Acute appendicitis and microbiota: Etiology and effects of the antimicrobial treatment

Research director Eveliina Munukka, PhD

Acute Appendicitis

• traditionally the standard treatment has been \textit{appendectomy}
  • the most common cause of emergency abdominal surgery
  • \(\sim 300,000\) appendectomies per year in United States, \(\sim 5000\) in Finland
  • complicated form always needs surgery
• complicated vs. uncomplicated disease form \(\rightarrow\) in Finland diagnosis is based on CT imaging (OPTICAP)

• obstruction of appendix followed by microbial overgrowth and/or bacterial infection as a primary reason
• treatment by antibiotics ?
The appendicitis acuta = APPAC

Original Investigation

Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis
The APPAC Randomized Clinical Trial

Paulina Salminen, MD, PhD; Hannu Paajanen, MD, PhD; Tero Rautio, MD, PhD; Pia Nordström, MD, PhD; Markku Aarmio, MD, PhD; Tuomo Rantanen, MD, PhD; Risto Tuominen, MPH, PhD; Sajja Hurme, MSc; Johanna Virtanen, MD; Jukka-Pekka Mecklin, MD, PhD; Juhani Sand, MD, PhD; Airi Jarri, MD; Irina Rinta-Kilikki, MD, PhD; Juha M. Grönroos, MD, PhD


- non-inferiority trial
- uncomplicated appendicitis patients (n = 530) were randomized either to antibiotics or appendectomy group
- *i.v.* ertapenem (1g/d), 3 d + *p.o.* levofoxacin (500 mg/d) ja metronidazol (3 x 500 mg/d), 7 d
- 73 % of ab patients were successfully treated.
- the likelihood of late recurrence within 5 years was 39.1%.
- long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.
APPAC II, APPAC III and MAPPAC

**APPAC II:** Optimization of the AB
- *i.v. + p.o vs. p.o.*

Ab1: *i.v.* ertapenem + *p.o.*
levofloxacin and metronidazole
Ab2: *p.o.* moxifloxacin

- open label

**APPAC III:** Spontaneous resolution?
- *Ab treatment vs. placebo*

Ab: *i.v* ertapenem + *p.o.*
levofloxacin and metronidazole

- double-blinded

**MAPPAC** (Microbiology Appendicitis Acuta)

- non-inferiority, randomized, multicenter trials, APPAC III double-blinded
Microbiological etiology of appendicitis

• Whether or how complicated and uncomplicated AA differ microbiologically?
  • appendix microbiome studied by NGS (Illumina MiSeq) and trad. culture combined with MALDI-TOF
  • gut microbiome of AA patient at the same time point *i.e.* novel microbiological markers that can be identified from rectal samples?
  • serum metabolome profiles

• Can microbiological factors explain the recurrence/treatment failure of AA?

• What is appendicolith?
**Sample collection, methods and analysis**

Rectal swabs:
- DNA extraction → NGS
- Aerobic culture → AMR profiles

Appendix:
- contents
  - DNA extraction → NGS
  - Aerobic and anaerobic culture → MALDI-TOF MS
- appendicolith
  - DNA extraction → NGS
  - Composition analysis → XRD (X-ray diffraction), µ-XRF (X-ray fluorescence), FTIR and µCT
- biopsy
  - DNA extraction → NGS
  - Deep freezing for later analysis
  - Immunohistochemistry, host expression analysis

- pathologic-anatomic diagnosis + blood culture + clinical parameters
Appendix culture and MALDI-TOF/MS identification

**Aerobic culture:**
Chromagar orientation, blood agar, Streptococcal blood agar, Yersinia agar

**Anaerobic culture:**
Kanamycin-vankomycin laked blood agar and FAA

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Turku Microbiome Biobank

- first microbiome biobank in Finland, launched at August 2018
- joint project: Turku University/Medical faculty, Tyks Clinical Microbiology and Auria Biobank
- facilities in MedisiinaD building in Kupittaa Health Campus
- Collaboration:
  - various departments and clinicians within Tyks (Gastroenterology, Infectious diseases, Gastroscopy, Hygiene unit, Yhteislaboratorio, TYKSlab etc.)
  - academy fellow, Reetta Satokari, University of Helsinki
  - academy fellow, docent Leo Lahti (bioinformatics)
  - Turku Centre for Biotechnology: bioinformatics, metabolomics
  - University of Jyväskylä, Dept. Of Health Sciences & Central Finland Central Hospital
  - Finnish Olympic Committee, responsible Dr. Maarit Valtonen,
- microbiome
- metabolomics
- Infections, biofilms
- dysbiosis
- imaging

- biobank
- population-based cohorts
- clinical studies

- biological specimen management
- data pool

- FMT
- FMT – general donor recruitment
- Autologous FMT
- interventions

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Thank You!

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Thank You!