



Review

CURRENT TRENDS IN THE USE OF LABORATORY BIOMARKERS IN DIAGNOSTICS IN EMERGENCY ABDOMINAL SURGICAL DISEASES IN CHILDHOOD /REVIEW/

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ABSTRACT

The search for laboratory predictors for early diagnosis of acute appendicitis and making an accurate diagnosis is a goal for modern paediatric surgeons. With the use of various laboratory methods of examination, it is not always possible to make a definitive diagnosis, especially in the presence of complications. Despite the development of medicine at the modern stage, the diagnosis and treatment of acute atypical appendicitis in children remains a current problem in abdominal surgery and is a challenge for modern surgeons. In this literature review, we analyse the inflammatory predictors used individually and in combination during the preoperative algorithm, reflecting the possibility of early treatment of the diagnosis of acute appendicitis.

Keywords: appendicitis, biomarkers, childhood

According to a systematic review by the International Association for the Study of Pain (IASP), symptoms of pain increase with age and are generally significantly higher in girls than in boys (1, 2). Lower socioeconomic status is associated with a higher prevalence of pain, which varies considerably: headache occurs in 6-83% of the population, abdominal pain in 4-53%, back pain in 14-24%. A systematic review of the literature up to 2021 found over 500 publications in which the immunological value of some of the biomarkers for acute abdomen sufficiently significant (3). About 75% of school-age children complain of abdominal pain, 5-10% have an organic cause, and only 1% of children are subject to surgical treatment (4).

The diagnosis of acute appendicitis is one of the most common emergency conditions in children (5). Methods have changed significantly over the years. The first reports of the appendix date back to the ancient Egyptians, who called it the "worm of the intestine". The first anatomical drawings of the

appendicular process were made by Leonardo Da Vinci in 1492. The first Appendectomy was performed by Claudius Amyand in 1723 in London during inguinal herniation surgery, in the sac of which the appendix had grown. For the first time in 1886, Reginald Heber Fitz (6), professor of pathological anatomy at Harvard proposed the term "appendicitis" during a thorough report on the clinical picture of the disease at the First Meeting of the American Medical Association, stating that the treatment consisted in removing the inflamed carrier (7).

In 1889, in his reasoned report to the Surgical Society of New York, Charles McBurney expressed his opinion on early appendectomy. In 1894, McBurney proposed making a small incision in the lower right quadrant of the abdominal wall (8). This approach became the basis for various modifications: the Otto Lanz incision, the Rocky-Davis vertical incision, the modified Fowler-Weir incision and the Rutherford-Morisson incision, and the pararectal incision proposed by Lenander in 1898, as well as the Murphy incision (9). *Treatise on Appendicitis* became a reference book for surgeons for decades spreading throughout Europe. Acute appendicitis is diagnosed in 5% of children with abdominal pain. The incidence in the age group between 0-

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1 year is about 0.086%. The most common cases are between 7 and 14 years – 73.98%. This diagnosis is the most common cause of peritonitis after the age of one (10).

The topographic-anatomical location of the inflamed appendix and other diagnoses are of great importance for the clinical symptoms of acute abdomen. A number of studies on children with perforated appendicitis show that the typical topography is found in 46.65% of patients, and an atypical location - in 53.35%. Atypically in the right hypochondrium it is established in case of malrotation, and in the left abdominal half - in the presence of abnormalities (11).

According to the morphological changes, the appendix is divided into uncomplicated (non-destructive - catarrhal and phlegmonous) and complicated (gangrenous).

There are 4 theories of inflammation of the appendix (12):

1. Lymphohematogenous dissemination-appendicitis in the course of the development of acute respiratory infections.
2. Enterogenic infection.
3. Neurogenic-vascular disorders - the reason is the formed "Cavite close".
4. Obstruction of the lumen of the appendix by stercolith, parasite, foreign body, lymphoid hyperplasia. This leads to oedema of the intestinal wall, with impaired blood flow and ischemia and necrosis (12).

In early childhood, appendicitis is a rare pathology. The difficult diagnosis, atypical course, specificity, surgical treatment and possible complications require knowledge and experience in paediatric surgery.

Over the past few decades, various prognostic systems have been proposed and used in clinical practice: Alvarado, Lintula, MASS, RIPASSA (13). The most commonly applied is the Alvarado scoring system, which was introduced in 1986. It is based on the following symptoms: pain in the ileocecal region of the abdomen; nausea; vomiting; fever; leucocytosis; positive Bloomberg symptom. The most widely used are the Alvarado scoring system and the Paediatric Appendicitis Score (PAS), which have sensitivities between 88 and 90%. They serve to categorize patients in need of additional examinations (14). Mortality in childhood ranges from 0.1 to 1%, with the highest in early childhood, which is related to the peculiarities

of the clinical course, difficulties in diagnosis, as well as the rapid onset of complications and their diversity (14).

Despite the numerous publications over the past 30 years on the diagnostic benefit of these scoring systems in avoiding unnecessary surgeries and reducing the number of invasive and radiation-risk diagnostic procedures, there are still not enough prospective, randomized studies to support their systematic application in children (15). All literature sources dealing with this problem indicate appendicitis as the most common reason for surgical treatment in childhood, as well as the most common cause of peritonitis in children (16).

To prevent complications and to secure timely diagnosis in childhood, it is necessary to improve diagnostic methods. The ability to perform a clinical examination in children, laboratory tests, and imaging studies provide the basis for making the correct diagnosis (16). However, they are not always sufficient to diagnose all cases of acute abdomen in children.

The rapid development, progression, and frequent complications of diseases in children necessitate the search for new objective indicators and a combination of diagnostic methods, used in a sequence that leads to the correct diagnosis as quickly and accurately as possible.

According to the study, acute surgical abdomen in children develops in various diseases, with urgent abdominal diseases not always expressing the symptoms accurately, and diagnosis and treatment are more difficult than in adults. The traditional approach to acute abdominal pain and differentiation between mesenteric lymphadenitis and appendicitis in children is based on a comprehensive history and status, as well as diagnosing the various etiological causes, based on age, location and accompanying symptoms (17).

The search for laboratory predictors for early differentiation of acute appendicitis and the establishment of an accurate diagnosis is a goal for modern paediatric surgeons. With the use of various laboratories, microbiological, immunological and instrumental methods of examination, it is not always possible to make a definitive diagnosis of acute appendicitis, especially when there are complications. Despite the development of medicine at the modern stage, the diagnosis and treatment of

acute appendicitis in children with atypism remains a current problem in abdominal surgery and is a challenge for modern surgeons.

In 2025 and 2026, serum biomarkers for paediatric appendicitis are increasingly being used in addition to clinical evaluations and imaging, helping to reduce unnecessary surgery and radiation exposure. While traditional markers remain standard, new proteins and combination models offer higher specificity for early or complex cases (17).

Standard serum biomarkers

Routine practice continues to rely on a “triple screen” of inflammatory markers, which are highly sensitive when used together.

White blood cell (WBC) count and neutrophils: Elevation (leucocytosis and neutrophilia) is the most common finding. A normal WBC count in 2026 is often used as a powerful tool to rule out appendicitis.

C-reactive protein (CRP)

A late-rising marker that typically peaks 24–48 hours after the onset of illness. While prognostic biomarkers suggest the likely outcome of a patient with the disease, regardless of treatment, predictive biomarkers provide information about whether that patient will respond to a particular agent. Some markers perform both functions. (17)

Surrogate biomarkers

In early-phase studies, surrogate biomarkers may allow the determination of treatment effects at earlier time points than the final clinical endpoint of interest, such as progression-free survival or overall survival (18). Valid surrogate biomarkers have both prognostic and predictive properties, as they demonstrate molecular mechanisms of action. However, the question remains whether the biomarker reliably predicts the effect of treatment on the clinical endpoint.

The study of the nonspecific immune response in children with acute abdomen has led to the concept of the systemic inflammatory response syndrome (SIRS), which is defined as the body's response to an inflammatory process and is characterized by generalized activation of vascular endothelium and polymorph nuclear leukocytes. It is induced by the production of cytokines - tumour necrosis factor (TNF), interleukin-6 (IL-6) and interleukin-10 (18). Diseases that mask acute surgical abdomen

primary and mesenteric lymphadenitis mimics appendicitis or intussusception. It leads to frequent unnecessary appendectomies in children. It is often associated with respiratory infections (18). The viral causes are Epstein-Barr; Adenovirus type 3, Influenza B and Coxsackie B. The bacterial causes are *Streptococci haemolytic*, *Yersinia* and *Salmonella* species (19). The abdominal pain appears suddenly and lasts more than 2-3 hours to one or two days. It is not constant in nature. It is localized mainly low down or around the navel. Characteristic symptoms are: abdominal pain, vomiting, and sometimes diarrhoea, low-grade fever - up to 39-40 degrees, the general condition is affected - weakness, loss of appetite. The Shchetkin-Blumberg symptom is negative; it is positive in inflammatory peritoneal reaction. CT scan reveals enlarged lymph nodes along the course of the mesentery. Laparoscopy is also considered in the differential diagnosis. Mesenteric lymphadenitis is often present in patients with appendicitis and is detected as an intraoperative finding. Inflammatory changes occur in the lymph nodes of the mesentery, the terminal section of the ileum, and in the nodes located in the blind area, the initial part of the ascending colon. The nodes enlarge (diameter 1-3 cm), have a pinkish-grey or white colour, a dense or soft consistency, and foci of necrosis are observed (2, 6). Sometimes micro abscesses in the form of yellowish-whitish dots are found under the serous membrane. In some patients, lymph nodes, fused into conglomerates with a diameter of 5-6 cm, resemble tumour-like formations. Antibiotic preparations are for more severe cases with bacterial infection. The main goal in the treatment of mesenteric lymphadenitis is the rapid evaluation and identification of patients who require urgent surgery. Indications for surgery are: evidence of peritoneal irritation (18, 19).

Kikuchi-Fujimoto disease (19) or histiocytic necrotizing lymphadenopathy of unknown aetiology is a rare, benign, and self-limiting cause of lymphadenopathy, often affecting the cervical nodes and rarely presenting with mesenteric lymphadenopathy. Meckel's diverticulum is a remnant of the omphaloenteric duct, present in up to 2% of the population. It was described by the anatomist J. E. Meckel in 1909. It occurs in about 1.5-2% of all people but often remains undetected throughout life in most and may be an incidental finding during

abdominal surgery. It is mainly a surgical complication in childhood (19, 20). It may contain ectopic cells from gastric mucosa and is located between 20-150 cm from the valve of Bauchin. The clinical picture is presented with painless rectorrhagia (40%), which leads to a significant drop in haemoglobin. It can cause intussusception, volvulus (30%), diverticulitis (20%) or mimic acute appendicitis (19). The similarity in the clinical picture in diverticulitis, perforation and appendicitis is striking. The specificity of the study reaches over 95% while the sensitivity is only 60% according to various authors in the world literature. The disease is most common in children under 3 years of age.

In diagnostic terms, laparotomy or exploratory laparoscopy is discussed to prove or rule out the disease. Some authors (20) report the use of angiography, but in narrow indications – in case of negative scintigraphy, in case of active bleeding from Meckel's diverticulum.

Yersinia enterocolitica plays an important role in the development of painful abdominal pain syndrome in children. The causative agent of intestinal yersiniosis was isolated in 1939 in the USA by R. Gilbert (19,20). The first human diseases caused by *Y. enterocolitica* were registered in 1962-1966 (20).

Abdominal pain is one of the most common and characteristic symptoms of yersiniosis infection. The polymorphism of the clinical manifestations of the disease makes early diagnosis difficult, which in yersiniosis is performed in children with infectious diarrhoea, including those associated with exanthema and hepatosplenomegaly; hepatitis of unknown aetiology, long-term history of abdominal pain of unclear aetiology, surgical pathology (acute appendicitis, mesenteric lymphadenitis). In cases up to 14 years of age with evidence of abdominal pain, *Y. enterocolitica* was the cause of the development of the disease in 54.2% of cases, in 42.4% it was the only etiological agent, in 11.8% - in combination with other pathogens (*Y. pseudotuberculosis*, *campylobacteriosis* and *clostridia*), and in 8.5% - *Y. pseudotuberculosis* (14, 28). Compared with the classic symptoms of gastroenteritis, pseudoappendicitis is more common among older children. The onset of the disease is acute - with abdominal pain, against the background of fever - 38-39 degrees (98%), general disorders (76%), diarrhoea (46%), enlarged liver (12%), polyadenopathy (10%), exanthema (8%), arthralgia (4%). Appropriate

treatment is necessary in the presence of this bacterium. (7, 12). Treatment of Yersiniosis should be carried out exclusively in hospital conditions, as it is a serious disease with numerous complications and a high probability of chronicity (19).

Under the guise of acute surgical abdomen, intestinal infections such as Crohn's disease and UC, which sometimes require surgical treatment, occur. Their frequency has been increasing in recent years. In 1923 г. H. F. Helmholtz made the first publication of ulcerative colitis in children. In 1932, B. B. Crohn, L. Ginsburg, C. B. Oppenheimer described a granulomatous intestinal disease as "terminal ileitis", later called by A. J. Betgen "regional ileitis", and now known as Crohn's disease (20). 10% of all patients with chronic intestinal diseases are children. Crohn's disease is an intestinal inflammation, usually occurring in episodes and probably caused by an autoimmune reaction. An infectious genesis is also discussed. It manifests with lower dyspeptic syndrome. Both sexes are equally affected with a frequency of 1/1000. The Polish surgeon Antoni Lesniowski first described the disease in 1904, and it was named after the American gastroenterologist B. B. Crohn in 1932 (10). In Crohn's disease, healthy and diseased intestinal sections usually alternate. The disease causes lower abdominal cramps with appendicitis-like colic, accompanied by weight loss. In one third of those affected, there is also: pain in the knee or ankle joints, skin changes, fatigue and tiredness, etc. If children suffer from Crohn's disease, the disease may feel different: they may grow more slowly and reach puberty later. Diagnosing the disease requires a sample using colonoscopy with a tissue sample taken. Abdominal ultrasound shows thickened intestinal walls. Magnetic resonance imaging (MRI) is used to unequivocally diagnose Crohn's disease. If the progression is mild, the use of cortisone, mesalazine is indicated, and in intestinal abscesses with wide resection of the pathologically manifested intestine from the underlying disease (14, 15).

Inflammatory markers

Additional inflammatory markers that are recommended in the diagnosis of complicated appendicitis in children are ESR, C-reactive protein, IL-6, IL-8, TNF- α , ferritin, and procalcitonin (PCT) (20). Because early symptoms are nonspecific, the combined use of

biomarkers is recommended for rapid Elevated IL-6 levels are more likely to develop complications (10), while decreasing levels are a good indicator of therapeutic efficacy of the applied antibiotic treatment and have a positive prognostic value in infectious origin of abdominal pain. Repeated assessment of markers with different half-lives helps to confirm the diagnosis and is suitable for monitoring the development of the disease. In the longer term, it helps to assess the duration of antimicrobial therapy. PCT is more likely to help distinguish between viral and bacterial pathological processes, but has limited value in defining the septic process in children compared to adults (48).

The majority of cases are due to acute appendicitis or acute mesenteric lymphadenitis (11, 13). The incidence of acute appendicitis is 25/10,000 paediatric patients per year between the ages of 10 and 17 years in the United States (7, 8). From 7% to 20% of patients diagnosed with OA have clinical suspicion of primary acute mesenteric lymphadenitis (AML). The diagnostic role of some inflammatory variables depends on their aetiology and pathogenesis (22). OA arises from an initial luminal obstruction of the appendix (12, 13) and leads to local oedema as a result of impaired blood and lymphatic flow. Soon the bacterial barrier function of the appendicular epithelium fails and bacterial invasion of the submucosal layers occurs. It is suggested that the serum cytokine response of a patient with OA is different from that of a patient with AML (15-17).

C-reactive protein (CRP) is a commonly used tool in emergency medicine for febrile patients or when an infectious process is suspected. It was discovered in 1930 and classified as an "acute phase protein," an early indicator of the inflammatory state (8, 9). CRP is produced by liver cells in response to cellular injury and inflammation and binds to cellular components that activate phagocytes and macrophages. Interleukin-6 (IL-6) is responsible for CRP synthesis and participation in the acute inflammatory process (13, 20). CRP controls may be useful for the response to the applied therapy. While cytokines are usually considered to be destructive, they also protect the organism when localized. The positive effects of cytokines are being investigated, while their role in the differentiation of surgical emergencies is also being investigated. Information on the relationship between

cytokines and therapeutic strategies for complicated acute surgical illnesses is needed (10). It is concluded that a CRP level >50 mg/l and a leukocyte count $>10.4 \times 10^9$, associated with proinflammatory markers, are important indicators for predicting acute inflammatory diseases in the abdominal cavity, while abdominal ultrasound and CT have significant diagnostic accuracy in urgent abdominal diseases in childhood (21, 22).

Procalcitonin

Of 14 studies of the utility of PCT concentrations in identifying an infectious cause, 13 were positive and only one was negative. The largest study of the use of PCT concentrations, conducted by Baykut et al. (n=400), evaluated these concentrations in surgical patients with infection and showed that they remained elevated until the fourth postoperative day, with a second increase occurring between the fourth and sixth postoperative days (17, 18). In particular, Jensen et al. (n=1200) compared a PCT-directed antibiotic strategy with the standard of care for sepsis and found no difference in outcomes (11, 12). They found that the PCT group had a longer median ICU stay, a higher rate of mechanical ventilation, and a reduced estimated glomerular filtration rate in complicated cases (250, 254). The largest such study, conducted by Bouadma et al. (n=621), demonstrated a 4-day reduction in antibiotic duration when PCT levels were used to guide therapy compared with the study group given the standard of care, without an increase in mortality ($p=0.003$). PCT levels above 0.5 ng/ml were more common in cases of perforated or necrotizing appendicitis than in uncomplicated appendicitis. The sensitivity (46%), specificity (90%), and predictive value of CRP suggest that procalcitonin is a better indicator of severe appendicitis (perforation or peritonitis). An elevated PCT level alone may be helpful as an adjunct to available clinical and laboratory data (8, 13). In children, only the combination of all diagnostic parameters has a high diagnostic value.

Ferritin

Ferritin is a protein that stores iron and can be abnormally elevated in a wide range of disease states, including malignancy, infection, inflammation, chronic liver disease, and other conditions. This has led to the association of elevated ferritin levels with surgical disease, although the expected diagnostic relevance of elevated ferritin levels in determining a specific

diagnosis can be challenging. The presentation of these conditions can be easily confused with other conditions such as sepsis with multiple organ failure or malignancy (8, 9, 11). The serum ferritin protein is considered benign, but when bound to iron in a compound it is highly toxic. The fact that serum ferritin levels can correlate with disease and with body iron stores, as well as with other phenotypic features in erythrocyte morphology, suggests that ferritin levels may be elevated in some patients with iron deficiency anaemia. This serves to explain a number of apparent paradoxes associated with serum ferritin levels, such as: 1) it can be a biomarker of cellular damage 2) a biomarker of free radical formation 3) it indicates the presence and/or severity of a number of diseases. It is likely that serum ferritin is mainly increased when cells are stressed and damaged (12, 19, 23). This is because serum ferritin levels can increase significantly in response to inflammation and/or various diseases (16, 17). Serum ferritin appears to be derived from damaged cells, but it contains iron, so it has actually lost or released most of its normal content (16). CRP and ferritin levels can be easily integrated into daily clinical practice in children. They are widely available biomarkers and have wide and diverse applications in the clinical world of paediatrics. Based on the available scientific evidence, it is important to note that biomarkers cannot replace clinical decision-making and that the evidence is complementary to clinical practice. This evidence is based on a review of the literature (17). CRP and ferritin levels cannot be used in isolation and are only appropriate in clinical situations. Given the extensive literature on elevated CRP and ferritin levels in paediatric practice and the availability of tests in standard clinical laboratories, they can be easily and readily integrated into daily routine (16, 19, 20). Elevated CRP levels in the presence of fever may indicate infection, particularly in patients with an exacerbation of inflammatory bowel disease or pancreatitis and may also be monitored for response to treatment in disease (17-19). The combination of elevated CRP and ferritin levels may indicate severe inflammation and impending morbidity. These markers in combination can guide treatment in sepsis (SCID) and are particularly useful when monitored for signs of response. Cytokines are a large group of proteins, peptides and glycoproteins that control the "behaviour" of other cells and themselves (Szczeny TJ, 2007).

Acute inflammatory reactions induce the production of IL-6 and are associated with infections and various tissue damage macrophages, B- and T-lymphocytes. Necessary for the immune system, cytokines modulate the balance between the humoral and cell-mediated immune response through special receptors (12, 22). They regulate the growth and maturation of cell populations, suppress or enhance the action of other cytokines (13, 16).

Classification

Interleukins are cytokines that are produced by lymphocytes. The term means "means of communication". A large part of interleukins in some rare diseases shows that in case of deficiency, autoimmune diseases or immune deficiency occur.

Lymphokines are produced by lymphocytes and play a major role in protecting the body from neoplastic transformations.

Chemokines are cytokines that mediate intercellular contacts. They can be classified functionally into three types (14, 16):

Type 1 - enhancing immune response - TNF- α ;

Type 2 - improving antigenic immune response - IL-10;

Type 3 - cytokines with proinflammatory function IL-6, IL-12, TNF- α .

Tumour necrosis factor alpha (TNF- α). Its central role is to synthesize a transmembrane cytoplasmic and extracellular protein. It accumulates intracellularly and affects the virus-infected cell. Its feedback activates or inhibits the production of both TNF- α itself and biologically active cytokines (16).

Interleukin 6 (IL-6) is a glycosylated cytokine with a significant role in the acute phase of inflammation. IL-6 is significantly increased during surgery. Its soluble forms activate proteolytic enzymes and suppress the function of hepatocytes, monocytes and lymphocytes. Interleukin-6 (IL-6) has been reported to be one of the most easily measurable cytokines and its levels in the blood of patients with acute appendicitis are above 1500 pg/ml, which is consistent with previously reported values. On the other hand, cytokine-related genetic polymorphisms may influence cytokine production or affect their development in appendectomy (14, 15). Therefore, the genetic aspect of cytokine biology should also be considered in future studies (20, 21). At certain

levels, IL-6 has a protective mechanism, but otherwise it is a proinflammatory marker (20, 21). Therefore, IL-6 is used as a marker in patients in intensive care and as a prognostic factor for the outcome of these conditions (37, 34). A decrease in IL-6 from the second day of antibiotic treatment is a marker for the effectiveness of treatment and is a positive prognostic sign in patients with infectious aetiology (18, 19).

Interleukin 10 is secreted by activated hematopoietic liver cells. Its biological activity initiates a “signalling cascade” of interaction on lymphocytes, NK cells, macrophages, monocytes, intestinal epithelial cells, astrocytes, etc. Its immunomodulatory effect includes:

- “positive effect”, supporting phagocytosis and antigen presentation
- “negative effect”, influencing Th1-helper lymphocytes, which suppress the proinflammatory response (17, 19).

The cytokine profile helps in prognostic assessment, as well as changes after surgery. (17, 18). Increased levels of TNF- α and IL-6 correlate with the occurrence of intussusception, and the reduction of these levels by inhibition of cyclooxygenase (COX) by indomethacin prevents their formation (16, 19).

ELISA determination of immunological parameters IL-6, IL-10, TNF- α , studied with Diaclone tests, according to the methodological guidelines based on the “double antibody sandwich”. Samples are read at an optical density of 450 nanometres by ELISA Reader, model Stat Fax 2100, manufactured by Awareness Technology Inc (15,16). Data were prospectively collected from 102 consecutive patients with right iliac fossa pain. Laparotomy was performed for suspected acute appendicitis in 55 of the 102 patients, of whom 49 patients had appendicitis, 6 patients had no appendicitis (NA), and the remaining 47 patients had nonspecific abdominal pain (NSAP) and did not undergo surgery. Among those with appendicitis, 31 had acute appendicitis (AA), 8 had gangrenous appendicitis (GA), and 10 had perforated appendix (PA). The mean WBC and CRP (SEM) values were significantly different in the AA, GA, and PA groups compared with the NSAP and NA groups ($P < 0.05$). However, the mean IL-6 levels were significantly different only in the PA group from the other

groups ($P < 0.05$). The sensitivity and specificity of serum CRP measurements were calculated to be 96% and 87%, respectively, while for IL-6 levels for the diagnosis of acute appendicitis they were 33% and 83%.

The incidence of recurrence in acute appendicitis treated nonoperatively varies across studies. Few studies have adequately evaluated the management of these patients with recurrent appendicitis. We aimed to investigate the incidence of recurrence and the management of patients with acute appendicitis who were initially treated nonoperatively. Patients identified in the National Health Insurance Hospitals in London database who were hospitalised for acute appendicitis for the first time between 2000 and 2010 and who received nonsurgical treatment were included. Recurrence and its treatment were recorded. The data were analysed to assess risk factors for recurrence and factors that influenced the management of recurrent appendicitis (20,21). Among 239 821 patients hospitalised with acute appendicitis for the first time, 12 235 (5.1%) patients were treated nonoperatively. Of these, 864 (7.1%) had a recurrence during a median follow-up of 6.5 years. Appendectomy was performed by open and laparoscopic approaches in 483 (55.9%) and 258 (29.9%) patients, respectively (22, 23). The remaining 123 (14.2%) patients were treated nonsurgical again. Recurrence was independently associated with younger age, male gender, percutaneous abscess drainage, and admission to a medical centre by multivariate analysis. In addition, age <18 years, a (CCI) <2 , admission to a medical centre, and longer time to recurrence were correlated with the use of laparoscopy to treat recurrence. Neither the type of appendicitis, percutaneous abscess drainage, nor the length of the first hospital stay influenced the choice of surgical approach. In conclusion, laparoscopic appendectomy can be performed in cases of recurrent appendicitis, and its use may not be related to the severity of the previous appendicitis (24-26).

CONCLUSION

The use of biomarkers in clinical trials serves a number of practical applications. Screening patients for eligibility, stratification into subgroups, monitoring treatment responses, and correlative studies for future reference.

Many trial protocols involve the collection of additional samples that are not necessarily used

for the specific trial, but rather for the purpose of designing future trials. Also, trials may be designed with the goal of reanalysing data later in light of new information revealed by further studies (e.g., new markers or genes).

Ideal markers that require minimally invasive sampling are reliable (i.e., internally consistent), inexpensive, highly sensitive and specific. Among other applications, biomarkers can serve as indicators warning of the need for early termination of the trial if the biological effect is below the maximum tolerated dose.

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