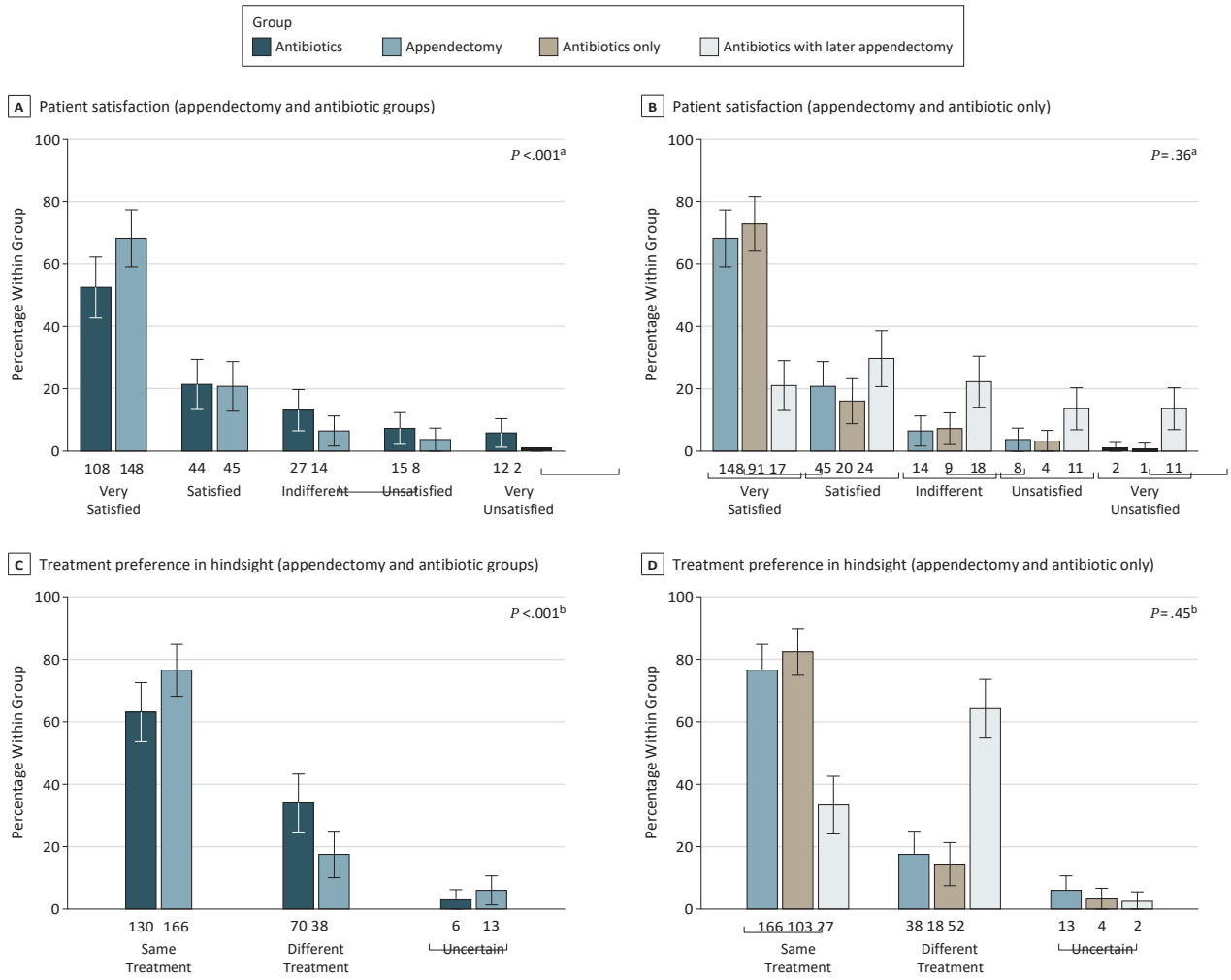


AA indicates acute appendicitis; CT, computed tomography; QOL, quality of life.

QOL (EQ-5D-5L)

The QOL between appendectomy and antibiotic group patients was similar (median health index value, 1.0; 95% CI,

Figure 2. Patient Satisfaction and Treatment Preference in Hindsight



A, Patient satisfaction in the appendectomy and antibiotic groups. B, Patient satisfaction with a subgroup analysis in appendectomy, antibiotics only, and antibiotics with later appendectomy groups. C, Treatment preference in hindsight in the appendectomy and antibiotic groups. D, Treatment preference in hindsight with a subgroup analysis in the appendectomy, antibiotics only, and antibiotics with later appendectomy groups. The error bars represent 95% confidence intervals.

[a] Difference between appendectomy and antibiotic groups (A) and appendectomy and antibiotics only (B). Multivariable cumulative logistic regression analysis to adjust the results for sex and age.

[b] Difference between appendectomy and antibiotic groups (C) and appendectomy and antibiotics only (D). Multivariable multinomial logistic regression analysis to adjust the results for sex and age.

0.86-1.0 in both groups; $P = .96$). The patient self-rated health VAS values did not differ between the groups ($P = .65$), with patients who underwent appendectomy reporting a median health of 79.7 (95% CI, 77.7-81.7) and patients taking antibiotics a median health of 79.5 (95% CI, 77.5-81.4).

Satisfaction With Care and Treatment Preference in Hindsight

The results of patient satisfaction are shown in Figure 2A. Patients who underwent appendectomy were more satisfied in the treatment (68% very satisfied, 21% satisfied, 6% indifferent, 4% unsatisfied, and 1% very unsatisfied in the appendectomy group and 53% very satisfied, 21% satisfied, 13% indifferent, 7% unsatisfied, and 6% very unsatisfied in the antiobiotic group; $P = .001$) than patients taking antibiotics; in a subgroup analysis, this difference was caused by the antibiotic group patients undergoing appendectomy. There was no difference in patient satisfaction after successful antibiotic treatment (no appendectomy) compared with appendectomy (COR, 7.8; 95% CI, 0.5-1.3; $P = .36$). Patients with appendectomy or with successful antibiotic therapy were more satisfied than antibiotic group patients later undergoing appendectomy (COR, 7.7; 95% CI, 4.6-12.9; $P < .001$; COR, 9.7; 95% CI, 5.4-15.3; $P < .001$, respectively). The patient satisfaction results in these 3 groups are presented in Figure 2B.

Treatment preference in hindsight is shown in Figure 2C and the results of the subgroup analysis in Figure 2D. There is a statistically significant difference in the reselection of treatment between the 3 groups of appendectomy, successful antibiotic therapy without the need for appendectomy, and

antibiotic treatment with later appendectomy. Patients in the later appendectomy group would statistically significantly more often choose the different treatment compared with patients in the antibiotics only group (OR, 11.2; 95% CI, 5.6-22.2; $P < .001$) or the appendectomy group (OR, 8.8; 95% CI, 4.9-15.9; $P < .001$).

Discussion

In this study comparing long-term QOL and patient satisfaction after appendectomy and antibiotic therapy for the treatment of uncomplicated acute appendicitis, there was no difference in QOL between these treatment groups assessing the APPAC trial patients at a median follow-up of 7 years. Patients who underwent appendectomy were more satisfied in the treatment than patients taking antibiotics; in a subgroup analysis, this difference was based on the antibiotic group patients undergoing appendectomy. Patient satisfaction after successful antibiotic treatment (ie, no appendectomy) compared with appendectomy was similar. Patients with appendectomy or successful antibiotic therapy were more satisfied than antibiotic group patients later undergoing appendectomy. However, despite this difference, 33% of these patients taking antibiotics who later underwent appendectomy would still again choose antibiotics as their primary treatment.

To our knowledge, no other study has been conducted on the long-term QOL and patient satisfaction of adult patients randomized to receive antibiotic therapy or appendectomy for the treatment of uncomplicated acute appendicitis. A study in a pediatric population showed similar results at a very short-term follow-up of only 24 hours, with nonoperative management proving to be as an effective strategy as surgery when chosen by the family and with no difference in QOL.[20] Another study in a pediatric population illustrated that the patients treated conservatively with antibiotics demonstrated higher patient QOL and health care satisfaction, and similar parental satisfaction was found in both groups.[21]

Quality of life is an important factor in measuring disease burden, and its additional value lies in considering the patients' subjective perceptions of well-being and treatment.[22] However, long-term QOL is difficult to measure in a comprehensive and realistic manner in cases of conditions causing more short-term burden to the patient. A QOL study in patients being treated with either open or laparoscopic appendectomy showed that although the burden of acute appendicitis should not be underestimated, the effect of appendectomy had a temporal and fully reversible effect on QOL.[23] Based on this limitation of QOL after the treatment of uncomplicated acute appendicitis, we added questions about patient satisfaction and treatment preference in hindsight to gain more perspective about the patient experiences with the different treatment options and their outcomes.

Patient satisfaction and preference are important factors that need to be considered in the overall assessment of different efficient treatment options. In our study, it was not surprising to discover that patients in the appendectomy group were more satisfied than the antibiotic group as the latter included patients taking antibiotics who later underwent appendectomy and thus were treated twice for the same disease. When these patients taking antibiotics who later underwent appendectomy were analyzed separately as the third group, patients with appendectomy or successful antibiotic therapy were more satisfied than antibiotic group patients later undergoing appendectomy and there was no difference between the appendectomy or antibiotics alone groups. The fact that 33% of patients who later underwent appendectomy after primary antibiotic treatment would still choose primary antibiotic treatment, accepting the risk of recurrence and potential later appendectomy, illustrates that in some situations, patients accept the risk of recurrence to possibly avoid surgery. A similar notion was stated in a recent meta-analysis[9] in which patients averse to the risk of recurrence would possibly choose primary immediate appendectomy, whereas patients averse to surgery may choose initial antibiotics. With increasing evidence of antibiotics for uncomplicated acute appendicitis, future studies are necessary to inform patients and clinicians about the possible benefits of each treatment approach for individual patients.[24]

A study regarding public perceptions about the treatment of acute appendicitis showed that the general public was knowledgeable in potential symptoms but less aware of the management options, with the belief that without surgery appendicitis would lead to perforation.[25] Another study showed that after information about the risks and advantages of surgery and antibiotic treatment for uncomplicated acute appendicitis, a population of medical students were more inclined to choose surgery, also noting that the answers may have been influenced by the manner in which the summary data of each treatment arm were presented.[26] A recent guideline[27] states that nonoperative management of uncomplicated acute appendicitis is feasible in patients wishing to avoid surgery and accept the risk of recurrence. With an increasing amount of studies,[4-8] meta-analyses,[9-11] and long-term follow-up results[12] indicating the feasibility of antibiotic therapy in the treatment of uncomplicated acute appendicitis, future studies should focus on a more multifactorial approach to making the treatment decision, including patient information and involvement in shared decision-making. The notion of this shared decision-making in treating uncomplicated acute appendicitis has been raised recently,[28-30] and future studies should focus on a more patient-centered approach informing about benefits for individual patients.[24] In addition, future studies need to address the biases in delivering the patient information and attempt to determine optimal ways to deliver as unbiased information as possible.

Once medical treatments become universally accepted clinical practice, they are very difficult to change, even if proven wrong or harmful.[31] Appendectomy has been the criterion standard treatment of acute appendicitis for more than a decade without having to differentiate between uncomplicated and complicated acute appendicitis. This creates an understandable and inevitable bias regarding new treatment alternatives for uncomplicated acute appendicitis, especially among surgeons. In their online survey, Hanson et al[14] reported that sur-

geons significantly more often chose surgery as their optimal treatment choice for uncomplicated acute appendicitis. Based on the presumed finding of this study that later appendectomy after antibiotic treatment decreases patient satisfaction, future studies should also be directed at reducing the failure and recurrence rates of antibiotic treatment for appendicitis[14] by identifying potential predictive factors indicating the risk of recurrence of uncomplicated acute appendicitis and thus enabling an optimization of the primary treatment choice. In addition, promising results have been reported for successful symptomatic therapy of uncomplicated acute appendicitis[32] and a double-blind randomized trial (APPAC III) comparing antibiotic therapy with placebo for the treatment of uncomplicated acute appendicitis is currently being conducted.[33] If future studies show a similar efficacy and safety of symptomatic treatment and antibiotic therapy, the strategy of appendectomy for all patients with uncomplicated acute appendicitis will be difficult to justify and even more studies are needed to evaluate the optimization and tailoring of these treatment choices for all patients.

Strengths and Limitations

The strengths of the study include the novelty of the results as, to our knowledge, long-term QOL and patient satisfaction has not yet been reported in a randomized clinical trial on adult patients comparing appendectomy with antibiotic therapy in treating uncomplicated acute appendicitis. Another strength is the follow-up rate of 80% at a median follow-up of 7 years, which together with the multicenter characteristic of the study enhances the likelihood that the study results are generalizable to routine surgical practice. In addition, by very effectively diagnosing the acute appendicitis and excluding patients with complicated acute appendicitis by CT in the APPAC trial,[4] this study population accurately represents patients with uncomplicated acute appendicitis.

As this observational study is based on the original APPAC trial, it has limitations based on the initial study protocol described in detail in the previous trial reports[4,34] as well as this additional study assessing the post hoc outcomes of postintervention QOL and patient satisfaction. One of the limitations of the initial trial includes the open approach for appendectomy, as currently laparoscopic appendectomy is the criterion standard associated with shorter hospital stays and less postoperative pain.[35] Another limitation of the initial protocol was the long duration of antibiotic treatment and hospitalization for the antibiotic group patients, who had to spend time in the hospital regardless of their clinical status. All of these limitations most likely have an effect on patient satisfaction. A strong limitation of this analysis is that it is a post hoc secondary outcome, as at the time of study protocol planning, the importance of patient preference or QOL was not yet recognized and the focus was on assessing whether antibiotic therapy was an effective and safe treatment option for treating uncomplicated acute appendicitis. Thus, baseline QOL is not available for comparison. In addition, the QOL measurement tools for acute care conditions can also be seen as a limitation as QOL is difficult to measure, especially in the case of emergency conditions that for most only have a short-term effect on a patient's life.

Conclusions

Long-term QOL is similar after appendectomy and antibiotic therapy for treating uncomplicated acute appendicitis. Patients taking antibiotics who later underwent appendectomy were less satisfied than patients with successful antibiotic treatment or appendectomy, underlining the importance of discovering potential parameters predictive of appendicitis recurrence.

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Author Contributions: Drs Sippola and Salminen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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