Acute Appendicitis Non-Operative Management Rate Trends Over Two Decades (2000 to 2019): The Israel experience

Doron Carmi MD MHA[1]*, Ziona Haklai MA[2]*, Ethel-Sherry Gordon PHD[2], Ada Shteiman MSC[2], and Uri Gabbay MD MPH[3,4]

[1]Shoham Community Health Center, Clalit Health Services, Shoham, Israel
[2]Health Information Division, Ministry of Health, Tel Aviv, Israel
[3]Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Quality Unit, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel

ABSTRACT **Background:** Acute appendicitis (AA) is a medical emergency. The standard of care for AA had been surgical appendectomy. Recently, non-operative management (NOM) has been considered, mainly for uncomplicated AA.

Objectives: To evaluate AA NOM trends over two decades.

Methods: We conducted a retrospective cohort study based on Israel's National Hospital Discharges Database (NHDD). Inclusion criteria were AA admissions from 1 January 2000 to 31 December 2019, with either primary discharged diagnosis of AA, or principal procedure of appendectomy. Predefined groups were children (5 <18 years) and adults (≥ 18 years). We compared the last decade (2010–2019) with the previous one (2000–2009).

Results: The overall AA incidence rate over two decades was 126/100,000/year; higher in children 164/100,000/year than 113/100,000/year in adults. Surgery was the predominant AA treatment in 91.9%; 93.7% in children and 91.1% in adults. There was an increase in AA NOM rates when comparing the previous decade (5.6%) to the past decade (10.2%); 3.2% vs. 9.1% in children and 6.8% vs. 10.7% in adults, respectively. Annual trends revealed a mild increase in AA NOM rates. Delayed appendectomy (within 90 days of AA NOM) was 19.7% overall; 17.3% in adults and 26.3% in children.

Conclusions: There was an increase in AA NOM rates during the last decade in the overall population. Since 2015, there has been a noticeable increase in AA NOM rates, probably associated with World Society of Emergency Surgery Jerusalem guidelines. Surgery is still the predominant treatment for AA despite the increasing trend in NOM.

IMAJ 2023; 25: 101–105

KEY WORDS: acute appendicitis, age groups, case fatality rate, incidence, non-operative management

*These authors contributed equally to this study

Acute appendicitis (AA) is one of the most common surgical emergencies. AA incidence rates differ by country and by age group. Lifetime risk of AA is 1 in 15 in the United States [1].

Until 2010, standard of care for AA was predominantly surgical appendectomy, which has a complication rate ranging from 5–28% depending on AA severity and the surgical technique according to different studies [2,3]. Systematic reviews comparing open vs. laparoscopic appendectomy have shown that the laparoscopic approach is associated with reduced wound infections and a lower rate of bowel obstruction [4,5].

A false positive diagnosis of AA is defined as white appendix (normal histopathology) ranging 6–20%, which decreased when diagnosis was supported by imaging [6,7]. It was commonly believed that the risk of complicated appendicitis is higher than the risk of appendectomy, justifying surgery even at the risk of white appendicitis. This dogma has been recently challenged. The introduction of imaging to the diagnosis of AA increased its accuracy [8].

In last decades, there was an increasing trend of non-operative management (AA NOM) [9,10]. AA NOM is based on antibiotic therapy, which became a common alternative in children and has been shown to be safe and effective compared to surgical treatment [11-18]. There were debates regarding AA NOM in adults given the high rate of complicated acute appendicitis [19].

During the 3rd World Congress of the World Society of Emergency Surgery (WSES), held in Jerusalem in July 2015, a consensus policy document was introduced that also legitimized the option of non-operative treatment for uncomplicated appendicitis [20].

Several research initiations had evaluated AA NOM, such as the Comparison of the Outcomes of antibiotic Drugs and Appendectomy (CODA) initiative, which showed that AA NOM was not inferior to surgical management. This initiative also found that nearly 30% of the AA NOM patients underwent appendectomy within 90 days of the initial AA NOM event. [21]

The aim of this study was to evaluate the trends of adoption of AA NOM in the Israeli population over two decades.

PATIENTS AND METHODS

We conducted a retrospective cohort study based on Israel's National Hospital Discharges Database (NHDD). NHDD is compulsory reporting system of structured data on hospitalization from all acute care hospitals. Discharge diagnoses are coded according to the international classifications of diseases (ICD-9CM) by professional medical informatics personnel at each hospital.

Inclusion criteria included acute hospital admissions of ages 5 years and older from 1 January 2000 to 31 December 2019 with a diagnosis of AA, which was defined as acute admission with either coded primary diagnosis of AA or coded principal procedure of appendectomy. AA NOM was identified when the coded primary diagnosis of AA lacked a coded procedure of appendectomy.

Exclusions criteria included delayed appendectomy within 90 days that was not considered as a new AA event but rather a delayed appendectomy following previous AA NOM.

DEFINITIONS

We included patients 5 years of age or older. For the purpose of this study, children were 5 years < 18 years, adults were ≥ 18 years of age. AA was defined as coded discharge diagnosis limited to codes 540*: acute appendicitis (540), acute appendicitis with generalized peritonitis, acute appendicitis with peritoneal abscess (540.1), and acute appendicitis without mention of peritonitis (540.9). We did not include coded diagnoses of appendicitis that were unlikely to be acute appendicitis, including appendicitis, unqualified (541), and other appendicitis (542). Accordingly, the surgical procedures were limited to codes 47.0*: appendectomy (47.0), laparoscopic appendectomy (47.01), other appendectomy (47.09). We did not include coded surgical procedures that were unlikely due to acute appendicitis, namely incidental appendectomy (47.1), laparoscopic incidental appendectomy (47.11), other incidental appendectomy (47.19), drainage of appendiceal abscess (47.2), other operations on appendix (47.9), appendicostomy (47.91), closure of appendiceal fistula (47.92), and other operations on appendix (47.99).,

The retrieved data were anonymized but contained patient demographics, admission date, admission type, coded diagnosis and procedures performed, and discharge date and type. AA incidence rate was computed as AA cases per 100,000/year of the respective population in each individual year. AA incidence rate of each decade was computed as the overall sum of AA cases during the respective period divided by the sum of the annual mid-year population size during the respective period. AA annual incidence rates trended over 20 years were evaluated through linear regression model.

The research focused on AA NOM rate trends during 2000–2019. Individual year AA NOM rate was defined as the annual number of AA NOM cases divided by the annual AA cases. The AA NOM rate ratio (RR) was defined by the NOM rate in the last decade (2010–2019), divided by the NOM rate in the previous decade (2000–2009). Delayed appendectomy rate was defined as appendectomy within 90 days of the initial AA NOM.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Differences in incidence rate were determined using Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

The overall AA incidence rate over two decades was 126/100,000 year. AA incidence rate in children was higher (164/100,000 year) then in adults (113/100,000 year).

Table 1 describes the AA NOM rates in the last decade (2010–2019) compared to the previous decade (2000–2009). Surgery was the predominant treatment during the entire period. There was a higher AA NOM rate in the last decade vs. the previous decade with an AA NOM rate ratio (RR) of 1.8 in the overall population, 1.6 in adults, and 2.8 in children.

The overall rate of delayed appendectomy within 90 days of the initial AA NOM was 19.7% over the two decades: 26.3% in children and 17.3% in adults.

Table 1. Non-operative management rate of acute appendicitis by decade and age group

	Non-operative management rate the entire period	Non-operative management rate previous decade (2000–2009)	Non-operative management rate last decade (2010–2019)
All	8.1%	5.6%	10.2%
Adults (≥ 18 years)	8.9%	6.8%	10.7%
Children (5 < 18 years)	6.3%	3.2%	9.1%

Figure 1 shows the annual trend of AA incidence rate per 100,000/years of the respective population (upper curve, left axis) and the respective annual rate of AA NOM rate for the annual AA cases during the 20 years (lower curve, right axis). The upper curve shows a stable, although fluctuant AA incidence rate. The lower curve shows a consistent mild increase of AA NOM rates until 2015, at which time there was a considerable increase, reaching a maximum of nearly 19% in 2019.

Figure 2A shows the annual trend of AA incidence rates per 100,000/years of the adult population (upper curve, left axis) and the respective annual rate of AA NOM rate out of the annual adults AA cases during the 20 years (lower curve, right axis). The upper curve shows a stable, although fluctuant AA incidence rate. The lower curve shows a consistent mild increase of AA NOM rates until 2014–2015, at which time there was a noticeable increase reaching a maximum of 17.1% in 2018.

Figure 1. Trend of acute appendicitis incidence rates and the respective rate of non-operative management by year of the entire population
AA = acute appendicitis, NOM = non-operative management

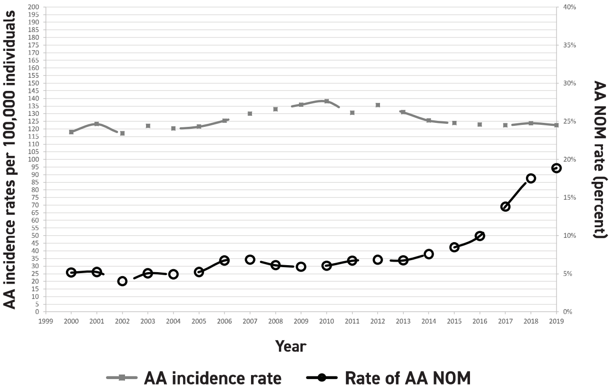
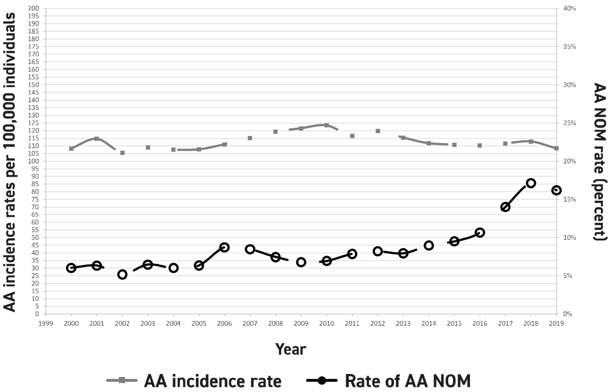


Figure 2. Annual rate of acute appendicitis in adults and children and the annual rate of non-operative management
AA = acute appendicitis, NOM = non-operative management

[A] Adults



[B] Children

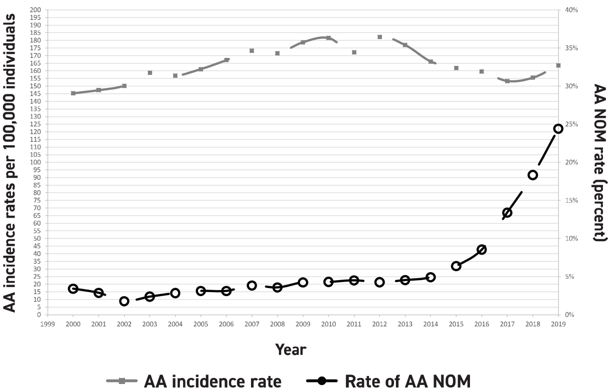
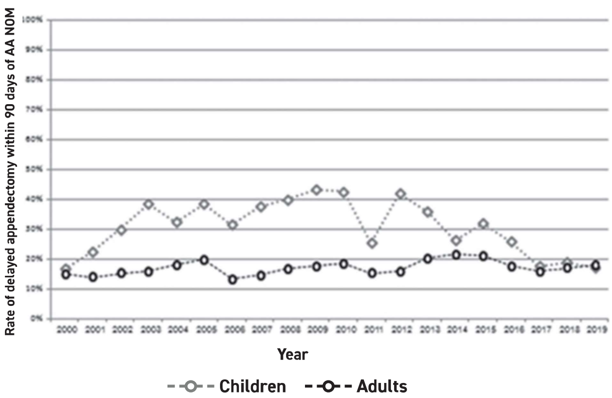


Figure 2B shows the annual trend of AA incidence rates per 100,000/years of the respective population of children (upper curve, left axis) and the respective annual rate of AA NOM rate during the 20 years (lower curve, right axis). The upper curve shows very fluctuant and very mild increased AA incidence rate. The lower curve shows a consistently mild increase of AA NOM rates until 2015, after which there was a considerable monotonous increase reaching a maximum of nearly 25% in 2019.

Figure 3 shows the annual delayed appendectomy rates within 90 days of an AA NOM. The upper curve shows delayed appendectomy rates in children, which shows a fluctuant converted U shape that ranged 18–43%. However, while AA NOM rate increased toward a maximum of nearly 25% [Figure 2] delayed appendectomy rates decreased. The lower curve shows relatively stable though fluctuant delayed appendectomy rate in adults ranged between 13–22%.

Figure 3. Rate of delayed appendectomy (within 90 days of AA NOM) by age group and year
AA = acute appendicitis, NOM = non-operative management



DISCUSSION

The average annual incidence of AA according to our research is slightly higher than the reported literature. The annual AA incidence rates fluctuated but remained stable over the 20 years. Similar trends were reported by Western countries [22]. The overall AA incidence rate in children was higher than in adults during the two decades and showed very mild increases over time. Past researchers found that individuals between the ages of 10 years and 19 years were at the higher risk for AA [23].

There was a consistently mild increase in AA NOM rates until 2014–2015, after which the increases became more noticeable in the overall population. The AA NOM rate of adults was 17% in 2018. Children showed a more considerable increase in AA NOM from 2015, reaching maximal rate of nearly 25% in 2019. Our results showed an increase in the nationwide adoption of AA NOM starting in 2015 when the WSES Jerusalem consensus guidelines were introduced. Evidence-based studies, such as the CODA initiative, showed non-inferiority of AA NOM compared with surgery [21]. Our results showed that surgery for AA was still the predominant management option, despite the increasing trend in AA NOM. The paradigm shift seems to be to delay in adults, compared to children, due to either being treated more cautiously or manifesting with higher rate of complicated AA.

The same study revealed that 30% of the AA NOM population had undergone delayed appendectomy (within 90 days) [21].

Unlike previous studies, our results showed a lower rate of delayed appendectomy in the overall AA NOM of 19.7%; 26.3% in children and 19.7% in adults. However, when examining annual rates of delayed appendectomy [Figure 3] there were fluctuations not necessarily associated with AA NOM rate. While AA NOM rates have increased considerably [Figure 2] since 2016–2019, delayed appendectomy rates have decreased. This result may reflect learning curves and experience. We assume that different hospitals had different adoption rates and cumulative experience.

Existing registries and databases are excellent sources to reveal epidemiological insights that are underutilized. Nevertheless, registries have several limitations. The data collected from different hospitals may be prone to different degrees of imprecision. A significant drawback of being based on administrative rather than clinical data is that the reason for AA NOM could not be defined and may have been due to specific conditions such as periappendicular abscess. Moreover, there were no data available on the time elapsed from the beginning of the symptoms to diagnosis. The wide use of preoperative imaging may have contributed to higher rates of accurate diagnosis of periappendicular abscess, which may explain part of the increase in non-operative management. It might be that the factual reason for the slow adoption of the NOM paradigm shift is that a considerable number of patients arrive at the emergency department with complicated AA rather that with simple uncomplicated AA. Unfortunately, these data are unavailable from administrative coded data.

Coded data may be biased as the precision of a retrospective study depends on the accuracy of the underlying data. While acute appendicitis enables a definite validation by surgery, in AA NOM validation is less definite.

The study strength is that the data source was a comprehensive registry of the Ministry of Health over two decades. Reliability is strong as this nationwide database was established on controlled and supervised reports of all general hospitals to the Ministry of Health, rather than a single medical center.

AA remains a considerable morbidity in both adults and children. According to the literature, simple non-complicated AA can be managed non-operatively, which is not inferior to surgery in both children and adults. AA NOM is considered a paradigm shift in emergency surgery, yet despite the increasing trend of AA NOM, appendectomy is still the predominant AA management strategy.

According to the literature, 30% of AA NOM will undergo delayed appendectomy (within 90 days); however, our results were considerably lower in the overall period (19.7%). The annual rates of delayed appendectomy fluctuation reached annual rates of over 40% in children and then decreased considerably to 19%. During the years 2016–2019 adoption rates of AA NOM increased considerably while delayed appendectomy rates decreased. These findings exclude direct association between rate of adoption of AA NOM and delayed appendectomy rate. Hence, the fluctuations in delayed appendectomy rate are most probably due to learning and experiencing curves.

CONCLUSIONS

We encourage the Ministry of Health to initiate quality indicators related to AA NOM rates in pediatric surgery wards. We encourage the Israeli Surgical Association to evaluate the underling obstacles to adoption of AA NOM in adults.

Correspondence

Dr. U. Gabbay
Dept. of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
Phone: (972-3) 937-2779
Email: medicounsel@gmail.com

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990; 132: 910-25.
2. Masoomi H, Nguyen NT, Dolich MO, Mills S, Carmichael JC, Stamos MJ. Laparoscopic appendectomy trends and outcomes in the United States: data from the Nationwide Inpatient Sample (NIS), 2004-2011. *Am Surg* 2014; 80: 1074-7.
3. Guller U, Hervey S, Purves H, Muhlbaier LH, Peterson ED, Eubanks S, Pietrobon R. Laparoscopic versus open appendectomy: outcomes comparison based on a large administrative database. *Ann Surg* 2004; 239: 43-52.
4. Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2010; (10): CD001546.
5. Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. Meta-analysis of the results of randomized controlled trials that compared laparoscopic and open surgery for acute appendicitis. *J Gastrointest Surg* 2012; 16: 1929-39.
6. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015; 386 (10000): 1278-87. Erratum in: Lancet. 2017 Oct 14; 390 (10104): 1736.
7. Seetahal SA, Bolorunduro OB, Sookdeo TC, et al. Negative appendectomy: a 10-year review of a nationally representative sample. *Am J Surg* 2011; 201: 433-7.
8. Zoarets I, Poluksht N, Halevy A. Does selective use of computed tomography scan reduce the rate of "white" (negative) appendectomy? *IMAJ* 2014; 16 (6): 335-7.
9. Bhangu A; RIFT Study Group on behalf of the West Midlands Research Collaborative. Evaluation of appendicitis risk prediction models in adults with suspected appendicitis. *Br J Surg* 2020; 107 (1): 73-86.
10. Mason RJ. Surgery for appendicitis: is it necessary? *Surg Infect* (Larchmt) 2008; 9: 481-8.
11. Ansaloni L, Catena F, Coccolini F, et al. Surgery versus conservative antibiotic treatment in acute appendicitis: a systematic review and meta-analysis of randomized controlled trials. *Dig Surg* 2011; 28: 210-21.
12. Paajanen H, Grönroos JM, Rautio T, et al. A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). *BMC Surg* 2013; 13: 3.

13. Imha W, Denm DH, Dc DV, Hmj J. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Collab* 2011; 11: CD008359.
14. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC Randomized Clinical Trial. *JAMA* 2015; 313: 2340-8.
15. Solomon CG, Flum DR. Clinical practice. Acute appendicitis-- appendectomy or the "antibiotics first" strategy. *N Engl J Med* 2015; 372: 1937-43.
16. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012; 344: e2156-e2156.
17. Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011; 150: 673-83.
18. Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *Br J Surg* 2016; 103 (6): 656-67.
19. Rub R, Margel D, Soffer D, Kluger Y. Appendicitis in the elderly: what has changed? *IMAJ* 2000; 2 (3): 220-3.
20. Di Saverio S, Birindelli A, Kelly MD, et al. WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. *World J Emerg Surg* 2016; 11: 34.
21. CODA Collaborative, Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med* 2020; 383 (20): 1907-19.
22. Ferris M, Quan S, Kaplan BS, et al. The global incidence of appendicitis: a systematic review of population-based studies. *Ann Surg* 2017; 266 (2): 237-41.
23. Buckius MT, McGrath B, Monk J, Grim R, Bell T, Ahuja V. Changing epidemiology of acute appendicitis in the United States: study period 1993-2008. *J Surg Res* 2012; 175 (2): 185-90.

Capsule

Sarcoma genes in the limelight

Sarcomas are cancers of muscles, bones, and other connective tissues that tend to develop in younger patients and are often aggressive and difficult to treat. Because of their relative rarity, the biology of sarcomas is not nearly as well understood as that of more common cancers. In a massive, multinational genomic study involving thousands of patients, their families, and controls, **Ballinger** and associates identified distinct biological pathways where mutations increase the inherited risk for developing sarcoma through alterations of telomere biology and mitotic function.

Science 2023; 379: 253

Eitan Israeli

Capsule

Unlinked recognition in alloreactivity?

Some individuals who receive blood transfusions develop alloantibodies against donor red blood cells (RBCs) for reasons that are not entirely clear. B cells are typically activated by CD4+ T cells that recognize the same antigen, but not necessarily the same structures or epitopes on that antigen, in a process called linked recognition. **Jajosky** and colleagues used a model for human blood transfusion and found that linked recognition may not be the whole story. Green fluorescent protein (GFP) was given as an alloantigen to mice, which then received transfusions of RBCs that expressed both intracellular GFP and another unrelated surface alloantigen. These mice subsequently developed antibody responses against the unrelated surface antigen, suggesting that previous priming events against intracellular antigens that are not physically linked to B cell target antigens may enhance naïve B cell responses to their targets.

Blood 2023; 10.1182/blood.2022016588

Eitan Israeli

Capsule

Activating the STING in tumors

Agents that activate the DNA-sensing cGAS-STING pathway have been explored for cancer immunotherapy in both preclinical and clinical settings, but how to optimally activate the pathway remains unclear. **Jneid** and colleagues found that incorporation of the naturally occurring STING ligand cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) into noninfectious enveloped viruslike particles (VLPs) selectively activated STING in antigen-presenting cells, including dendritic cells, when administered intratumorally. Compared with a nontargeted synthetic STING agonist, VLPs delivering cGAMP systemically enhanced tumor-specific T cell responses and antitumor effects during immune checkpoint blockade in mice. These results demonstrate that selectively targeting STING agonists to antigen-presenting cells may improve their therapeutic effects, particularly in poorly immunogenic tumors.

Sci Immunol 2023; 8: eabn6612

Eitan Israeli