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SURGICAL AND NON-SURGICAL TREATMENT OF PAEDIATRIC APPENDICITIS: CAN ALGORITHMS HELP US TO PREDICT PERFORATION?

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The recent interest in and evidence of non-surgical treatment with antibiotic therapy has led to the recurring issue of differentiating acute no-complicated appendicitis (AnA) and acute complicated appendicitis (AcA) when these are presented in an emergency department. To create the initial version of an acute appendicitis (AA) diagnostic and treatment algorithm, we analysed treatment results of 178 children with AnA and AcA treated at the Children's Clinical University Hospital in Rīga in the period between 2010 and 2013. Evaluation of the clinical symptoms, laboratory and radiological findings was included in development of the algorithm. The algorithm was created in 2016 and accepted by the hospital administration. We present the algorithm's updated version of 2020. The introduction of diagnostic scores and algorithms has standardised and improved the diagnosis of paediatric AA. New diagnostic tests with higher sensitivity and specificity may improve the accuracy of diagnostic algorithms. Measuring multiple effective biomarkers simultaneously may improve the accuracy of diagnostic algorithms and predict the severity of paediatric AA. Machine learning algorithms may be able to process a much larger amount of data and provide a faster conclusion, helping the surgeon make the right decision in diagnosing appendicitis in children and prevent unnecessary surgery.

Keywords: *diagnostic, treatment algorithm, biomarkers, acute appendicitis.*

INTRODUCTION

Acute appendicitis (AA) is among most frequent abdominal surgical pathologies in the paediatric population (Wier *et al.* 2013). Although both children and adults are affected, risk of perforation and severe complication is higher in children (Livingston *et al.*, 2007; Bonadio *et al.*, 2015). Recent tendencies in non-invasive management of AA demonstrated a need for an effective tool for distinguishing complicated and non-complicated AA (Simillis *et al.*, 2010). This implies a necessity of developing a modern, easy-to-use diagnostic tool that will help paediatric surgeons with classification of AA. A plethora of different independently developed algorithms have already introduced and published worldwide, but there is still a lack of a unified approach (Podevin *et al.*, 2017; Children's Alabama, 2019; Di Saverio *et al.*, 2020). More and more novel diagnostic measures are being introduced and the amount of input data for these algorithms increases, potentially rendering them more complex and harder to use for doctors in conditions of an emergency department (ED) (Kentsis *et al.*; 2010; 2012; Kharbanda *et al.*, 2012; Bakal *et al.*, 2016).

Digitalisation of diagnostic tools may help in handling an increasing amount of input data, reducing the load from surgeons and helping with possible misdiagnosis. Use of machine-learning techniques in medicine has already begun (Deo, 2015). Results of several pilot projects of using machine learning (ML) in predicting severity of appendicitis have already published and showed their feasibility (Akmese *et al.*, 2020; Aydin *et al.*, 2020; Marcinkevics *et al.*, 2021).

The recent interest in and evidence of non-surgical treatment with antibiotic therapy leads to the recurring issue of differentiating no-complicated appendicitis (AnA) and acute complicated appendicitis (AcA) when these are presented in an emergency department (ED). Swift confirmation of AA is impeded by a variety of factors such as atypical presentation and multiple differential diagnoses, thus making complications more likely.

Laboratory markers such as white blood-cell count and C-reactive protein (CRP), together with abdominal ultrasound (USG) and computed tomography are useful in lowering the rate of unnecessary surgical interventions (Coursey *et al.* 2010). USG can be used to diagnose AA and, in most cases, can even differentiate between AnA and AcA. However, all this depends on the skill of the radiologist or USG specialist (Rawolle *et al.*, 2019). The high radiation exposure of computed tomography limits its usage due to the long-term cancer risk (Wray *et al.*, 2013). Novel biomarkers have the potential to provide similar information as accurately as these visual diagnostic methods (Kentsis *et al.*, 2010).

Interleukin-6 (IL-6) has a role in different processes, such as activating acute-phase protein synthesis in the liver, or haematopoiesis, B-cell production. It also participates in the formation of Th17. IL-6 is a multifunctional inflammatory marker (Castell *et al.*, 1989; Rincon, 2012; Wu *et al.*, 2016). It has been concluded that IL-6 is an ideal marker for bacterial infections and could serve as an early rapid diagnostic tool in clinically suspected appendicitis (Kharbanda *et al.* 2012; Wu *et al.* 2016).

Neutrophil gelatinase-associated lipocalin (NGAL) is hypothesised to increase in the bloodstream together with neutrophils in the respiratory and gastrointestinal tracts, and in the renal system when epithelial tissue is damaged. This can be the result of different kinds of stress, for example, inflammation, infection, or ischaemia (Fodor *et al.* 2015; Bakal *et al.* 2016; Selleck, Senthil, and Wall 2017). It is possible that both previously mentioned biomarkers, IL-6 and NGAL, would be present in higher amounts in the serum of patients with AcA compared with those with AnA, since in uncomplicated cases the organ tissues are subjected to less stress. Focus on immunological pathways is growing, and consequently the magnitude of proposed biomarkers, although none has currently achieved widespread use (Selleck *et al.*, 2017). In comparison to IL-6 and CRP, no other biomarkers have been proven effective in diagnosing AA.

Another biomarker of inflammation, also produced by neutrophils, is leucine-rich alpha-2 glycoprotein 1 (LRG1). It is hypothesised to have a particularly vital and diagnostic precision ratio, and therefore LRG1 might determine specificity in AA development, together with drug-independent values in serum (Kentsis *et al.*, 2012; Kharbanda *et al.*, 2012; Serada *et al.*, 2012; Naka and Fujimoto, 2018). It is produced and secreted by hepatocytes, macrophages, and intestinal epithelium, and it increases in acute-phase responses of microbial infection at inflammatory sites (Kentsis *et al.*, 2012; Kharbanda *et al.*, 2012; Serada *et al.*, 2012; Naka and Fujimoto, 2018). LRG1 transcription is stimulated by numerous pro-inflammatory markers such as IL-6, IL-1, IL-22, TNF-α and lipopolysaccharides. Its normal serum level is hypothesised to be 21–50 μg/ml. LRG1 is thought to play a role in the activation and chemotaxis of neutrophils as they enter areas of inflammation (Serada *et al.*, 2012).

The search for a single ideal biomarker may seem pointless, but when used in conjunction with a medical history and clinical findings, it is feasible to improve the quality of diagnostic techniques, prevent complications and lower overall hospital expenses by reducing unneeded imaging and other procedures. In this study, the aim was to investigate whether IL-6, NGAL, and LRG1 biomarker could distinguish between AnA and AcA.

MATERIALS AND METHODS

Non-surgical treatment of uncomplicated appendicitis systematically started in 2012 in the Children's Clinical University Hospital (CCUH). Therefore, surgeons after confirming the diagnosis of AA immediately had to separate children with AnA from those with AcA, because the treatment was surgical only for the AcA group (Fig. 1 and 2).

During the study period of 2014 to 2015, the Alvarado score alone was used to separate AnA and AcA cases, but the results showed that the diagnosis and treatment should be im-

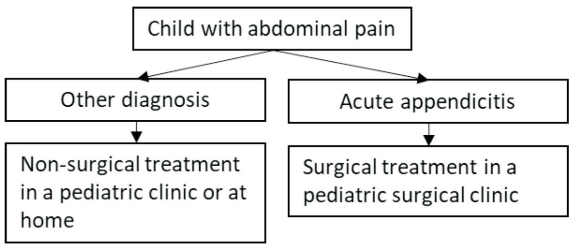

Fig. 1. Abdominal pain management steps in the CCUH before 2012.

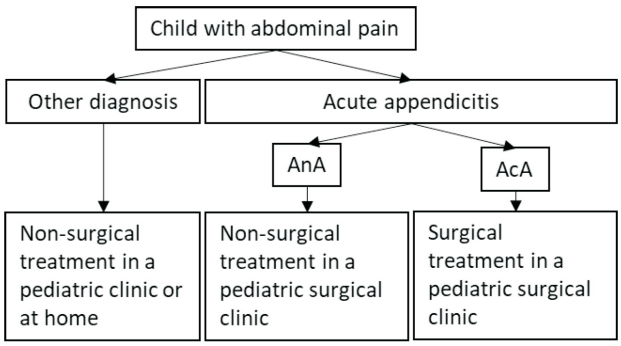

Fig. 2. Abdominal pain management steps in the CCUH after 2012.

proved and standardised. It was decided to create a diagnostic and treatment algorithm for use in the ED as well as in the paediatric surgery clinic (Zviedre *et al.*. 2019).

A prospective study was performed. A total of 178 patients aged 7 to 18 years with suspicion of AA at CCUH were included in the period from 2010 to 2013 (Zviedre *et al.*, 2019). In 2016, an initial version of an AA diagnostic and treatment algorithm was created and accepted by the hospital administration for practical use for patients with suspicion of AA and confirmed diagnosis of AA. Clinical symptoms, Alvarado score (Alvarado, 1986), laboratory and radiological findings were included in the algorithm (Zviedre *et al*., 2019). The first evaluation of the algorithm was done by a performing a retrospective study of patients suspected for AnA in CCUH in 2017 (Taurina *et al*., 2020).

A second re-evaluation was performed in 2019 as an internal hospital audit report (hospital internal document code KA-2/2020 from 20.04.2020), based on the retrospective analysis of the treatment results of 100 randomised patients, 7 to 18 year old, 50 patients — operated on and 50 — not operated, with subsequent improvement of the initial version of the algorithm in 2020. Standard statistical methods and MS Excel were used for data processing.

RESULTS

The algorithm including diagnostic as well as treatment sections, with separation of patients in two age groups 7 years and 7 to 18 years old). Clinical, laboratory, and radiology criteria were used to distinguish between AnA from AcA, i.e. absent to mild worsening in the general condition and negative symptoms of peritoneal irritation, WBC > 10.7 × 10^3/µl, CRP > 8.4 mg/l, IL-6 > 39.2 pg/ml and appendix diameter > 7 mm, wall thickness > 2 mm, not compressible on USG for AnA and moderate to severe worsening in the general condition and positive symptoms of peritoneal irritation, WBC 10.7 × 10^3/µl, CRP 8.4 mg/l, IL-6 39.2 pg/ml and appendix diameter 7 mm, wall thickness 2 mm, not compressible on USG for AcA. The clinical and laboratory criteria served as thresholds for a patient's inclusion into one of the groups (internal hospital document REK-052/01 from 2017). The criteria were based on the previous studies (Zviedre *et al.,* 2019; Taurina *et al.,* 2020).

The internal hospital audit report of 2019 (hospital internal document code KA-2/2020 from 20.04.2020) revealed some major discrepancies in patient data compared with the algorithm: for AnA, in 32% of cases CRP level was higher and in 24% of cases WBC count was lower than the specified level while for AcA in 34% of cases CRP was lower than the specified level.

Based on these results, changes were made in the next version of the algorithm in 2020, keeping the same laboratory criteria values and keeping the clinical criteria compulsory, while allowing the surgeon to choose one of laboratory or USG criteria, corresponding to the findings of the patient (internal hospital document REK-052/02 from 20.01.2021. English version, the original document is in Latvian) (Fig. 3).

The overall incidence of paediatric AA treated surgically and non-surgically, within the entire Republic of Latvia (AA LV) during 2014 to 2020 and CCUH during 2012 to 2020 is shown in Table 1. The non-surgical treatment of paediatric AA in Latvia was performed mostly in CCUH. The incidence of AcA in CCUH during 2014 to 2020 has shown a tendency to decline, from 38.93% in 2014 to 20.06% in 2020, and this tendency is the more evident during the period from 2017 to 2020 (Fig. 4).

DISCUSSION

Through a century-long history, diagnosis of AA was almost synonymous with appendectomy (Wagner *et al*., 2018). The first major shift in treatment occurred in 1981 with introduction of laparoscopic appendectomy by Kurt Semm, which later became a standard approach technique (Semm, 1983).

Another major shift began recently, with advances in non-invasive treatment of AnA. Based on current available literature, the use of conservative treatment with antibiotics is considered a feasible alternative to surgery in specific situations (Svensson *et al.* 2012; 2015; Huang *et al.* 2017).

New advantages of non-surgical treatment appeared in the context of COVID-19 pandemic: it provides lower risk of staff infection, and IV therapy can be obtained in any inpatient ward. It removes the load on the surgical ward and team — an appendectomy requires contact of two doctors and two nurses with a patient for 40–90 minutes and suspends the operating room for at least two hours after the operation. Surgical stress increases the risk of COVID-19 complications as well as risks associated with intubation, ventilation, anaesthesia.

A non-surgical treatment approach calls for suitable identification of AnA and AcA. Correct classification is important in choosing a suitable treatment pathway and reducing risk of possible postoperative complications. Use of differ-

Table 1. Number of AA patients treated in Latvia (LV) total and Children's Clinical University Hospital in Rīga (CCUH)

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020
AA LV children total			620	625	654	633	653	692	554
AA LV children operated			561	517	547	512	519	556	438
AA CCUH children total	209	215	244	292	329	333	362	382	339
AA CCUH children operated	174	193	200	195	217	204	213	228	222

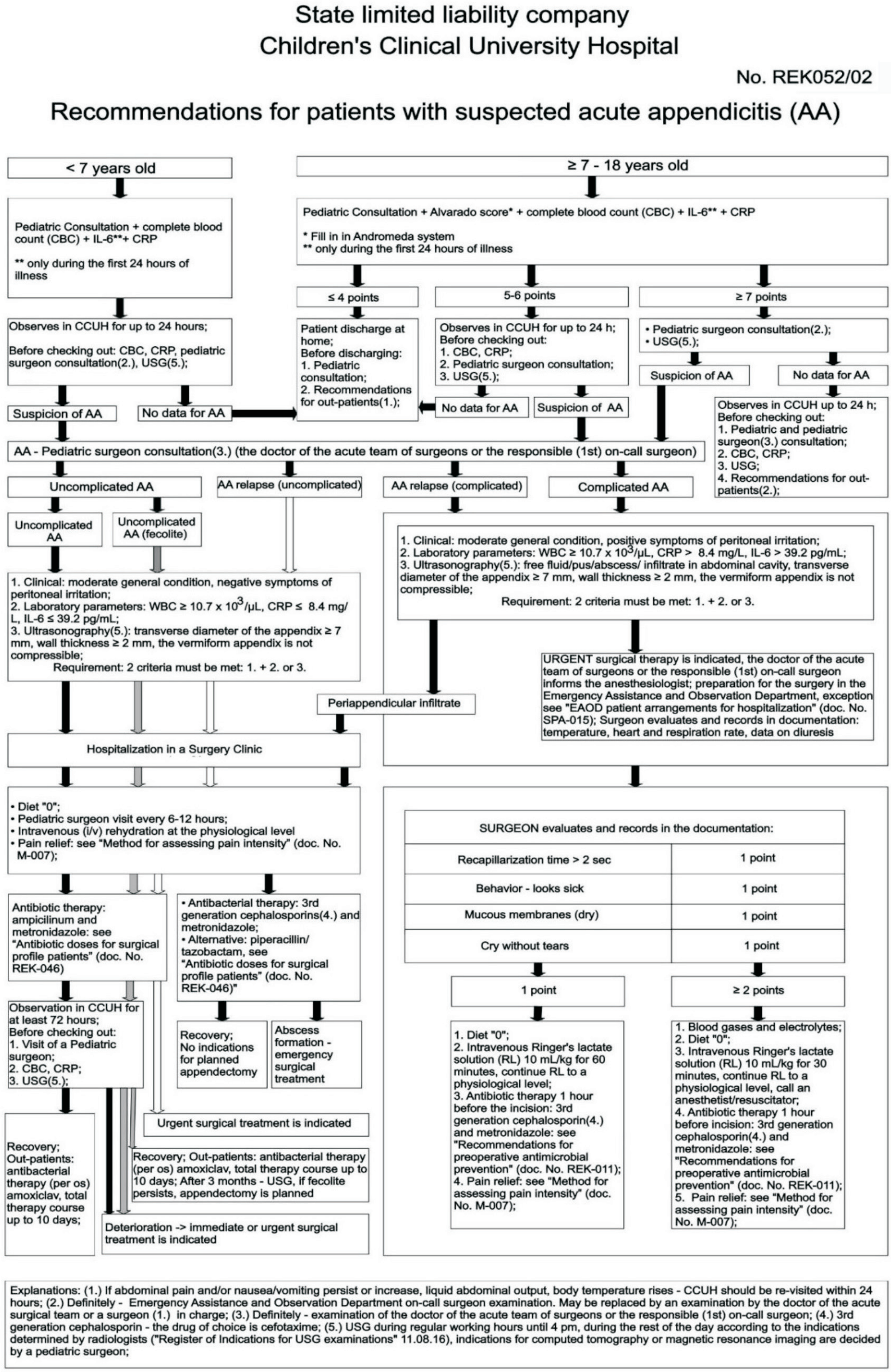

Fig. 3. Recommendations for patients with suspected appendicitis. English version, the original document is in Latvian. (REK-052/02 from 20.01.2021).

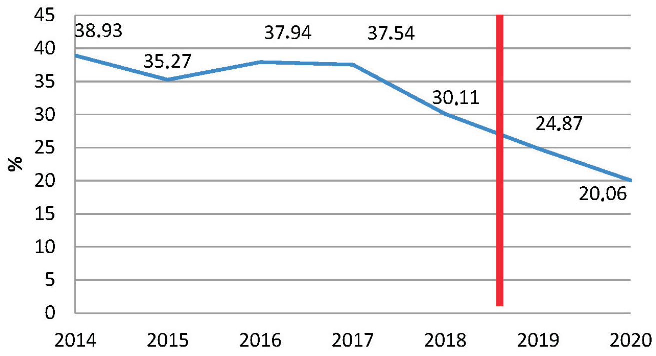

Fig. 4. Incidence of complicated appendicitis in CCUH 2014–2020. The vertical (red) line indicates the time of the first implementation of the AA diagnostic and treatment algorithm.

ent laboratory tests, in addition to clinical evaluation, allowed to develop clinical algorithms with diagnostic scores, the most popular being the Alvarado score and Paediatric Appendicitis Score (PAS) (Samuel 2002). With wider adoption of these scores, in addition to use of imaging studies, as well as several new laboratory tests, diagnosis and treatment of paediatric appendicitis has changed dramatically over the two last decades (Wagner *et al.* 2018).

The search for a single ideal biomarker may seem pointless, but when used in conjunction with medical history and clinical findings, it is feasible to improve the quality of diagnostic techniques, prevent complications and lower overall hospital expenses by reducing unneeded imaging and other procedures. In our previous studies, we investigated whether IL-6, NGAL and LRG1 could distinguish between AnA and AcA (Kakar *et al.* 2020; 2021).

The dynamics of AA treatment results is a very complex process with many influencing factors and therefore difficult to analyse. Considering the overall drop AcA incidence from 38.93% to 20.06% during 2014 to 2020, and in particular from 37.54% to 20.06% between 2017 and 2020 during the implementation period of AA diagnostic and treatment algorithm, we would like to be cautious optimistic that the algorithm had a role in this positive improvement.

The appendicitis diagnostic perspective is an appendicitis diagnostic algorithm development perspective. What makes up an algorithm? 1. Firstly, examination and diagnostic methods used — history, complaints, physical examination, laboratory data, imaging, including development of new, more sensitive tests. Clinical evaluation data such as history of complaints and physical examination are core to initial suspicion of AA.

2. Secondly, selection of diagnostic criteria. Development of a diagnostic algorithm is always associated with a problem: which parameters to include? Which criteria to choose? Why do we set aside a part of them, sometimes a large part? As patients are many and the surgeon's time is limited, we are searching for several, the best and most sensitive criteria to analyse. We need to process the obtained diagnostic criteria values and influencing factors, i.e. what registration and summarising methods should be used, how do we analyse them and how do we make a conclusion, and is it time consuming. Another group of influencing factors are administrative and other parallel reforms, including staff, logistics, competency, education, pandemic, telemedicine, etc.

Algorithms are no longer only in Word, Adobe, or PowerPoint format. ML algorithms as a part of artificial intelligence can build a predictive model, based on sample data used as a "training" (Deo, 2015). As a most frequent cause of acute abdominal surgery in children, appendicitis is a very well-studied nosology. Internationally, there are large amounts of anonymous patient data, involving history, laboratory results and outcome, which are already collected, structured and used for scientific purposes. This data may be compiled together and used as sample data for training of a ML algorithm and later lead to development of a diagnostic tool for AA. A universal AA diagnostic tool may become possible with help of ML algorithms. Although several attempts are already published, use of such technologies in medicine should be a subject of caution (Akmese *et al.*, 2020; Aydin *et al.,* 2020; Marcinkevics *et al.*, 2021). Further studies are necessary to create a feasible tool for surgeons in clinic.

Our own diagnostic marker studies as well as international literature shows that there are diagnostic tools allowing to separate children with AnA and AcA in early stages. It is possible that a new (ML) method can be developed to create diagnostic and treatment algorithms with the capability for larger and faster data processing. The self-improvement quality of such programmes is for further consideration.

CONCLUSION

Since the introduction of non-surgical treatment, the diagnosis of appendicitis in children has become more difficult. The introduction of diagnostic scores and algorithms has standardised and improved the diagnosis of paediatric AA. New diagnostic tests with higher sensitivity and specificity may improve the accuracy of diagnostic algorithms. Measuring multiple effective biomarkers simultaneously may improve the accuracy of diagnostic algorithms and predict the severity of paediatric AA. ML algorithms may be able to process a much larger amount of data and provide a faster conclusion, helping the surgeon make the right decision in diagnosing appendicitis in children and prevent unnecessary surgery.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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BĒRNU VECUMA PACIENTU APENDICĪTA ĶIRURĢISKĀ UN NEĶIRURĢISKĀ ĀRSTĒŠANA: VAI ALGORITMS VAR PALĪDZĒT PROGNOZĒT PERFORĀCIJU?

Interese par bērnu vecuma pacientu akūta apendicīta neķirurģisku ārstēšanu ar antibiotiku terapiju pēdējā laikā pievērsusi uzmanību problēmai atšķirt akūtu nekomplicētu apendicītu (AnA) un akūtu komplicētu apendicītu (AkA) neatliekamās palīdzības nodaļā. Lai izveidotu akūtā apendicīta (AA) diagnostikas un ārstēšanas algoritma sākotnējo versiju, tika analizēti 178 AnA un AkA pacientu ārstēšanas rezultāti Bērnu klīniskajā universitātes slimnīcā Rīgā laika posmā no 2010. līdz 2013. gadam. Algoritmā bija plānots iekļaut klīniskos simptomus un laboratorisko un radioloģisko izmeklējumu rezultātus. Algoritms tika izveidots 2016. gadā un apstiprināts slimnīcas administrācijā. Mēs piedāvājam algoritma atjaunināto 2020. gada versiju. Diagnostikas skalu un algoritmu ieviešana ir standartizējusi un uzlabojusi bērnu AA diagnostiku. Jauni diagnostikas marķieri ar augstāku jutību un specifiskumu var uzlabot diagnostikas algoritmu precizitāti. Vairāku efektīvu biomarķieru vienlaicīga noteikšana var uzlabot diagnostikas algoritmu precizitāti un paredzēt bērnu AA smagumu. Uz mākslīgo intelektu balstītie algoritmi var apstrādāt daudz lielāku datu apjomu un nodrošināt ātrākus secinājumus, palīdzot ķirurgam pieņemt pareizo lēmumu, diagnosticējot AnA un AkA bērniem un novēršot nevajadzīgas operācijas.