International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 7, Issue 2, pp: (63-92), Month: October 2019 - March 2020, Available at: www.researchpublish.com

CURRENT TRENDS OF ACUTE APPENDICITIS IN AFRICA: A CLINICAL REVIEW

[1]Alegbeleye Bamidele Johnson

[1]Department of Surgery,

St Elizabeth Catholic General Hospital, Shisong;

P.O Box 8, Kumbo-Nso, Cameroon

Abstract: **Appendicitis remains an intriguing disease entity, and there are severe unresolved postulations in the mind of clinicians worldwide. The primary concern is the likelihood of progression to perforation and the potential implications in contemporary African settings. A systematic review study has not been carried out for appendicitis research in Africa.**

***Aim*: To examine the literature critically and to present an update on current controversies on acute appendicitis with some particular emphasis on contemporary African settings.**

***Method*: A review of publications obtained from Medline search, medical libraries, and Google.**

***Results*: Twenty-four audits were included in the quantitative analysis. Some were excluded from the subgroup analyses. Negative appendicectomies occurred at a rate of 18 % (488/3 862). Women were more likely to have a negative appendicectomy than men (32% versus 12%, p < 0.02). The perforation rate for appendicectomy patients was 28% (880/3 480), and the mortality rate was 3% (522/3 454). The current global research efforts are focused on the role of 'antibiotics' in the treatment and genetics of acute appendicitis**

***Conclusion*: Appendicitis remains a significant health challenge in Africa due to the attendant high incidence of perforations and complications. The current trend suggests that a nonsurgical, antibiotic approach in the treatment of uncomplicated appendicitis may be beneficial but remains 'controversial' with very low acceptance in Africa. This article reviews the current 'state of the art' in the evaluation and management of appendicitis that is leading to stratified care for patients, mainly in contemporary African settings.**

Keywords: **Appendicitis; Appendicectomy; Pathophysiology; Contemporary African Setting; Trends.**

1. INTRODUCTION

Acute appendicitis (AA) refers to severe inflammation of the vermiform appendix, most likely due to obstruction of the lumen of the appendix from various causes [1]. Appendicitis remains an intriguing disease entity. Despite years of extensive research, there are severe unresolved postulations in the mind of clinicians worldwide, addressed in this meta-analysis. From Cape Town in southern Africa to Cairo city in northern Africa, the disease attracts attention to date. Robert B. Sanda remains resolute on why there are several unresolved postulations on appendicitis, despite years of extensive research?" [1].

Saidi HS *et al.* submitted that "although, AA is one of the commonest surgical emergencies, but appears to have a relatively lower incidence in Africa" [2]. The major concern in patients with the ongoing -disease course in our contemporary African setting is that the inflamed appendix often eventually progresses to wall rupture because it is left untreated [3]. Other authors submitted that "given the likelihood of progression to perforation and potential health gains

with early treatment, rates of rupture have been advocated as a public health measure of access to medical care" [4, 5]. In such African settings, therefore, "audits of appendicitis have consistently demonstrated higher perforation and complication rates compared to those in developed countries [4-8]. These higher incidences of perforated appendicitis have been attributed to longer delays of presentation to hospitals [9], socioeconomic disadvantage [10], and health system constraints [4] common to Africa and developing regions" [4-10].

Furthermore, Yang *et al.* reported that "the generally accepted and definitive cure for the disease is surgical removal of the appendix via appendicectomy" [11]. However, antibiotics are now being advocated as first-line therapy, mainly in western countries, to an extent [12]. This use of antibiotics remains to date highly controversial and generally unacceptable in contemporary African settings [12]. "The overall situation in most African countries is completely different, including political, social, economic and health indices which are unique from these other western settings; therefore, the generalizability of these studies may be somewhat limited"[12, 13]. Accordingly, "appendectomy is one of the most commonly performed surgical procedures and represents a heavy burden on modern health systems [12, 13]. Notwithstanding the extensive concerted effort on appendicitis studies even in Africa, limited understanding of the etiology and absence of reliable discriminators for disease severity still exist. Consequently, limited clinical research has produced uncertainty about best practice, with prevailing international variation in delivery and, as a result, variation in the outcome" [12, 13].

2. OBJECTIVE

We aim to provide an up-to-date critical review of the literature into the current controversies in the etiopathogenesis, diagnosis, and clinical management of acute appendicitis with some particular emphasis on the contemporary African settings.

3. MATERIALS AND METHODS

All peer-reviewed, published, original research studies in which appendicitis was addressed in Africa were eligible for inclusion in this review. We identified relevant articles to date using a manual library search, journal publications on the subject; our searches also include Medline, Embase, and Cochrane Library as well as ClinicalTrials.gov (01/01/2000-01/06/2019) for current trials in acute appendicitis. Research themes of relevant references were collected and analyzed. Consequently, information relating to the epidemiology, etiopathogenesis, clinical presentation, investigations, management, and complications was extracted from the materials.

4. RESULTS

4.1 HISTORICAL BACKGROUND

In his drawings in 1492, Leonardo Da Vinci demonstrated the vermiform appendix. Later on, "the first descriptions of the appendix in the 16th century were made by Vesalius and DaCarpi" [14, 15]. "Further progress on this work by Lorenz Heister was registered at the beginning of the 18th century, who then speculated that the appendix might be the reason for inflammation in the right lower region of the abdomen. Consequently, the first known appendectomy (AE) was done by Claudius Amyand, who operated on an 11-year old boy with a right scrotal hernia and perforated appendix in the hernia sac" [15]. In 1891, McBurney, in his paper, also emphasized the importance of early emergency appendicectomy and "first described the muscle-splitting incision that bears his name and which is commonly used today" [16]. Since the end of the 19th century, AE has become one of the frequent operations in clinical practice. An enormous number of books and articles about the management of AA have been published since that period [15]. Kurt Semm did the first laparoscopic AE in 1983 [17]. He concluded that a laparoscopic technique provides faster recovery, a lower infection complication rate, and a better cosmetic result after the operation [17]. Moreover, spontaneous resolution and conservative treatment of AA has been a subject of debate [18]. In 1956, Coldrey *et al.* reported on antibiotic treatment of AA [19]. Recently, several studies have been published about non- operative treatment of AA (20, 21). Erasmus published the first audit for appendicitis in Africa- South Africa in 1939, in his study "to assess the nature of the disease and its impact on different racial groups" [11, 22]. "Erasmus formed two major conclusions when contrasting the disease between ethnic groups, namely: i) There were a significantly higher incidence rates of appendicitis in white patients than that in black patients, ii) but, with significantly less morbidity and mortality. Consequentially, these two observations formed the groundwork and direction for the further study of appendicitis in Africa over the next 70 years in general" [22].

4.2 EPIDEMIOLOGY

4.2.1 Incidence

Several works of literature submitted that "the true incidence of AA in most developing African countries like Cameroon, Ghana, Nigeria, etc., is largely unknown due to poor medical record-keeping and unreliable population census" [23-25]. Similarly, "estimates of population incidence of AA in countries like Ghana [26], Madagascar [27], Central African Republic [28] and Ethiopia [29] have relied on small population counts. AA shows a stark difference in incidence rate between developed and developing countries that is more than ten folds in some instances, such as between Finland and Thailand and between Spain and Ghana" [30-32]. The available reports from Nigeria, Cameroon, Ghana, and South Africa showed "the incidence rate of 2.1-10.8 per 100,000 per annum, and these figures are remarkable for being the lowest incidence rate we can find in world literature" [26, 33, 34]. "What can account for the huge difference in the annual incidence rates of appendicitis between European and African countries as represented by Ireland (174/100,000) and Ghana (18/100,000)?" [26, 33, 34].

Walker *et al.* in 1989 queried that, "why is the incidence rate higher for white South African children (215-395 per 100,000) in comparison to black children (5-19 per 100,000) in the same country? [35]. Why does appendicitis run in families? [36,37]. Why is the rate lower in girls compared to age-matched boys?" [38].

In a related development, several other reports have noted the significant seasonal variation in the incidence of AA [39-41]. "Even in the same countries, appendicitis tends to show longer-term temporal difference in incidence that has been thought to be related to changes in social indices like quality of housing and sanitation as exemplified by a standardized incidence rates of 570 per 100,000 in 1955 and 370 per 100,000 in 1987 occurring in Italy and also a standardized incidence rate of 652 per 100,000 in 1970 and 164 per 100,000 in 1999 in Greece" [42, 43].

4.2.1.1 *Trends in Incidence*

Some authors suggested that "there have been reports of increasing incidence of AA in African countries by in the last few decades; surprisingly, this contrasts with the common findings of reducing incidence in a larger part of the developed world" [44-46]. "Several reasons could be adduced to this, ranging from the very youthful African population and changing to the Western lifestyle [45, 46]. The increasing number of 'fast food' restaurants where mainly high-carbohydrate, low-fiber diets, confectionaries, and sweets are served could have contributed to the increase in the incidence [47-49]. Large consumption of sweets and sugary foods has been implicated by some authors" [47- 49].

Despite these "significant changes in the overall incidence rate of AA, the rate of perforated appendicitis has shown different tendencies. Only minor changes or a reverse trend have

been seen in incidences of perforated appendicitis compared to non-perforated AA

[50-52]. As a result of the preceding, the incidence of AA in some countries has been decreasing, and in some other countries increasing, the reasons for these changing trends remain a subject of vivid debate" [50-52].

4.2.2 Age differences

Al-Omran *et al.* in their study suggested that "one of the most striking epidemiologic features of AA is the age-specific incidence with associated marked variations; interestingly, the peak incidence for AA usually occurs in the 2nd or 3rd decade of life, and the disease declined with age increment and was lowest in young children and older adults" [40]. Moreover, the age distribution in several African countries follows the same trend compared to that in developed countries [53-55]. The rate for perforated appendicitis and complications after the surgery for AA is found to be higher at both ends of the age groups [55-58]. Interestingly, Andersson *et al.* found that variation in the incidence between the age groups was seen mainly among non-perforated appendicitis, while for a perforated disease, it was almost stable at all ages [59].

4.2.3 Gender differences

The rates for AA are higher for men than for women, based on reports from most studies and "the male/female ratio varies from 1.1 to 3.2; and this observation is consistent with the findings of other African studies" [59-62]. The main difference has been noticed in age groups under 30 years old [59-62]. "The lifetime risk of undergoing an AE is 12% for men and 23% for women [58]. The probability of negative appendicitis is over two times higher for women than that for men[60]; moreover, the possibility for perforated appendicitis has been reported to be 0.82 times lower in women than in men" [59].

4.2.4 Geographic variation

Economic and public health factors may likely explain the different incidences of AA found across various geographic regions, rather than by environmental factors [61-63]. "Geographical differences are reported, with lifetime risks for AA of 16% in South Korea [55], 9.0% in the USA [56], and 1.8% in Africa [26]. A declining incidence has been reported over the last decade; on the other hand, geographical differences show a higher incidence in Asia than in the U.S. and the lowest incidence in Africa" [30, 50, 53, 55, & 64]. "Ours is an environment where public health indices like sanitation, sewage disposal, quality of water supply are such that water-borne gastrointestinal diseases like poliomyelitis, hepatitis viruses, shigellosis, cholera, typhoid enteritis, giardiasis, and amoebiasis are prevalent [65, 66]. Endemic poverty and a lack of strict compliance with sanitary standards enforceable by public health authorities play contributory roles" [65, 66]. It has been suggested that "the endemicity of these water-borne gastrointestinal pathogens listed above in the water supply of children living in developing countries makes the frontline immune systems in the gastrointestinal systems tolerant of many less potent pathogens. This hypothesis may explain why in both Nigeria and Ghana, for example, typhoid perforation of the ileum vies with appendicitis for supremacy in incidence" [65, 66].

4.2.5 Seasonal variation

"The peak incidence of AA occurring during the summer months has also been noted [30, 50, 53, 55, 64, & 67]. Seasonal variations in AA are reported in several studies across many regions. Most studies report a summer peak with a winter nadir; USA [39], Canada [40], Italy [41], Israel [68], and Russia [69]. One study in northern Saudi Arabia showed a winter low but a spring peak which coincides with the sandstorm season characterized by the rise in infections and allergic conditions of the upper respiratory tract which concur with earlier studies on the spread of allergens during this season in Saudi Arabia" [23, 70-73]. According to Ashley *et al*., "a similar seasonal variation to ours was reported four decades earlier in Britain [24]. Our observation of an association between AA and air pollution was corroborated by Kaplan *et al.* in their 2009 study from Western Canada [74]. The significance of these observations is underscored by pathological studies linking AA to eosinophilic degranulation" [75, 76]. "Seasonal variation of AA with its peak associated with a season characterized by high ambient pollen and other phyto-allergens or sandstorm is an observation that can neither be explained by diet nor fecaliths but may have a bearing on immune modulation playing a role" [75, 76].

4.2.6 Environmental and genetic factors

As reported by Sadr Azodi *et al.* in 2009, they strongly support the view that the causative factors relating to AA are wholly environmental, and most of these environmental and genetic factors are probably still under investigation [77]. The above findings were also corroborated by Ergul in 2007 [78]; "who identified a three-fold risk of AA had been shown in patients with a family history of AA, which also suggests the presence of genetic factors.

Although AA has been identified since ancient history, its true purpose is yet to be discovered. Moreover, AE is associated with a reduced risk of ulcerative colitis and an increased risk of Clostridium difficile colitis, and hence its role has been suggested to be related to the immune balance of the bowel" [11, 79]. "The probable function of the vermiform appendix in this 'controversial' immune role is to act as a container for healthy bacteria of the bowel or indeed as a lymphoid organ" [80].

4.3 ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of AA is surprisingly not fully understood. According to Adehossi *et al.*, the commonly suggested etiology for AA is the theory of luminal obstruction. Although, many different reasons can contribute to the development of the disease; but, "obstruction can be caused by an appendicolith (a fecalith, stoned feces in the lumen of the appendix), and others may include intra-intestinal material, a tumor or parasites" [81, 82]. Swischuk *et al.* in 2015 confirmed that "lymphoid hyperplasia has been suggested to be the underlying cause of purulent appendicitis if a fecalith (or other obstructing processes) is not present, and the cause of the hyperplasia being unknown" [83].

4.3.1 Mechanical obstruction

Obstruction of the appendix lumen may result from a variety of causes, including fecolith, lymphoid hyperplasia, primary and metastatic tumors, parasites and foreign bodies, etc.

4.3.1.1 *Fecolith*

Fecolith, as one of the most usual causative agents in mechanical obstruction, was "first hypothesized by Rendle Short in 1920, which was spurred by the observation of an upsurge of appendicitis in Britain at the beginning of the twentieth

century" [84]. He observed "a causal relationship of AA with a low cellulose content of imported food. Subsequently, another British surgeon working in East and Southern Africa in the early 1970s, Denis Burkitt, built on this hypothesis. He submitted that the high fiber content of the diet of Africans allows for the low transit time of gastrointestinal contents and softer consistency of stool, which assuaged the need for straining at defecation" [85-87].

"The mechanical hypothesis implicates two factors in the etiology of AA, which consists essentially of fecaliths and high intra-colonic pressure. In the first instance, Burkitt and his team demonstrated a significant difference in the incidence of fecaliths in appendicitis and non-pathological specimens of the vermiform appendix in a comparative study of patients in Toronto and Johannesburg" [88]. Several other authors worldwide have corroborated these findings. The incidence of fecolith is 11-52% in patients operated on for AA [89-92].

Nevertheless, fecoliths are also present in a non-inflamed appendix in 32% of cases of white people and 4% in African people. In the same study, the incidence of fecolith in an AA case was 52% and 23% in white and African blacks, respectively [88]. Interestingly, Ramdass *et al.* showed that the incidence of fecolith is almost the same in an inflamed as well as in a non- inflamed appendix [93]. In a study from China, the incidence of the fecolith was 9.6% in normal appendices [94]. After the occlusion occurs, appendiceal intraluminal high pressure might turn to obstruct material back into the caecum, and evidence for a proper cause of AA is missing [15]. Consequently, it is possible, therefore, that the real incidence of fecoliths in cases of AA is much higher.

4.3.1.2 *Lymphoid hyperplasia*

Lymphoid hyperplasia can develop due to an immune reaction to immunological challenges (also called lymphadenitis), mostly viruses, and can occur anywhere in the bowel, but it is often seen in the terminal ileum and appendix [95]. This can cause AA, obstruction, or be the reason for chronic right lower quadrant pain (RLQP) [96, 97]. "The significant increase in lymphoid follicles in young adults and their gradual disappearance with age suggests a pathogenic role for lymphoid tissue in the development of AA" [15, 98]. However, lymphoid hyperplasia without any infection can be found from a histo-pathologically normal appendix as well [94, 97].

4.3.1.3 *Tumors*

Primary tumors of the appendix are a relatively rare cause of AA. An incidence of appendiceal tumors varies between the 0.4-1.7percent for all appendectomies [99-101]. A minority of appendiceal tumors has been diagnosed preoperatively, and in most cases, diagnosis has been done intra-operatively or by a pathologist [99, 102].

Carcinoid tumor is the most common primary appendiceal neoplasm. The overall incidence of appendiceal carcinoid tumors varies from 0.4% to 1%. Within the gastrointestinal tract, the occurrence of carcinoid tumors of the appendix is 1.7% [103], and it accounts for up to two-thirds of all appendiceal tumors [104, 105]. "Primary adenocarcinoma of the appendix is rare with an incidence of 0.08-0.2% of all appendectomies and accounts for 4-6% of primary malignant appendiceal neoplasms" [99]. Nonetheless, the malignancy risk for patients undergoing interval appendectomy (IA) after conservative treatment of complicated appendicitis is 28-29% [106].

Mucocele of the appendix is characterized by dilatation of the obstructed appendicular lumen by mucinous secretions. It is encountered in 0.1-0.4% of all appendectomies with a female predominance [107, 108]. "The etiology can be either benign (simple mucocele or retention cyst, mucosal hyperplasia, *mucinous cystadenoma*), or malignant (*mucinous*

cystadenocarcinoma)" [109]. Of all mucoceles, 23-50% are incidental findings at surgery and should be carefully removed to prevent perforation, peritoneal contamination, and the development of *pseudomyxoma peritonei* [107]. The extent of resection depends on the histology of the mucocele [108].

4.3.2 Infection

Several specific infections with viruses, bacteria, and parasites have been linked to AA.

4.3.2.1 *Viral infection*: Studies are evaluating the role of viral etiology of appendicitis [110]. Moreover, seasonal outbreaks of lymphotropic enteric viral or microbial infections might be the reason for a seasonal variation in AA. Although some evidence has been found [111], the level of proof is weak, and further studies are needed to confirm the connection.

4.3.2.2 *Bacterial infection:* Several researchers have made giant strides at elucidating the microbiome in AA; this is so because few authors opined that "the appendix may serve as a microbial reservoir for repopulating the gastrointestinal

tract in times of necessity, but available data on this fact is limited. The bacterial growth in removed inflamed appendices consists of a mix of aerobic and anaerobic bacteria, most frequently dominated by *Escherichia coli* and *Bacteroides fragilis.* A small yet novel study using next-generation sequencing found a larger number and greater variation of (up to 15) bacterial phylae than expected in patients with AA [112]. Notably, the presence of *Fusobacterium* appeared to correspond to disease severity (including the risk of perforation), corroborating findings from archival material in two other studies" [113, 114].

Other authors suggested that "the evidence of a role in immune balance comes from epidemiological studies demonstrating a reduced risk of developing ulcerative colitis after AE, with a slightly increased risk of Crohn's disease [115]. Further, AE has been associated with increased risk of future severe *Clostridium difficile* colitis requiring colectomy [116]; Whether these findings point to alterations of the human gut microbiome or to the removal of a lymphoid organ with a role in human immune function is currently unknown" [117]. Tubercular appendicitis is quite a rare entity and found mostly in developing countries, and in most cases, the appendix is involved by local extension of ileocaecal or genital tuberculosis [118]. Overall, "one can conclude that bacteria from the appendix may be important pathogens in AA and its complications, but their initial role in the etiology of AA remains uncertain" [118].

4.3.2.3 ***Parasitic infection:*** Parasitic infestation of the appendix is quite rare in most other world regions'. However, in the developing world, AA has also been closely related to the high frequency of occurrence of intestinal parasites. "The commonly associated parasites are *Schistosoma mansoni*, *Schistosoma haematobium*, *Enterobius vermicularis*, *Ascaris lumbricoides*, *Entamoeba histolytica*, and pin-worm, among others. Badmus *et al.* [119], and Adebamowo *et al.* [120] have reported some cases of schistosomal appendicitis from southwestern Nigeria." Similar findings have been reported mostly in Southern Europe studies, which revealed the most common helminth as *Enterobius vermicularis* or pinworms, and can be found in 4-28% of children worldwide, followed by amoebae, *Ascaris*, *trichuriasis*, and *taeniae* [121]. In a study from South Africa, the parasitic infection was found in 8.6% of cases with AA [122]. "A majority of studies report a lower incidence of inflammatory changes or chronic infection of the appendix, in patients with appendiceal pinworms" [121, 123]. Currently, the actual role of parasites as a cause of AA has been controversial. They are found in uninflamed and histologically normal appendices, and their role in the pathogenesis of AA is unclear [121, 123].

4.3.3 Hygiene habits

Barker and his team suggested that "the observed increase in the incidence of AA at the end of the 19th century was a consequence of the adoption of a housing policy in Britain and Ireland which enforced the provision of safe drinking water and sanitary measures like sewage and waste disposal" [61, 62]. In comparison, in recent years with urbanization and increasing prosperity, the energy intake of Africans has risen, and fat intake has increased considerably. At the same time, their fiber intake has fallen to a level that is the same or even lower than that in many western populations, but the incidence rates of AA have remained unchanged [124, 125]. In addition, "Lee *et al.* in 2010 reported that the incidence of the AA was as high as 227/100'000 inhabitants during the study time of 2005-2007 years in Korea, where food has high fiber content" [55]. Clearly, in such a context, the level of fiber intake no longer correlates with the very low occurrence of the disease: since with similar low fiber intake, the disease remains very infrequent in urban Africans but is common and variable in white populations in developed countries [55, 126].

"In the 1980s, Barker *et al.,* advanced a hygiene hypothesis, attributing the rise in appendicitis to improvements in water supplies and sewage disposal in Britain" [61, 62]. They hypothesized that "these improvements greatly reduced the exposure of infants to enteric organisms, which in turn altered children's response to later virus infections, such that they now triggered AA. The virus did this by causing appendiceal lymphoid hyperplasia, which occluded the appendix leading to microbial infection" [61, 62]. In summary, there is no current consensus about the strong evidence between hygiene and the incidence of AA [61, 62].

4.4 CLASSIFICATIONS OF APPENDICITIS

In a typical clinical scenario, established evidence showed that "appendicitis does not, in most cases, lead to necrosis and perforation. On the contrary, there is evidence of spontaneous recovery from AA. These facts support the theory of at least two courses of the inflammatory process – **A**) Self-limiting mild inflammation with spontaneous recovery or response to antibiotic treatment alone and **B**) The acute perforating severe pathway" [51, 58, 59, 127].

Based on the above theory, AA is commonly classified as **a**) uncomplicated acute appendicitis or **b**) complicated acute appendicitis.

4.4.1 Uncomplicated acute appendicitis: "This involves none of the previous and represents the early phase of the disease or the milder inflammation type. Some studies categorize the mere existence of an appendicolith as a sign of complicated appendicitis, but in this review, the involvement of an appendicolith is not categorized as complicated appendicitis unless otherwise stated" [51, 58, 59, 127].

4.4.2 Complicated acute appendicitis: In most studies, "this type is considered to include appendicitis with perforation, necrosis of the appendicular wall, appendicular abscess, and appendicitis with an appendicolith, which is further subdivided into two (2) categories including: (i) Appendix abscess, where there was on admission a localized abscess in the right iliac fossa. (ii)Generalized peritonitis, where the patient had generalized peritonitis but secondary to acute appendicitis, Classification into perforated appendicitis, and non-perforated appendicitis is used in several studies, but, for clinical use, this division may be too concise" [58, 127, 128].

"Classification, according to the severity of inflammation, has also been presented.

The disease severity score for appendicitis is a five-step grading; 1=inflamed, 2=gangrenous, 3=perforated with free fluid, 4=perforated with an abscess, and 5=perforated with generalized peritonitis" [58, 129].

This classification, based on the severity of inflammation, is of great importance in the treatment of appendicitis, as shown in **Table 1**.

In addition to the above, "early diagnosis of complicated appendicitis is one of the major challenges in the decision of treatment. The problem with all classifications is the differences in the interpretation of clinical, histopathological, and radiological findings between specialists" [58, 130].

TABLE 1: CLASSIFICATION ACCORDING TO THE SEVERITY OF INFLAMMATION

GRADING/SCORE	SEVERITY OF DISEASE
1	Inflamed Appendix
2	Gangrenous
3	Perforated with free fluid
4	Perforated with an abscess
5	Perforated with generalized peritonitis
The disease severity score and the attendant limitations ***References [58, 129, 130]***	

4.5 DIAGNOSTICS OF ACUTE APPENDICITIS

"AA is the most common diagnosis of acute abdomen leading to surgery in emergency units, and yet the diagnostics are not easy [53, 131, 132]. The negative AE rate is 19%–30% of all appendectomies if the decision to operate is based on a clinical examination alone [133, 134]. The diagnostic accuracy has increased over the last decades due to the widespread use of CT in the diagnostics of acute abdomen patients" [135].

"The number of misdiagnoses is significantly higher **in women of fertile age** due to the difficulty of differentiating lower abdominal pain related to gynecological problems from acute appendicitis" [133, 134, 136]. **In children**, "the diagnostics can be challenging. The younger the patient, the more difficult the diagnostics are. Young patients' history is received from accompanying adults and is often observational; small children do not have the ability to describe their symptoms comprehensively. Another challenging group of patients is **pregnant women**. Changing physiology and anatomy alter clinical findings. The incidence of abdominal emergencies is one out of 500–700 pregnancies and surgery is needed in 0.2%–2% of the cases. AA is the most common cause of surgery" [137].

In the elderly, "the differential diagnostics become more of a challenge. The elderly have comorbidities, malignancies, and other underlying causes expressing as the symptoms of an acute abdomen. At the same time, AA becomes more infrequent. Consequently, the outcome of AE **in the elderly** is significantly worse than in younger patients, with a higher incidence of complicated appendicitis and postoperative morbidity" [138]. "Regardless of the wide use of diagnostic imaging and convincing results in individual studies on the sensitivity and specificity of diagnostic scores combined with imaging, the population-based reviews show no decrease in the rate of negative appendectomies, and the question of how to differentiate complicated appendicitis from uncomplicated appendicitis persists" [139, 140]. "The negative appendectomy and perforated appendicitis rates are both important quality measures of the treatment of acute appendicitis. There is an inverse relationship between these two measures [141]. The negative appendectomy and

perforated appendicitis rates are both important quality measures of the treatment of acute appendicitis. There is an inverse relationship between these two measures" [141].

4.5.1 Clinical Presentation, Diagnosis and Laboratory Work up

"Physical examination and medical history remain the cornerstones of good clinical practice in patients presenting with acute abdominal pain localized in the right lower abdominal quadrant. White blood cell (WBC) count, erythrocyte sedimentation rate, and sometimes serum C-reactive protein (CRP) may be helpful" [53, 142-145]. "Urinary sediment examination and a pregnancy test should be undertaken to exclude urinary tract infection, urolithiasis, and pregnancy when applicable. However, a recent report on the diagnostic value of medical history, clinical presentation, and indices of inflammation, including CRP in a group of 496 patients with suspected AA showed that none of the individual variables had sufficiently high discriminating power to be used as a diagnostic test" [146]. "The presence of anorexia, nausea, and right-sided rectal tenderness had no diagnostic value. In one study, leukocyte and WBC counts, CRP, rebound tenderness, guarding, and gender were independent predictors of AA; the combined area under the receiver operating characteristic (ROC) curve was 0.93 for AA, showing the value of combining several parameters. A normal serum CRP level was recently shown to correlate strongly with a normal appendix in patients with suspected appendicitis" [147]. "A meta-analysis of studies addressing these issues has shown an increased likelihood of AA when a positive psoas sign, fever, or pain migrating to the right lower abdominal quadrant was present; vomiting before the onset of pain made appendicitis less likely [148]. A study by Bohner showed a maximum positive predictive value of 85 percent when a combination of three out of five clinical parameters were present [149]. Rectal examination was not shown to contribute to a definite diagnosis of AA" [150].

4.5.1.1 *Biomarkers*

"Biomarkers are used to supplement history and clinical exam, especially in children, women of fertile age, and the elderly where the diagnosis is difficult. No inflammatory marker alone, including white blood cell (WBC) count, c-reactive protein (CRP) or other novel tests including pro-calcitonin, can identify appendicitis with high specificity and sensitivity" [151, 152]. However, "WBC count is obtained in virtually all patients being assessed for appendicitis, where available. A range of novel biomarkers has been suggested over the last decade, including bilirubin [153], but these lack external validity and repeatedly suffer from low sensitivity, meaning they are unlikely to come into clinical practice" [153].

4.5.2 Computer Aided Decision Making and Scoring Systems

"Combining clinical history, physical examination, and laboratory studies have led to the development of scoring systems and computer-aided algorithms to help clinicians in the decision making in appendicitis. In clinical studies, several of these computer-aided algorithms can reduce the number of unnecessary appendectomies [154]. These modalities were shown to be cost-beneficial, but they require the introduction of new and costly equipment and expertise" [155, 156].

"In contrast to this computer-aided decision making, scoring systems can be applied without special equipment and do not require new skills [157]. However, despite the reported excellent results, these systems are not routinely used [158, 159]. Of the many standardized scoring systems for the diagnosis of AA, the Alvarado criteria [160], which generate the MANTRELS score (Table 2), appear to be the most effective [161]. A score of more than seven points has a relatively high sensitivity (88% to 90%), but the specificity is generally no better than 80% and is especially low in women" [162, 163]. "Modifications have included removing the leukocyte count criteria or reducing the threshold to five points, but these modifications further impair the specificity of the system, particularly in pediatric patients [164, 165]. While these and other criteria may assist junior staff and nonsurgical personnel in identifying patients with AA, they are not likely to be helpful for experienced surgeons who possess astute clinical judgment. The normal-appearing appendix can be left in situ, thus reducing the rate of negative AE [166-168]. AE can be carried out safely and quickly with this technique" [169,170]. Some authorities recommend that "the appendix be removed in all cases, however, because a normal macroscopic appearance does not exclude the presence of histological appendicitis with certainty [171,172]. Moreover, it has been suggested that recurrent pain can arise from appendices that have neurochemical or immunological abnormalities even in the absence of overt inflammation" [173, 174]. "A substantial proportion of patients report a history of recurrent episodes of pain before AE (recurrent appendicitis) or of prolonged pain, which may or may not is accompanied by histological evidence of fibrosis or chronic inflammation (chronic appendicitis)" [175, 176].

TABLE 2: ALVARADO SCORING SYSTEM

Clinical or laboratory feature	Points
Migration of pain from the mid-abdomen to right lower quadrant	1
Anorexia or acetonuria (a surrogate marker of food avoidance)	1
Nausea and vomiting	1
Tenderness in the right lower quadrant	2
Rebound tenderness	1
Elevated temperature (≥38°C)	1
Leukocytosis (>10,400 cells/mm3)	2
Shifted white blood cell count (>75% neutrophils)	1
Total possible points 10	**10**
Data from reference [160]	

4.5.3 Imaging Techniques

Several literature reports suggested that "the diagnosis of AA is often challenging and of utmost importance to the surgeons providing care, hence preoperative imaging is now widely accepted by most surgeons and emergency medicine physicians in the workup of AA [177-179]. Several imaging studies, like Ultrasound Scan (USS) or Computerized Tomographic Scan (CT), are used in conjunction with clinical examination, the primary method for diagnosis" [177-179]. In patients with AA, early diagnosis and prompt intervention are imperative, especially because of some possible array of life-threatening complications [177, 180]. While, in some instances, a clinical diagnosis can be made correctly, it is not infrequent to require other supportive investigations to make a correct diagnosis. This supportive investigation helps to reduce the rate of negative AE, which has been reported to be as high as 15-30% [177, 181]. It also helps to avoid subjecting patients to unwarranted surgery with the attendant risks [181, 182].

4.5.3.1 *Plain Abdominal Radiography*

Some authors submitted that "several imaging techniques have been advocated to improve diagnostic accuracy in patients with suspected AA. In a study by Rao *et al.* [164], the diagnostic utility and hospital resource impact of plain abdominal radiography in patients with suspected AA were evaluated. The authors reviewed medical records of 821 consecutive patients hospitalized for suspected AA. Seventy-eight per cent had plain abdominal radiography, 64 per cent had appendicitis. Radiographic findings were noted in 51 per cent of patients with and 47 per cent of patients without appendicitis" [164]. "No individual finding on the plain abdominal radiographs was sensitive or specific. The authors found that plain abdominal radiographs in patients with suspected appendicitis are frequently misleading. They also found that the radiographs are costly in relation to making a specific and correct diagnosis. They concluded that abdominal radiographs should not be routinely obtained in such patients" [164].

4.5.3.2 *Trans-abdominal Ultrasonography*

There have been concerns about the use of Ultrasound Scan (USS) because of operator dependency outcome [177-179]. Results from Alegbeleye study showed that "we may be underestimating the value and benefit of ultrasound in the preoperative workup in AA especially in the developing countries" [177-179]. "Ultrasonography continues to play an important role in the evaluation of patients with acute abdominal pain [177, 180]. Its peculiar advantages of ready availability, low cost, and absence of ionizing radiation makes it an attractive initial imaging modality in such situations" [177, 180]. The robust role of the USS is in reinforcement of the clinical diagnosis of AA [177, 180, 181]. There have however been variations in the results obtained from various studies that have assessed its role in diagnosing AA. This is not unconnected with the differences in the levels of experience and the technique used by the Sonologists [177, 180-182].

Moreover, the Alegbeleye study [177] reported a retrospective cross-sectional study which was conducted in Shisong, Cameroon "over two years from January 2015 to December 2016, which assessed the accuracy of preoperative ultrasound scan in the evaluation of patients with suspected AA" [177, 180- 182]. In this series, of 103 patients whose ages ranged from 15 to 65 years with a mean age of 30.6±18 years with a male to female ratio of 1.5:1, there were seventy-five patients found to have ultrasound diagnosis of AA, 68 of which correlated with histopathology. There were 16 patients with equivocal ultrasound findings, while ten patients had normal scans, and two patients had a misdiagnosis of ovarian cyst. Of the ten, eight had histopathological features of AA. The sensitivity of ultrasound in this study was 90.2%, while specificity was 85.6% [177, 180- 182]. It was concluded that Ultrasound scan in patients with suspected AA provides

high sensitivity and specificity in the diagnosis and, therefore, a formidable tool for diagnosing AA in low resource center [177]. The radiological criteria for AA, the accuracy of various imaging modalities, and the limitations of the available research are described in this series [183]. Even in well establish centers worldwide, there are obviously differences in interpretation of Ultrasonographic findings amongst radiologists or sonologists, also termed interobserver variability [183]. However, this interobserver variability in the ultrasonography interpretation of appendicitis is of significant impact in resource-limited surgical emergency settings like ours, which is a rural tropical population in the developing country [183].

4.5.3.3 *Computed Tomography (CT)*

In a related development, there is also growing evidence that CT scanning is superior to ultrasonography in diagnosing AA [184, 185-187]. "Although CT has the disadvantage of exposing the patient to radiation, its consistent sensitivity, and specificity of over 90 percent in many studies, and the low inter and intra-observer variability, have made CT the optimal non-invasive diagnostic procedure in a patient with suspected appendicitis" [184, 186-189]. A study by Rao *et al.* [168] demonstrated that "routine appendiceal CT, undertaken in patients who present with suspected appendicitis, results in improved patient care and reduced use of hospital resources. Focused, thin-section helical CT seems to be the optimal CT technique [190]. Enhancement with intravenous contrast in combination with contrast administered both orally and rectally is usually advocated, but Rao has shown that equal results can be achieved without oral contrast [168]. In recent studies, unenhanced thin-section helical CT yielded results similar to those of enhanced CT, which questions the essence of contrast enhancement" [185,191]. "Wise *et al.* [184] recommended a standard abdominopelvic CT scan as the initial examination; the focused appendiceal CT using colonic contrast material can be kept in reserve for difficult cases."

4.5.3.4 *Magnetic resonance imaging (MRI)*

"This tool is used incidentally in the work-up of patients with suspected AA. It has been shown that MRI can diagnose and rule out AA with high degrees of accuracy, but its current levels of availability, its high costs, and certain patient restrictions limit its widespread use" [169-171]. "MRI has not been shown to be superior to helical CT, but it has the definite advantage of not involving radiation exposure, which is particularly important in pregnancy" [192].

4.5.4 Diagnostic Laparoscopy

Laparoscopic inspection of the abdominal cavity enables the surgeon to diagnose AA accurately [179]. According to Ogbonna BC *et al.* [179], "early laparoscopy in patients with acute non-specific abdominal pain is associated with higher diagnostic accuracy and better quality of life than occurs after close observation followed by surgical intervention if signs of peritonism developed [193]. It has been shown that leaving an appendix that appears normal during a laparoscopic inspection is safe" [179, 194-196]. Osime O *et al.* (2005) reported that "the criteria for the diagnosis of AA during a laparoscopic inspection are the presence of unequivocal inflammatory changes, such as pus, fibrin, or vascular injection of the serosa. Rigidity and lack of mobility at manipulation are more uncertain signs of inflammation" [133].

"Removing a normal appendix is associated with a 6.7 percent to 13 percent risk of early complications and 4 percent risk of late complications, such as incisional hernia and chronic pain in the first years after the operation [172,173]. If a normal appendix is left in situ during diagnostic laparoscopy, the number of unnecessary appendectomies will decrease, particularly in the group of fertile women (17 per cent-38 percent), but also in men (11 percent)" [179, 194-197]. "The diagnostic yield of laparoscopy in patients suspected of AA is high, but laparoscopy may be too invasive to justify its use only for diagnostic purposes; As a result, this reasoning seems particularly true in the era of helical CT" [179, 194-197].

5. CONSERVATIVE TREATMENT OF APPENDICITIS

5.0.1 Non-operative treatment of acute appendicitis

Livingston *et al.* in 2007 propounded "the theory of two different pathways of appendicitis which equally have raised discussion over the antibiotic treatment of AA. The 'non-operative' theory suggests that the inflammation does not necessarily lead to necrosis and perforation. The course of the disease can be self-limiting and thus prone to resolve with antibiotics or even without treatment" [51]. In a similar study by Livingston *et al.* in 2011 submitted that "the investigators supporting antibiotic treatment refer to diverticulitis, which is treated by antibiotics and drainage if needed unless generalized peritonitis is involved" [90]. The authors also reported that "the antibiotic treatment of AA is not a new

idea. It has been suggested over the last decades but has not received full acceptance. The latest studies report promising results."

In a related development, Di Saverio *et al.* in 2014 reported that "the observational NOTA (Non-Operative Treatment for acute Appendicitis) study used amoxicillin-clavulanate for non-specific lower right quadrant abdominal pain with a failure rate of 14%. The diagnosis of appendicitis was made using the Alvarado and AIR (Appendicitis Inflammatory Response) scores, thus including a reasonable amount of misdiagnoses" [198]. "The largest multicentre APPAC study used ertapenem 1g/day for three days, followed by oral levofloxacin (500mg/d) combined with metronidazole (500mg x 3/day) for seven days. The patients with suspected appendicitis were randomized into open appendectomy or non-operative treatment with antibiotics as described. Patients with complicated appendicitis observed in CT (perforation, abscess, appendicolith) were excluded. The success rate of conservative treatment was 69% in the APPAC study (Salminen *et al.* 2015)" [20]. "The result was comparable to other randomized studies on conservative treatment [199, 200]. The main problem with conservative treatment is the reliable recognition of patients with uncomplicated AA. The APPAC study used low-dose CT to confirm the diagnoses. In earlier studies, the sensitivity of CT in recognizing uncomplicated AA has been only 30%–60%" [201]. "One of the reasons for the failures of antibiotic treatment may have been the difficulty of recognizing the right patients. Another problem with the conservative treatment is the significant increase in the use of broad-spectrum antibiotics, with possible long-term effects considering the already growing antibiotic resistance problem. Thirdly, the risk of leaving appendicle tumors behind in the adult population is considerable. The incidence of tumors in removed appendices has been reported to be 1%, but the incidence is considerably higher in the elderly" [202, 203]. "There is no guaranteed way to exclude the tumor possibility by imaging or another non-operative means. Routine colonoscopy and/or imaging after conservative treatment of an appendicular abscess are suggested for excluding tumors" [204]. "There are only two non-randomized studies in children regarding conservative treatment for AA. The first of these was based on selecting patients with mild symptoms (Hartwich *et al.* 2015) [205] and the second on patient selection by the preference of the patients and parents (Steiner *et al.* 2015) [206] for non-operative treatment. The success rate was 81% in the first and 71% in the latter study. In the absence of randomized controlled trials, treatment with antibiotics is not yet accepted in the treatment of AA in children."

In a related development, "most Clinicians in the contemporary African population are reluctant to consider non-operative treatment for AA for similar reasons as above" [207, 208]. "In the majority of the patients studied that demonstrate the consistent delayed presentation in the developing world mainly because greater than 80% of the patients come for treatment after 24 hours of the onset of symptoms" [33, 45, 53, 58, 114, 122, 126, 143]. Besides, "many of these patients had experienced recurrent episodes of right lower quadrant pain with the administration of several different brands of oral and parenteral medications. Studies have demonstrated that the average risk of perforation after 36 hours of the onset of symptoms is between 16% and 36%" [33, 45, 53, 58, 114, 122, 126, 143].

"Most patients had appendicectomy within 24 hours of presentation to the hospital. Additional delays witnessed were often due to the need for ancillary investigations, the need to re-evaluate the patient for an appropriate diagnosis or funds for surgical intervention in patients without health insurance policies" [33, 45, 53, 58, 114, 122, 126, 143]. With these concerns still unresolved, "a recent review on the treatment of appendicitis suggests that non-operative treatment should be performed in adult patients included in randomized controlled trials only, or the patients should at least be informed of the 25%– 30% failure rate during the first year as well as of the disadvantages and the benefits of both operative and non-operative treatment" [33, 45, 53, 58, 114, 122, 126, 143]. Moreover, "Bhangu *et al.* in 2015 reported that the present understanding is that antibiotic treatment can be used on a subgroup of patients with accurate diagnoses (including CT imaging) and mild symptoms that are otherwise suitable for conservative treatment. The appropriate criteria are yet to be identified in future trials" [209].

5.0.2 Treatment of an appendicular abscess

"Prolonged or atypical symptoms such as high fever, abdominal tenderness over three days, diarrhea, and a palpable low right quadrant mass refer to an intra-abdominal abscess. The diagnosis is, in most cases, retrieved by CT or, in children, with the US, both indicating a collection of fluid with a capsule in the lower right quadrant of the abdomen and an inflammatory process around the area. Immediate surgery of an appendicular abscess has been considered demanding, often leading to bowel resections and an increased complication rate" [210]. According to a recent trial, "laparoscopic AE is safe and feasible even in the abscess stage when performed by experienced surgeons. The length of hospital stay has been found equal in the laparoscopic and conservative treatment groups, but there were fewer additional interventions in

the operatively treated patients" [210, 211]. "The common clinical practice for an appendicular abscess is conservative treatment, with or without interval AE, i.e., removing the appendix after a period of time when the acute infection has been successfully treated. Conservative treatment includes the application of a drain, typically by a radiologist, the extraction of a bacterial sample to identify the infectious agents, and the administration of intravenous antibiotics. An area of considerable debate is the necessity of interval AE. Similar risks of recurrent appendicitis and of missed pathological findings apply to the conservative treatment of abscess as acute appendicitis; If an appendicolith is involved, the risk of residual appendicitis is considerably high – a retrospective cohort study reported a 2.8 relative risk" (Tannoury *et al.* 2013; Ein *et al.* 2005) [212, 213]. "In specimens of an interval AE after an appendicular abscess, the number of unexpected findings has been as high as 12%–28%, and 16% in the elderly" (Carpenter *et al.* 2012; Wright *et al.* 2015) [215, 216]. "The evidence supporting interval AE is controversial. Some studies recommend performing interval AE in all patients [212, 216], whereas others suggest abandoning interval AE and recommend close follow-up, colonoscopy, and imaging to rule out underlying tumors" [217].

5.1 OPERATIVE TREATMENT OF APPENDICITIS

The timing of surgery has been a controversial issue in the operative treatment of AA. Livingston *et al.* in 2007[51] reported that "delaying the operation has been thought to yield the risk of perforation, thus leading to complications. This assumption is based on the theory that inflammation of the appendix inevitably results in necrosis and perforation [51]. In many cases, however, AA resolves without an operation, and the necrotic disease may represent a different pathway of AA rather than the end result of inflammation" [51]. Current literature on this issue is controversial.

According to Chen CC *et al.*, "some studies show no difference in surgical site infection or complication rates if surgery is delayed 12–24 h after admission to the emergency department, nor do they report there a difference in the perforation rate [218]. Delaying surgery by more than 48 hours has been shown to increase the complication rate (Fair *et al.* 2015)" [219]. Saar et al. in 2016 embarked on a "prospective study of 266 patients that showed increased morbidity if appendectomy was delayed more than 12 hours after the onset of abdominal pain" [220]. However, "the earlier studies measured the time from admission to surgery. The patients' pre-hospital delay is unpredictable, and a probable conclusion is, therefore, that an in-hospital delay of up to 12–24 hours is acceptable when the diagnosis is unclear" [220].

5.1.1 Open appendectomy

5.1.1.1 *Technique*

The operative treatment of AA was first performed over a hundred years ago (McBurney 1894). "The general technique of open AE has changed only in minor details over the years. The incision is usually made in the lower right quadrant (LRQ) of the abdomen, overlying McBurney's point, two-thirds of the distance from the umbilicus towards the anterior iliac spine. Some surgeons prefer to mark the point of maximum pain to optimize the placement of the incision relative to appendix origin" [221]. "Para-umbilical and lower midline incisions have been used, especially if the diagnosis has been uncertain. The appendix is mobilized and lifted out of the wound. Sometimes the mobilization of the caecum is needed. The mesentery of the appendix with the appendicular artery, rising from the ileocaecal artery, is ligated. The appendix is then ligated and excised close to its origin in the caecum. The traditional surgical technique includes the crushing of the appendicular lumen to avoid any intra-luminal material in between the ligation of the appendix" [221]. "After excision, the stump is either buried with a purse-string suture into the bottom of the caecum or left unburied. Sometimes additional sutures are used to complete the burying in the case of inflamed tissue in the stump. The routine burying of the appendicular stump decreased with the introduction of the laparoscopic technique and has been found to be unnecessary" [221].

5.1.1.2 *Wound closure*

The AE wound closure technique has followed the general trends in abdominal surgery. "Earlier, the peritoneum was closed but is presently left unclosed. The muscle layer is closed by a few interrupted sutures, and the fascia is sutured with continuous, slowly absorbing suturing material. Delayed closure of the skin was favored in the early years. Later, together with the use of prophylactic antibiotics, closure with a few interrupted non-absorbable sutures became routine. Absorbable sutures are presently favored, especially in pediatric surgery, as the discomfort of suture removal is a considerable burden on children. Skin closure with absorbable sutures has been shown to be as safe as other skin closure methods in regard to wound complications. In pediatric patients, the safety of intradermal suturing after AE has been demonstrated even in complicated appendicitis cases" [222, 223]. "Currently, open appendectomy wounds in children are

routinely closed with intradermal absorbable suturing. Furthermore, studies support better cosmetic result after intradermal absorbable suturing" (Xu *et al.* 2015), [224].

5.1.2 Laparoscopic appendectomy

"The first laparoscopic AE was performed by a gynecologist in the 1980s (Semm 1983). Technological development and the wide-spread adoption of laparoscopic technology were fast during the 1990s. Laparoscopic AE was primarily recommended for female patients as the technique allows the diagnosis of gynecological conditions often mimicking AE" [225, 226]. "The benefit was next noted in the context of obese patients for whom an open operation is often challenging and demands extended incisions. Obese patients are also at risk for wound complications (wound rupture, infection, and incisional hernia) [226-228]. Laparoscopy offers the option of leaving a normal appendix in place; the macroscopic appearance is not, however, necessarily reliable" [226, 229]. "A study demonstrated that the surgeon's ability to identify inflammation without perforation and neoplasms is poor. Some 33% of the inflamed appendixes were deemed normal, and only 3 out of 16 neoplasms were macroscopically noted. They concluded that all appendices should be removed in the case of explorative laparoscopy for suspected AA [229]. It took two decades for laparoscopic AE to convince the surgeons. As the laparoscopic technique has increased its popularity in surgery in general, and the instruments and technique have developed, many prefer laparoscopic AE to the open technique today" [229]. According to Hansen *et al.*, in 1996, "there has been some concern about a possible increase in intra-abdominal abscess development after laparoscopic operation for perforated appendicitis, but the results are controversial. Some studies suggest that the laparoscopic approach offers better possibilities for the lavation of the abdominal cavity of pus than open AE [230, 231]. Laparoscopic AE has also been considered expensive and time-consuming compared to the open technique. The benefits of laparoscopy are smaller wounds, shorter hospital stay, and shorter sick leaves" [232]. "The overall expenses with the fewer hospital days and shorter leave from work equalize the difference in immediate expenses. However, laparoscopic appendectomy requires a learning curve, whereas the open technique is straightforward and easily adapted. The current trend based on a meta-analysis of randomized trials is favoring laparoscopic appendectomy as the first-line operative treatment for appendicitis" [227].

"Laparoscopic appendectomy is favored for pediatric patients in the treatment of appendicitis even if the outcome in children is found to be the same with both open and laparoscopic appendectomy [233, 234]. A population-based study recommends open surgery for young children less than six years of age and in complicated appendicitis cases. The recommendation is based on the higher rates of intra-abdominal abscesses after laparoscopy in complex AA and a high number of such cases in the young age group" [233, 234]. "In most studies, a laparoscopic procedure is reported to be safe during pregnancy [235, 236]. Most studies support laparoscopic appendectomy at least during the first and second trimester of pregnancy and open AE in the third trimester" [235, 236]

5.1.2.1 *Technique*

Sahm M *et al.* from their study submitted that "for appendectomy, the laparoscopy ports are placed for a convenient approach towards the caecum, the operator positioned on the left side of the patient [237]. The camera port is placed in the umbilical region or on the left upper quadrant of the abdominal wall. Two additional ports are commonly used. Coagulating instruments or clips are used to ligate the vessels of the appendix. For the ligation of appendix clips, ligation loop strings or a stapler are used. A large retrospective study supports the routine use of endo-loops and selective use of a stapler, which is a more expensive device but feasible in complicated circumstances" [237]. Other authors contributed that "clips, metal or polymeric material, have also been found safe, feasible and economical if the width is sufficient for the ligation of the appendix [238, 239]; the stump is not buried. The appendix is extracted from the abdomen through a port wound in a retrieval bag or inside a port to avoid introducing bacteria to the wound. Variations in the surgical technique depend on the surgeon's laparoscopy skills and the circumstances of the operation" [238, 239].

5.1.2.2 *Novel Techniques*

"A single-port laparoscopic technique has been introduced in most laparoscopic operations to reduce the number of ports needed, targeting surgery without scars and decreasing the risk of wound complications [240]. The technique is based on a gel port, which is commonly placed through the umbilicus. Multiple instruments can be placed through the gel port and used in the same way as is done in conventional laparoscopy [240]. The curved arms allow working through a single port. Variations of the single port technique have been developed especially for appendectomy, such as using laparoscopy only to visualize and capture the appendix and then pulling the appendix trough the same incision to make the actual excision" [240]. "The single-port technique also seems to be a feasible option for children [241]. However, the technique

has little advantage over conventional laparoscopy and is hence likely to be practiced only in units specialized in this kind of surgery [242]. Natural orifice trans-luminal endoscopic surgery (NOTES) takes advantage of the natural luminal organs to approach the target of surgery. A flexible endoscope is used to operate either through the alimentary tract or vagina. A hybrid technique has been introduced with a single laparoscopy port assisting the flexible endoscope" [243]. "The advantage of this technique is completely scarless surgery. On the other hand, it requires penetration through an organ, which is a considerable risk, with completely new complications [244]. Due to the complexity of this surgery, it is unlikely that the technique will be widely adopted in the treatment of AA" [245].

6. COMPLICATIONS OF APPENDECTOMY

There are only a few population-based studies on the complications of AE. According to Brugger *et al.*, in 2011, "open and laparoscopic appendectomies have equal complication rates, varying from 8% to 31%, but the types of complications vary according to the technique used [246]. The classification of complications is heterogeneous through the studies, making it difficult to compare the outcomes" [246].

6.1 Wound infection

"Surgical site infection (SSI) is the most common complication after open AE. The commonly used classification for SSI is superficial/incisional and deep/organ/space infection according to the layer of the abdomen that is affected. Sadr Azodi *et al.* in 2008, they submitted that the major risk factor for post-appendectomy surgical site infection is complicated AA" [77]. "The overall wound infection rate after AE is approximate 3%–5% compared to the 10% after complicated disease. Other risk factors for infection are obesity, co-morbidity such as diabetes, pre-operative SIRS (severe inflammatory respiration syndrome), and smoking [77]. Besides, open AE seems to be an independent risk factor for incisional SSI compared to laparoscopy. However, the finding may be influenced by selection bias because many surgeons still prefer open AE in perforated appendicitis" [247, 248]. Grosfeld *et al.* 1968 reported that "delayed wound closure was the method of choice in contaminated wounds until the 1970s [249]. As the delayed closure leads to morbidity, discomfort, and prolonged hospital stay, it has later been abandoned by most surgeons" [250]. According to Siribumrungwong *et al.* (2014) believes that "the routine use of prophylactic antibiotics has decreased the SSI rate, and the primary closure has proved to be safe [251]. The most common method currently is to perform primary closure with prophylactic intravenous antibiotics administered in the induction of anesthesia in open AE. The antibiotics are continued after the operation in the case of perforated appendicitis [252]. The commonly administered antibiotics are intravenous *cefalosporins*, *ciprofloxacin*, or *gentamycin* combined with metronidazole or broad-spectrum antibiotics such as *ertapenem* or *piperacillin*, which have shown equal effectiveness in both complicated and uncomplicated appendicitis (Daskalakis *et al.* 2014)" [252]. "The duration of antibiotic treatment is not well defined. According to the study by van Rossem *et al.* (2015), examining perforated AA cases, the treatment is clearly indicated, whereas, in other kinds of complicated cases (necrosis, appendicolith), there has been no difference in SSI whether the treatment course lasts three days or longer [253]. Drainage is used in selected patients, usually with an abscess or a considerable amount of pus at the time of the operation. By this widely adopted pathway of care, the overall wound infection rate has dropped from 20% to 5%" [253].

6.2 Intra-abdominal abscess

In the early years of laparoscopic appendectomies, open AE was considered better in perforated cases to avoid intra-abdominal abscess formation. Many studies have found significantly higher rates of abscesses after laparoscopic appendectomies" [247, 248]. "The results are controversial, however. A Swedish study with a population of 160,000 patients found a 0.3% abscess rate after open and 0.5% after laparoscopic AE; the difference was statistically significant but has questionable clinical significance. Other studies have shown that the intra-abdominal abscess rate may not be especially related to laparoscopic appendectomy. Perforation of the appendix has been proven to be a significant factor in abscess formation, but the role of laparoscopy is controversial, as many studies show no difference in abscess formation between laparoscopic and open appendectomy" [254, 255]. These results support the trend of performing laparoscopy in perforated appendicitis.

6.3 Other complications after appendectomy

"Two major studies on the short- and long-term outcome of AE are presented in Bowel obstruction, bowel lesion or perforation, and wound ruptures are the next common complications reported after AE. In a population-based Swedish study on post-AE morbidity, wound rupture and postoperative bowel obstruction were related to open AE more frequently than to laparoscopic appendectomy (LA). A bowel lesion was reported to be more common after LA. Overall surgical

complications were more frequent after open AE" [247]. "Due to a large study population, statistical significance was shown, but the clinical significance can be questioned for these results. Another comprehensive single-institute study found a significant difference in the rate of readmissions in favor of open appendectomy. The long-term results were equal for both surgical techniques" [256]. "A rare entity of AE complication is stump appendicitis, which refers to the infection of the residual of a previously removed appendix. It can occur days or even decades after the primary operation. The diagnosis is challenging and requires adequate imaging. The treatment of choice is the resection of the remnant appendix" [257].

6.4 Mortality after appendectomy

Mortality related to AE is not well investigated. "Few studies report mortality rates on a population basis, the results varying from 0.09% to 0.24% in developed countries, and from 1% to 4% in low-income countries" [26, 258-260]. "A Scandinavian population-based study showed increased mortality related to negative AE [261, 262]. Furthermore, a study by Faiz *et al.* (2008) from England found a relation of increased mortality to the male sex, age, co-morbidity, and open surgery" [260]. "Another earlier study by Margenthaler *et al.* in 2003 reported 1.8% mortality among veteran patients [263]. The authors found mortality to be related to complications, current pneumonia, completely dependent functional status, bleeding disorder, and steroid use [263]. An increased number of deaths among these patients were probably related to the high mean age of the patients (50 years)" [263].

7. NEW TRENDS IN APPENDICITIS

7.1 GENETICS OF APPENDICITIS

Genetics refers to gene expression, and concerning this clinical review, the genetics of appendicitis, according to Orlova E *et al.,* 2019, cannot be over-emphasized [264, 265]. Globally, "there is no consensus among clinicians on the underlying pathophysiology AA, which appears to represent a unique disease process distinct from inflammatory disorders elsewhere in the gastrointestinal tract (Murphy *et al.,* 2008)" [264, 265]. "The role of host genetics in the predisposition towards developing AA is poorly understood, but the available volume of evidence suggests that genetic factors presumably may contribute to the susceptibility. For example, heritability estimates of appendicitis derived from linkage genes, complex segregation, and twin studies range between 27% and 56%" [36, 264, 266, 267].

Furthermore, "genes were also prioritized based on greatest evidence of regulation by expression quantitative trait loci (eQTLs) near the GWAS signals, which was defined as a RegulomeDB score of 1, "likely to affect binding and linked to the expression of a gene target." Genes targeted by eQTLs across multiple associated loci were prioritized. eQTL locations and target genes were obtained from RegulomeDB (version 1.1, publicly available at regulome.stanford.edu)" [264, 268]. "In one current study, the authors - Kristjansson *et al*., 2017 found that an association was observed for a locus on 4q25 near PITX2 with AA in Northern European adults [264, 269]. Eight other loci were equally identified, which elaborated symbolic significance in the discovery of a genome-wide association study (GWAS). Associations were subsequently followed up by measuring gene expression across resected appendices with varying levels of inflammation (N = 75)" [264, 269]. However, "this association was not found in children, which invariably suggest that potentially different genetic mechanisms or effect sizes of genetic risk factors for appendicitis between children and adults. Other potential genetic variants that probably could account for the heritability of appendicitis have yet to be discovered" [264, 269].

In a related development, Orlova E *et al.,* (2019) [264], "submission from a genome-wide association study of self-reported appendectomy performed with 18,773 affected adults and 114,907 unaffected adults of European American ancestry; revealed that there was a significant association with AE observed at 4q25 near the gene PITX2 (rs2129979, p-value = 8.82 × 10−14) and was replicated in an independent sample of Caucasians (59 affected, 607 unaffected; p-value = 0.005) [264, 270]. Consequently, a meta-analysis of the associated variant across our two cohorts and cohorts from Iceland and the Netherlands (in which this association had previously been reported) showed strong cumulative evidence of association (OR = 1.12; 95% CI 1.09–1.14; p-value = 1.81 × 10−23) and some evidence for effect heterogeneity (p-value = 0.03) [264, 271-273]. Eight other loci were equally identified, which elaborated symbolic significance in the discovery GWAS. Associations were subsequently followed up by measuring gene expression across resected appendices with varying levels of inflammation (N = 75). During the study, the researchers measured the expression of 27 genes based on physical proximity to the GWAS signals, evidence of being targeted by eQTLs near the signals according to Regulome DB (score = 1), or both" [Boyle *et al.* 2012][264, 268]. "Four of the 27 genes (including PITX2) showed

significant evidence (p values < 0.0033) of differential expression across categories of appendix inflammation [264,269]. An additional ten genes showed nominal evidence (p-value < 0.05) of differential expression, which, together with the significant genes, is more than expected by chance (p-value = 6.6 × 10−12). The implications of the findings suggest that PITX2 impacts morphological development of intestinal tissue, promotes an anti-oxidant response, and its expression correlates with levels of intestinal bacteria and colonic inflammation. These newer reports are milestone development in our understanding of the role of familial genes and heredity in AA" [264, 274, 275].

Further studies to elucidate the distinctive role of PITX2 in AA are now being warranted and highly recommended by clinicians in general.

8. PANEL: KEY MESSAGES

1. AA remains a significant health challenge in Africa due to attendant high morbidities and mortalities.

2. The incidence of perforated AA remains significantly high in Africa at large, attributable to delayed presentation to hospitals, socioeconomic disadvantage, and health system constraints typical to Africa and developing regions.

3. The etiopathophysiology of AA remains poorly understood, and many patients stay with an equivocal diagnosis, which continues to be one of the most challenging dilemmas.

4. Diagnostic biomarkers, clinical scoring systems, and high-resolution imaging facilities may be valuable adjuncts to clinical evaluation globally but are often not available to the African clinicians due to high overhead cost or limited skills of such health-workers, particularly in the contemporary African settings

5. The open AA technique continues to be popular in African settings; even though laparoscopic AE has increased in popularity globally but laparoscopy requires a higher level of skill as well as complex instrumentation and more resources; with the current significant level of resource-constraints therefore, laparoscopic appendicectomy appears for now like a "mirage" that is unattainable, obviously in most health facilities across sub-Saharan Africa.

The latest research focus is the elaboration of specific gene-expression in appendicitis from the results of a genome-wide association study (GWAS) of AE worldwide, but Africa is yet to catch-up with this moving train in that field of research in general.

9. FUTURE TRENDS IN APPENDICITIS

1. A strong call for gradual adoption of scoring systems, endoscopic tools, laparoscopy to improving diagnostic techniques in AA.

2. There is an urgent public health concerted effort aimed at improving the health care seeking habit of the population in most African communities.

3. There is a need for improving healthcare infrastructures in most of our local or district hospitals in favor of emergency surgeries in general.

4. There are a progressive trend and campaign for the adoption of laparoscopic AE, especially in most rural settings of Africa and the world at large, to maximize the gains by all and sundry.

5. Future research studies and funding on the distinctive role of genetics in AA is highly recommended by clinicians worldwide.

6. Future study proposal also to entail a large, multicenter randomized trial, with clear inclusion criteria, and outcome reporting of an intention-to-treat basis will help validate the body of present data and may invariably be an alternative to current practice.

10. CONCLUSIONS

AA remains a significant health challenge in Africa due to the attendant high incidence of perforations and complications. Primary care providers should be well versed in identifying the symptoms and signs of AA. There must be early and prompt diagnosis, adequate resuscitation as well as early surgery in patients with AA to keep the morbidity and mortality low. In patients with equivocal findings, imaging studies and laboratory tests should be ordered to help confirm the diagnosis. The standard of care is AE; therefore, a surgical consult is needed. Recent evidence suggests that a nonsurgical, antibiotic approach in the treatment of uncomplicated AA may be beneficial but remains controversial. However, large,

multicenter randomized trials, clear inclusion criteria, and outcome reporting with an intention-to-treat basis will help validate this approach as an alternative to current practice.

Interestingly, the latest focus is the elaboration of specific gene-expression in AA from the results of a genome-wide association study (GWAS) of AE with the largest number of cases to date with independent replication. Other genetic variants that account for the heritability of AA have yet to be discovered. This article, therefore, reviews the current 'state of the art' in the evaluation and management of AA that is leading to stratified care for patients mainly in contemporary African settings.

11. DECLARATIONS

ACKNOWLEDGEMENTS: Not Applicable

FUNDING: This research received no specific grant from any funding agency in the public, commercial, or not-for profit sectors.

AVAILABILITY OF DATA AND MATERIALS: All data generated or analyzed during this study are included in this published article.

DISCLOSURES: The Author has no disclosures.

AUTHORS' CONTRIBUTIONS: The Author conceived of the study and participated in its design and coordination as well as helped to draft the manuscript; the author also read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not Applicable

INFORMED CONSENT: Not Applicable

COMPETING INTERESTS: The Author declares that there is no conflict of interest.

REFERENCES

[1] Lander A. Appendicitis -A Collection of Essays from Around the World. 1ST edition. InTech, Janeza, Croatia. 2011

[2] Saidi HS, Adwok JA. Acute appendicitis: an overview. East Afr Med J. 2000; 77(3):152–156.

[3] Berry J Jr., Malt RA. Appendicitis near its centenary. Ann Surg. 1984; 200(5):567–575.

[4] Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol. 2000; 4(1):46–58.

[5] Walker AR, Segal I. Appendicitis: an African perspective. JR Soc Med. 1995; 88(11):616–619.

[6] Rogers AD, Hampton MI, Bunting M, Atherstone AK. Audit of appendicectomies at Frere Hospital, Eastern Cape. S Afr J Surg. 2008; 46(3):74–77.

[7] Gadomski A, Jenkins P. Ruptured appendicitis among children as an indicator of access to care. Health Serv Res. 2001; 36(1 Pt 1):129–142.

[8] Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990; 132(5):910–925.

[9] Braveman P, Schaaf VM, Egerter S *et al.* Insurance-related differences in the risk of ruptured appendix. N Eng J Med. 1994; 331(7):444–449.

[10] Herrod HG, Chang CF. Potentially avoidable pediatric hospitalizations as defined by the Agency for Healthcare Research and Quality: what do they tell us about disparities in child health? Clin Pediatr (Phila). 2008; 47(2):128–136.

[11] Yang E, Kahn D, Cook C. Acute appendicitis in South Africa: a systematic review. S Afr J Surg 2015;53(3&4): 1-8

[12] Hansson J, Korner U, Ludwigs K, Johnsson E, Jonsson C, Lundholm K. Antibiotics as first-line therapy for acute appendicitis: evidence for a change in clinical practice. World J Surg 2012 Sep; 36(9):2028-2036.

[13] Lee SL, Yaghoubian A, Stark R, Shekherdimian S. Equal access to healthcare does not eliminate disparities in the management of adults with appendicitis. J Surg Res. 2011;170(2):209–213

[14] Seal A. Appendicitis: a historical review. Can J Surg 1981 Jul; 24(4):427-433.

[15] Prystowsky JB, Pugh CM, Nagle AP. Current problems in surgery. Appendicitis. Curr Probl Surg 2005 Oct; 42(10):688-742.

[16] McBurney C. II. The Indications for Early Laparotomy in Appendicitis. Ann Surg 1891; Apr; 13(4):233-254.

[17] Semm K. Endoscopic appendectomy. Endoscopy 1983 Mar; 15(2):59-64.

[18] Migraine S, Atri M, Bret PM, Lough JO, Hinchey JE. Spontaneously resolving acute appendicitis: clinical and sonographic documentation. Radiology 1997 Oct; 205(1):55-58.

[19] Coldrey E. Treatment of Acute Appendicitis. Br Med J 1956 Dec 22; 2(5007):1458-1461.

[20] Salminen P, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T *et al.* Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. JAMA 2015; 313(23): 2340-2348.

[21] Steiner Z, Buklan G, Stackievicz R, Gutermacher M, Erez I. A role for conservative antibiotic treatment in early appendicitis in children. J Pediatr Surg 2015 Sep; 50(9):1566-1568.

[22] Erasmus JPF. The incidence of appendicitis in the Bantu. S Afr Med J. 1939; 13:601–607.

[23] Ashley DJ. Observations on the epidemiology of appendicitis. Gut 1967; 8:533-538.

[24] Sanda RB, Zalloum M, El-Hossary M, Al-Rashid F, Ahmed O, Awad A *et al.* Seasonal variation of appendicitis in northern Saudi Arabia. Ann Saudi Med 2008; 28:140-141.

[25] The National Institute of Statistics, Bamenda Regional Office, Bui-Division -Population Data of Cameroon in 2016: Republic of Cameroon 2016 population and housing Statistics. January 2016.

[26] Ohene-Yeboah M, Abantanga FA. Incidence of acute appendicitis in Kumasi, Ghana. West Afr J Med 2009; 28:122-125.

[27] Langenscheidt P, Lang C, Puschel W, Feifel G. High rates of appendicectomy in a developing country: An attempt to contribute to a more rational use of surgical resources. Eur J Surg 1999; 165:248-52.

[28] Zoquereh DD, Lemaitre X, Ikoli JF, Delmont J, Chamlian A, Mandaba JL *et al.* Acute appendicitis at the National University Hospital in Bangui, Central African Republic: Epidemiologic, clinical, paraclinical and therapeutic aspects. Sante 2001; 11:117-25.

[29] Horntrich J, Schneider W. Appendicitis from an epidemiological viewpoint. Zentralbl Chir 1990; 115:1521-9.

[30] Ilves I, Paajanen HE, Herziq KH, Fagerstrom A, Miettinen PJ. Changing incidence of acute appendicitis and nonspecific abdominal pain between 1987 and 2007 in Finland. World J Surg 2011; 35:731-8.

[31] Chatbanchai W, Hedley AJ, Ebrahim SB, Areemit S, Hoskyns EW, de Dombal FT. Acute abdominal pain and appendicitis in north east Thailand. Pediatr Perinat Epidemiol 1989; 3:448-59.

[32] Andreu-Bellester JC, Gonzales-Sanchez A, Ballester F, AlmelaQuilis A, Cano-Cano MJ, Millan-Scheiding M *et al.* Epidemiology of appendectomy and appendicitis in the Valencian community (Spain), 1998-2007. Dig Surg 2009; 26:406-12.

[33] Alegbeleye study: Epidemiologic study of acute appendicitis in the tropics

[34] Morris J, Barker DJ, Nelson M. Diet, infection, and acute appendicitis in Britain and Ireland. J Epidemiol. 1987; 41:44-9

[35] Walker RP, Segal I. What causes appendicitis? Journal of Clinical Gastroenterology 1990; 12:127-129

[36] Basta M, Morton NE, Mulvihill JJ, Radovanović Z, Radojicić C, Marinković D. Inheritance of acute appendicitis: familial aggregation and evidence of polygenic transmission. Am J Hum Genet. 1990. 46:377-382.

[37] Brender JD, Marcuse EK, Weiss NS, Koepsell TD. Is Childhood appendicitis familial? Am J Dis Child. 1985 Apr. 139(4):338-40.

[38] Humes D, Speake WJ, Simpson J. Appendicitis. Clinical Evidence, Jul 1; 2007. pii: 0408

[39] Luckmann R, Davis P. The epidemiology of acute appendicitis in California: racial, gender, and seasonal variation. Epidemiology 1991 Sep; 2(5):323-330.

[40] Al-Omran M, Mamdani M, McLeod RS. Epidemiologic features of acute appendicitis in Ontario, Canada. Can J Surg 2003; 46:263-8.

[41] Gallerani M, Boari B, Anania G, Cavallesco G, Manfredini R. Seasonal variation in onset of acute appendicitis. Clin Ter 2006; 157:123-7.

[42] Basoli A, Zarba-Meli E, Salvio A, Crovaro M, Scopelliti G, Mazzocchi P *et al.* Trends in the incidence of appendicitis in Italy during the past 30 years. Minerva Chir 1993; 48:127-32.

[43] Papadopoulos AA, Polymeros D, Kateri M, Tzathas C, Koutras M, Ladas SD. Dramatic decline of acute appendicitis in Greece over 30 years: Index of improvement of socioeconomic conditions or diagnostic aids? Dig Dis 2008; 26:80-4.

[44] Oguntola AS, Adeoti ML, Oyemolade TA. Appendicitis: Trends in incidence, age, sex, and seasonal variations in South-Western Nigeria. Ann Afr Med 2010;9:213-7

[45] Osman AA. Epidemiological study of appendicitis in Khartoum. Int Surg 1974; 59; 218-23.

[46] Offili OP. Implications of the rising incidence of appendicitis in Africans. Cent Afr Med 1987; 33:243-5.

[47] Mangete ED, Kombo BB. Acute appendicitis in Port-Harcourt, Nigeria. Orient J Med 2004; 16:1-3.

[48] Burkitt DP, Walker AR, Painter NS. Effect of dietary fiber on stools and transit-times, and its role in the causation of disease. Lancet 1972; 30:1408-12.

[49] Segal I, Walker AR, Wadee A. Persistent low prevalence of Western digestive diseases in Africa: Confounding etiological factors. Gut 2001; 48:730-732.

[50] Lin KB, Lai KR, Yang NP, Chan CL, Liu YH, Pan RH *et al.* Epidemiology and socioeconomic features of appendicitis in Taiwan: a 12-year population-based study. World J Emerg Surg 2015 Sep 17; 10:42-015-0036-3. eCollection 2015.

[51] Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of non-perforated and perforated appendicitis: implications for pathophysiology and management. Ann Surg 2007 Jun; 245(6):886-892.

[52] Korner H, Soreide JA, Pedersen EJ, Bru T, Sondenaa K, Vatten L. Stability in incidence of acute appendicitis. A population-based longitudinal study. Dig Surg 2001; 18(1):61-66.

[53] Ajao OG. Appendicitis in a tropical African population. J Natl Med Assoc 1979Oct; 71(10):997-999.

[54] Willmore WS, Hill AG. Acute appendicitis in a Kenyan rural hospital. East Afr Med J 2001 Jul; 78(7):355-357.

[55] Lee JH, Park YS, Choi JS. The epidemiology of appendicitis and appendectomy in South Korea: National registry data. Journal of Epidemiology 2010; 20(2):97-105

[56] Lamps LW. Infectious causes of appendicitis. Infect Dis Clin North Am 2010; 24(4): 995-1018.

[57] Marzuillo P, Germani C, Krauss BS, Barbi E. Appendicitis in children less than five years old: A challenge for the general practitioner. World J Clin Pediatr 2015 May 8; 4(2):19-24.

[58] Balogun OS, Osinowo A, Afolayan M, Olajide T, Lawal A, Adesanya A. Acute perforated appendicitis in adults: Management and complications in Lagos, Nigeria. Ann Afr Med 2019; 18:36-41

[59] Andersson R, Hugander A, Thulin A, Nystrom PO, Olaison G. Indications for operation in suspected appendicitis and incidence of perforation. BMJ 1994 Jan8; 308(6921):107-110.

[60] Omo-Dare P, Thomas HO. Diagnosis and management of acute appendicitis in Nigerian. W. Afr. Med. J. 1966; 15: 217.

[61] Mohebbi HA, Mehrvarz S, Kashani MT, Kabir A, Moharamzad Y. Predicting negative appendectomy by using demographic, clinical, and laboratory parameters: a cross-sectional study. Int J Surg 2008 Apr; 6(2):115-118.

[62] Barker AP, Davey RB. Appendicitis in the first three years of life. Australian and New Zealand Journal of Surgery 1988; 58:491-494

[63] Barker JP, Morris J, Nelson M. Vegetable consumption and acute appendicitis in 59 areas in England and Wales. British Medical Journal 1986; 292:927-930

[64] Richardsen I, Schöb DS, Ulmer TF, Steinau G, Neumann UP, Klink CD, Lambertz A (2015): Etiology of Appendicitis in Children: The Role of Bacterial and Viral Pathogens, Journal of Investigative Surgery (2015), DOI: 10.3109/08941939.2015.1065300

[65] Abantanga FA, Nimako B, Amoah M. The range of abdominal surgical emergencies in children older than 1 year at the Komfo Anokye teaching hospital, Kumasi, Ghana. Ann Afr Med 2009; 8:236-42.

[66] Rahman GA, Abubakar AM, Johnson AW, Adeniran JO. Typhoid ileal perforation in Nigerian children: An analysis of 106 operative cases. Pediatr Surg Int 2001; 17:628-30.

[67] Salo M, Marungruang N, Bodil Roth, et al. Evaluation of the microbiome in children's appendicitis. Int J Colorectal Dis 2017;32:19–28

[68] Freud E, Pilpel D, & Mares AJ. Acute appendicitis in childhood in the Negev region: some epidemiological observations over an 11-year period (1973-1983). J Pediatr Gastroenterol Nutr. 1988; 7(5):680-4.

[69] Khaavel AA, Birkenfeldt RR. [Nature of the relation of acute appendicitis morbidity to meteorological and heliogeographical factors]. Vestn Khir Im I I Grek. 1978; 120(4):6770.

[70] Kwaasi AAA, Tipirneni P, Harfi H *et al.* (1992a). Date palm (Phoenix dactylifera L) is a potent allergen. Ann Allergy. 1992; 68:78.

[71] Kwaasi AAA, Parhar RS, Tipirneni P *et al.* (1992b). Characterization of antigens and allergens of date palm (Phoenix dactylifera L) pollen: immunological assessment of atopic patients using whole extracts or its fractions. Allergy. 1992; 47:535-44.

[72] Kwaasi AAA, Tipirneni P, Harfi H *et al.* (1993). Major allergens of the date palm (Phoenix dactylifera L) pollen: identification of IgE binding components by ELISA and immunoblot analysis. Allergy. 1993; 48:511-8.

[73] Kwaasi AAA, Parhar RS, Al-Mohanna FAA *et al.* (1998). Aeroallergens and viable microbes in sandstorm dust. Allergy. 1998; 53:255-65.

[74] Kaplan GG, Dixon E, Panaccione R *et al.* (2009). Effect of ambient air pollution on the incidence of appendicitis. CMAJ 2009;181:591-7

[75] Santosh G, & Aravindan KP. Evidence of eosinophil degranulation in acute appendicitis. Indian J Pathol Microbiol. 2008; 51:172-174.

[76] Aravindan KP, Vijayaraghavan D, Manipadam MT. Acute eosinophilic appendiciticis and the significance of eosinophil-edema lesion. Indian J Pathol Microbiol. 2010;53:258-61

[77] Azodi Sadr O, Andren-Sandberg A, & Larsson H. Genetic and environmental influences on the risk of acute appendicitis in twins. Br J Surg. 2009; 96:1336-40.

[78] Ergul E. Heredity and familial tendency of acute appendicitis. Scand J Surg. 2007; 96:290-2.

[79] Frisch M, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. Brit Med J 2009; 338: b716.

[80] Blomqvist P, Ljung H, Nyren O, Ekbom A. Appendicectomy in Sweden 1989- 1993 assessed by the inpatient Registry. J Clin Epidemiol 1998; 51: 859-865.

[81] Adehossi E, & Parola P. Schistosomal appendicitis. The Lancet. Infectious Diseases 2004; 4(8): 498

[82] Hegazi MA & Patel TA. Acute amoebic appendicitis: Case reports and review of parasitic appendicitis. Journal of the Pediatric Infectious Diseases Society 2013; 2(1): 80-82.

[83] Swischuk LE, Chung DH, Hawkins HK, Jadhav SP, Radhakrishnan R. Non-fecalith- induced appendicitis: etiology, imaging, and pathology. Emerg Radiol 2015 Dec;22(6):643-649

[84] Short AR. The causation of appendicitis. Br J Surg 1920; 8:171-188.

[85] Burkitt DP. Relationship between diseases and their etiologic significance. Am J Clin Nutr 1977; 30:262-7.

[86] Burkitt DP. Appendicitis and diabetes. Br Med J 1977; 1:1413-4.

[87] Burkitt DP, Moolgaokar AS, Tovey FI. Aetiology of appendicitis. Br Med J 1979; 1:620.

[88] Jones BA, Demetriades D, Segal I, Burkitt DP. The prevalence of appendiceal fecaliths in patients with and without appendicitis. A comparative study from Canada and South Africa. Ann Surg 1985; 202: 80-2.

[89] Byrnes RM. South Africa: a country study. Washington: GPO for the Library of Congress. http://countrystudies.us/south-africa/ 1996. (Accessed September 30, 2019).

[90] Livingston EH, Fomby TB, Woodward WA, Haley RW. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. Arch Surg. 2011; 146(3):308-14.

[91] Engin O, Muratli A, Ucar AD, Tekin V, Calik B, Tosun A. The importance of fecaliths in the aetiology of acute appendicitis. Chirurgia (Bucur) 2012 Nov-Dec; 107(6):756-760.

[92] Singh JP, Mariadason JG. Role of the faecolith in modern-day appendicitis. Ann R Coll Surg Engl 2013 Jan; 95(1):48-51.

[93] Ramdass MJ, Young Sing Q, Milne D, Mooteeram J, Barrow S. Association between the appendix and the fecalith in adults. Can J Surg 2015 Feb; 58(1):10-14.

[94] Chan W, Fu KH. Value of routine histo-pathological examination of appendices in Hong Kong. J Clin Pathol 1987 Apr; 40(4):429-433.

[95] Swartley RN, Stayman JW,Jr. Lymphoid hyperplasia of the intestinal tract requiring surgical intervention. Ann Surg 1962 Feb; 155:238-240.

[96] Yildiz S, Bulut M. Aggravated lymphoid hyperplasia mimicking barium-induced appendicitis. Emerg Radiol 2008 Sep; 15(5):345-347.

[97] Singhal R, Angmo N, Somaiah N, Majumdar H, Chaturvedi KU. A retrospective review of the histopathology and clinicopathologic correlates of appendices removed from patients of acute appendicitis. Minerva Chir 2007 Feb; 62(1):11-18.

[98] Ryan WL. Appendicitis: Symptoms, Diagnosis, and Treatments. New York: Nova Science Publishers, Inc; 2010.

[99] Bucher P, Mathe Z, Demirag A, Morel P. Appendix tumors in the era of laparoscopic appendectomy. Surg Endosc 2004 Jul; 18(7):1063-1066.

[100] Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol 2008 Feb;34(2):196-201.

[101] In't Hof KH, van der Wal HC, Kazemier G, Lange JF. Carcinoid tumour of the appendix: an analysis of 1,485 consecutive emergency appendectomies. J Gastrointest Surg 2008 Aug; 12(8):1436-1438.

[102] Yilmaz M, Akbulut S, Kutluturk K, Sahin N, Arabaci E, Ara C *et al.* Unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis. World J Gastroenterol 2013 Jul 7; 19(25):4015-4022.

[103] Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. Ann Surg 2004 Jul; 240(1):117-122.

[104] Ozcelik CK, Turanli S, Bozdogan N, Dibekoglu C. Clinical experience in appendiceal neuroendocrine neoplasms. Contemp Oncol (Pozn) 2015; 19(5):410-413.

[105] Shapiro R, Eldar S, Sadot E, Papa MZ, Zippel DB. Appendiceal carcinoid at a large tertiary center: pathologic findings and long-term follow-up evaluation. Am J Surg 2011 Jun; 201(6):805-808.

[106] Carpenter SG, Chapital AB, Merritt MV, Johnson DJ. Increased risk of neoplasm in appendicitis treated with interval appendectomy: single-institution experience and literature review. Am Surg 2012 Mar; 78(3):339-343.

[107] Dachman AH, Lichtenstein JE, Friedman AC. Mucocele of the appendix and pseudomyxoma peritonei. AJR Am J Roentgenol 1985 May; 144(5):923-929.

[108] Ruiz-Tovar J, Teruel DG, Castineiras VM, Dehesa AS, Quindos PL, Molina EM. Mucocele of the appendix. World J Surg 2007 Mar; 31(3):542-548.

[109] Bennett GL, Tanpitukpongse TP, Macari M, Cho KC, Babb JS. CT diagnosis of mucocele of the appendix in patients with acute appendicitis. AJR Am J Roentgenol 2009 Mar; 192(3):W103-10.

[110] Alder AC, Fomby TB, Woodward WA, Haley RW, Sarosi G, Livingston EH. Association of viral infection and appendicitis. Arch Surg 2010 Jan; 145(1):63-71.

[111] Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med 2000 Jul; 36(1):39-51.

[112] Guinane CM, Tadrous A, Fouhy F, Ryan CA, Dempsey EM, Murphy B *et al.* Microbial composition of human appendices from patients following appendectomy. mBio. 2013; 4(1):e00366-12. doi:10.1128/mBio.00366-12.

[113] Swidsinski A, Dorffel Y, Loening-Baucke V *et al*. Acute appendicitis is characterized by local invasion with Fusobacterium nucleatum/necrophorum. Gut. 2011; 60(1): 34-40.

[114] Abdurrazzaaq A, Afuwape O, Ademola A, Fasina O. Bacterial Pattern in Acute Appendicitis. The Annals of African Surgery, January 2018; 15(1):8-13

[115] Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. Gut. 2007; 56(10): 1387-92.

[116] Clanton J, Subichin M, Drolshagen K, Daley T, Firstenberg MS. Fulminant Clostridium difficile infection: An association with prior appendectomy? World J Gastrointest Surg. 2013; 5(8): 233-8

[117] Decadt B, Sussman L, Lewis MP, Secker A, Cohen L, Rogers C *et al.* Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain. Br J Surg. 1999; 86(11): 1383-6.

[118] Chandra- Sharath BJ, Girish TU, Thrishuli PB, Vinay HG. Primary Tuberculosis of the Appendix: A Rare Cause of a Common Disease. J Surg Tech Case Rep. 2013 Jan-Jun; 5(1): 32–34.

[119] Badmos KB, Komolafe AO, Rotimi O. Schistosomiasis presenting as acute appendicitis. East Afr Med J 2006; 83: 528-532.

[120] Adebamowo CA, Akang EE, Ladipo JK, Ajao OG. Schistosomiasis of the appendix. Br J Surg 1991; 78: 1219-1221.

[121] Arca MJ, Gates RL, Groner JI, Hammond S, Caniano DA. Clinical manifestations of appendiceal pinworms in children: an institutional experience and a review of the literature. Pediatr Surg Int 2004 May; 20(5):372-375.

[122] Chamisa I. A clinicopathological review of 324 appendices removed for acute appendicitis in Durban, South Africa: a retrospective analysis. Ann R Coll Surg Engl 2009Nov; 91(8):688-692.

[123] Soliman LA. Parasitic lesions of the appendix with reference to their importance in the differential diagnosis of appendicitis. Trans R Soc Trop Med Hyg 1966; 60(4):493-496.

[124] Ahmed SA. Epidemiology of appendicitis in Northern Nigeria: A 10-year review. Sub- Saharan African Journal of Medicine 2014; 1(4):185.

[125] Feeley A, Musenge E, Pettifor JM, Norris SA. Changes in dietary habits and eating practices in adolescents living in urban South Africa: the birth to twenty cohorts. Nutrition 2012 Jul; 28(7-8):e1-6.

[126] Kong VY, Bulajic B, Allorto NL, Handley J, Clarke DL. Acute appendicitis in a developing country. World J Surg 2012 Sep; 36(9):2068-2073.

[127] Badoe EA. Acute Appendicitis in Accra. Ghana Medical Journal, September 1967; 6: 69-75

[128] Farzal Z, Farzal Z, Khan N & Fischer A. The diagnostic dilemma of identifying perforated appendicitis. The Journal of Surgical Research 2015; 199(1): 164-168.

[129] Garst GC, Moore EE, Banerjee MN, Leopold DK, Burlew CC, Bensard DD *et al.* Acute appendicitis: A disease severity score for the acute care surgeon. The Journal of Trauma and Acute Care Surgery 2013; 74(1): 32-36.

[130] Kim TH, Cho BS, Jung JH, Lee MS, Jang JH & Kim CN. Predictive factors to distinguish between patients with non-complicated appendicitis and those with complicated appendicitis. Annals of Coloproctology 2015; 31(5): 192-197.

[131] Sulu B, Gunerhan Y, Palanci Y, Isler B, Caglayan K. Epidemiological and demographic features of appendicitis and influences of several environmental factors. Ulus Travma Acil Cerrahi Derg 2010 Jan; 16(1):38-42.

[132] Kalenga NC, Makinga NP, Ferndale LC. Appendicectomies at a tertiary hospital: disease profile and surgical practices at Grey's Hospital, Pietermaritzburg. Open Access J Surg. 2017; 2(4): 555-592. DOI: 10.19080/OAJS.2017.02.555592.

[133] Osime OC, Ajayi P. Incidence of negative appendectomy: experience from a company hospital in Nigeria. Cal J Emerg Med. 2005; 6(4):69-73.

[134] Lima AP, Vieira FJ, De Moraes Oliveira GP, Ramos PD, Avelino ME *et al.* Clinical-epidemiological profile of acute appendicitis: retrospective analysis of 638 cases. Rev. Col. Bras. Cir. 2016; 43(4): 248-253

[135] Laurell H, Hansson LE, Gunnarsson U. Manifestations of acute appendicitis: a prospective study on acute abdominal pain. Dig Surg. 2013; 30(3):198-206.

[136] Lee M, Paavana T, Mazari F, Wilson TR. The morbidity of negative appendicectomy. Annals of the Royal College of Surgeons of England 2014; 96(7): 517-520.

[137] Bouyou J, Gaujoux S, Marcellin L, Leconte M, Goffinet F, Chapron C *et al.* Abdominal emergencies during pregnancy. Journal of Visceral Surgery 2015; 152(6): 105-15.

[138] Segev L, Keidar A, Schrier I, Rayman S, Wasserberg N & Sadot E. Acute appendicitis in the elderly in the twenty-first century. Journal of gastrointestinal surgery 2015; 19(4): 730-735.

[139] Raja AS, Wright C, Sodickson AD, Zane RD, Schiff GD, Hanson R *et al.* Negative appendectomy rate in the era of CT: An 18-year perspective. Radiology 2010; 256(2): 460-465.

[140] Flum DR, Morris A, Koepsell T & Dellinger E. Has misdiagnosis of appendicitis decreased over time?: A population-based analysis. JAMA 2001; 286(14): 1748-1753.

[141] Tan WJ, Acharyya S, Goh YC, Chan WH, Wong WK, Ooi LL *et al.* Prospective comparison of the Alvarado score and CT scan in the evaluation of suspected appendicitis: A proposed algorithm to guide CT use. Journal of the American College of Surgeons 2015; 220(2): 218-224.

[142] Edino ST. Surgical abdominal emergence in northwestern Nigeria. Nigerian Journal of Surgery 2002; 8: 13-17.

[143] Adekunle OO, Funmilayo JA. Acute appendicitis in Nigeria. J R Coll Surg Edin 1986; 31: 102-105.

[144] Adesunkanmi ARK, Agbakwuru EA, Adekunle KA. Pattern and outcome of acute appendicitis in semi-urban and rural African communities: A study of 125 patients. Nigerian Medical Practitioner 1998; 36: 8-11.

[145] Edino ST, Mohammed AZ, Ochicha O, Anumah M. Appendicitis In Kano, Nigeria: A 5-Year Review of Pattern, Morbidity and Mortality Annals of African Medicine 2004; 3(1): 38 - 41

[146] Soldo I, Biljak VR, Bakula B, Bakula M, Simundic AM. The diagnostic accuracy of clinical and laboratory parameters in the diagnosis of acute appendicitis in the adult emergency department population - a case control pilot study. Biochem Med (Zagreb) 2018; 28(3): 030712

[147] Davies AH, Bernau F, Salisbury A *et al.* C - reactive protein in right iliac fossa pain. Journal of the Royal College of Surgeons of Edinburgh 1991 Aug; 36(4):242-4. PMID: 1941740.

[148] Kabir SA, Kabir SI, Sun R, Jafferbhoy S, Karim A. How to diagnose an acutely inflamed appendix; a systematic review of the latest evidence?. Int J Surg. 2017 Apr; 40:155-162.

[149] Bohner H, Yang Q, Franke K, Ohmann C. Significance of anamnesis and clinical findings for diagnosis of acute appendicitis. Acute Abdominal Pain Study Group. Z Gastroenterol 1994; 32: 579-583.

[150] Kremer K, Kraemer M, Fuchs KH, Ohmann C. The diagnostic value of rectal examination of patients with acute appendicitis. Langenbecks Arch Chir Suppl Kongressbd 1998; 115: 1120-1122.

[151] Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg. 2013; 100(3): 322-329.

[152] Leeuwenburgh MM, Stockmann HB, Bouma WH *et al.* A simple clinical decision rule to rule out appendicitis in patients with non-diagnostic ultrasound results. Acad Emerg Med. 2014; 21(5): 488-96.

[153] Cuschieri J, Florence M, Flum DR, Jurkovich GJ, Lin P, Steele SR *et al.* Negative appendectomy and imaging accuracy in the Washington State Surgical Care and Outcomes Assessment Program. Ann Surg. 2008; 248(4): 557-63.

[154] Shindoh J, Niwa H, Kawai K *et al.* Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. J Gastrointest Surg. 2010; 14(2): 309-14.

[155] Hansson J, Khorram-Manesh A, Alwindawe A, Lundholm K. A model to select patients who may benefit from antibiotic therapy as the first line treatment of acute appendicitis at high probability. J Gastrointest Surg. 2014; 18(5): 961-967.

[156] Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomized controlled trials. Brit Med J. 2012; 344: e2156.

[157] De Dombal FT, Dallos V, McAdam WA. Can computer aided teaching packages improve clinical care in patients with acute abdominal pain? BMJ 1991; 302: 1495-1497.

[158] McAdam WA *et al.* Twelve years' experience of computer-aided diagnosis in a district general hospital. Ann R Coll Surg Engl 1990; 72: 140-146.

[159] Ohmann C, Yang Q, Franke C. Diagnostic scores for acute appendicitis. Abdominal Pain Study Group. Eur J Surg 1995; 161: 273-281.

[160] Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986; 15: 557-564.

[161] Christian F, Christian GP. A simple scoring system to reduce the negative appendicectomy rate. Ann R Coll Surg Engl 1992; 74: 281-285.

[162] Fenyo G. Routine use of a scoring system for decision-making in suspected acute appendicitis in adults. Acta Chir Scand 1987; 153: 545-551.

[163] Ohmann C, Franke C, Yang Q. Clinical benefit of a diagnostic score for appendicitis: results of a prospective interventional study. German Study Group of Acute Abdominal Pain. Arch Surg 1999; 134: 993-996.

[164] Rao PM, Rhea JT, Rao JA, Conn AK. Plain abdominal radiography in clinically suspected appendicitis: diagnostic yield, resource use, and comparison with CT. Am J Emerg Med 1999; 17: 325-328.

[165] Puylaert JB *et al.* A prospective study of ultrasonography in the diagnosis of appendicitis. N Engl J Med 1987; 317: 666-669.

[166] Stroman DL, Bayouth CV, Kuhn JA, Westmoreland M, Jones RC, Fisher TL *et al.* The role of computed tomography in the diagnosis of acute appendicitis. Am J Surg 1999; 178: 485-489.

[167] Funaki B, Grosskreutz SR, Funaki CN. Using unenhanced helical CT with enteric contrast material for suspected appendicitis in patients treated at a community hospital. AJR Am J Roentgenol 1998; 171: 997-1001.

[168] Rao PM, Rhea JT, Novelline RA, Mostafavi AA, Lawrason JN, McCabe CJ. Helical CT combined with contrast material administered only through the colon for imaging of suspected appendicitis. AJR Am J Roentgenol 1997; 169: 1275-1280.

[169] Incesu L, Coskun A, Selcuk MB, Akan H, Sozubir S, Bernay F. Acute appendicitis: MR imaging and sonographic correlation. Am J Roentgenol 1997; 168: 669-674.

[170] Rao PM, Boland GW. Imaging of acute right lower abdominal quadrant pain. Clin Radiol 1998; 53: 639-649.

[171] Kraemer M, Ohmann C, Leppert R, Yang Q. Macroscopic assessment of the appendix at diagnostic laparoscopy is reliable. Surg Endosc 2000; 14: 625633.

[172] Gough IR et al. Consequences of removal of a "normal" appendix. Med J Aust 1983; 1: 370-372.

[173] Larsson PG, Henriksson G, Olsson M, Boris J, Ströberg P, Tronstad SE *et al.* Laparoscopy reduces unnecessary appendicectomies and improves diagnosis in fertile women. A randomized study. Surg Endosc 2001; 15: 200-202

[174] Olsen JB, Myren CJ, Haahr PE. Randomized study of the value of laparoscopy before appendicectomy. Br J Surg 1993; 80: 922-923.

[175] De Kok HJ. A new technique for resecting the non-inflamed not-adhesive appendix through a mini-laparotomy with the aid of the laparoscope. Arch Chir Neerl 1977; 29: 195-198.

[176] De Kok HJ. Laparoscopic appendectomy: a new opportunity for curing appendicopathy. Surg Laparosc Endosc 1992; 2: 297-302.

[177] Alegbeleye BJ. Ultrasound Scan in the Evaluation of Acute Appendicitis in the Tropics. CPQ Medicine 2019; 6(2): 01-08

[178] Sammalkorpi HE, Mentula P, Leppaniemi A. A new adult appendicitis score improves diagnostic accuracy of acute appendicitis- a prospective study. BMC Gastroenterology 2014; 14: 114.

[179] Ogbonna BC, Obekpa PO, Momoh JT, Ige JT, Ihezue CH. Another look at acute appendicitis in tropical Africa and the value of laparoscopy in diagnosis. Trop. Doct., 1993; 23(2): 82-84.

[180] Elahifar MA, Taheri H, Bighamian A. Diagnostic value of ultrasonography in patients with suspected acute appendicitis. Nepalese Journal of Radiology 2012; 2(2); 13-19.

[181] Himeno S, Yasuda S, Odia Y, Mukoyama S, Nishi T, Mukai M *et al.* Ultrasonography for the diagnosis of acute appendicitis. Tokia J Exp Clin Med. 2003; 28(1): 39-44.

[182] Leite NP, Pereira JM, Cunha R, Pinto P, Sirlin C. CT Evaluation of appendicitis and its complications: imaging techniques and key diagnostic findings. AJR Am J Roentgenol. 2004; 185(2): 406-417.

[183] Alegbeleye BJ. Interobserver Variability in Ultrasound Scan Interpretation for Suspected Acute Appendicitis: a Cross-Sectional Cohort Study. Open J Surg. 2019; 3(1): 001-009.

[184] Wise SW, Labuski MR, Kasales CJ, Blebea JS, Meilstrup JW, Holley GP *et al.* Comparative assessment of CT and sonographic techniques for appendiceal imaging. AJR Am J Roentgenol 2001; 176: 933-941.

[185] Pickuth D, Heywang-Kobrunner SH, Spielmann RP. Suspected acute appendicitis: is ultrasonography or computed tomography the preferred imaging technique? Eur J Surg 2000; 166: 315-319.

[186] Horton MD, Counter SF, Florence MG, Hart MJ. A prospective trial of computed tomography and ultrasonography for diagnosing appendicitis in the atypical patient. Am J Surg 2000; 179: 379-381

[187] Stroman DL, Bayouth CV, Kuhn JA, Westmoreland M, Jones RC, Fisher TL *et al.* The role of computed tomography in the diagnosis of acute appendicitis. Am J Surg 1999; 178: 485-489.

[188] Funaki B, Grosskreutz SR, Funaki CN. Using unenhanced helical CT with enteric contrast material for suspected appendicitis in patients treated at a community hospital. AJR Am J Roentgenol 1998; 171: 997-1001.

[189] Walker S, Haun W, Clark J, McMillin K, Zeren F, Gilliland T. The value of limited computed tomography with rectal contrast in the diagnosis of acute appendicitis. Am J Surg 2000; 180: 450-4.

[190] Weltman DI, Yu J, Krumenacker J, Jr., Huang S, Moh P. Diagnosis of acute appendicitis: comparison of 5- and 10-mm CT sections in the same patient. Radiology 2000; 216: 172-177.

[191] Lane MJ, Liu DM, Huynh MD, Jeffrey RB Jr, Mindelzun RE, Katz DS. Suspected acute appendicitis: non-enhanced helical CT in 300 consecutive patients. Radiology 1999; 213: 341-346

[192] Gupta H, Dupuy DE. Advances in imaging of the acute abdomen. Surg Clin North Am 1997; 77: 1245-1263.

[193] Van den Broek WT, Bijnen AB, Van Eerten PV, De Ruiter P, Gouma DJ. Selective use of diagnostic laparoscopy in patients with suspected appendicitis. Surg Endosc 2000; 14: 938-941.

[194] Bouillot JL, Salah S, Fernandez F, al-Hajj G, Dehni N, Dhote J *et al.* Laparoscopic procedure for suspected appendicitis. A prospective study in 283 consecutive patients. Surg Endosc 1995; 9: 957-60.

[195] Barrat C, Catheline JM, Rizk N, Champault GG. Does laparoscopy reduce the incidence of unnecessary appendicectomies? Surg Laparosc Endosc 1999; 9: 27-31.

[196] Deutsch AA, Shani N, Reiss R. Are some appendectomies unnecessary? An analysis of 319 white appendices. J R Coll Surg Edinb 1983; 28: 35-40.

[197] Gough IR, Morris MI, Pertnikovs EI, Murray MR, Smith MB, Bestmann MS. Consequences of removal of a "normal" appendix. Med J Aust 1983; 1: 370-372.

[198] Di Saverio S, Sibilio AF, Giorgini EF, Biscardi AF, Villani SF, Coccolini FF *et al*. The NOTA study (non-operative treatment for acute appendicitis): Prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Annals of Surgery 2014; 260(1): 109-117

[199] Rocha LL, Rossi FM, Pessoa CM, Campos FN, Pires CE & Steinman M. Antibiotics alone versus appendectomy to treat uncomplicated acute appendicitis in adults: What do meta-analyses say? World Journal of Emergency Surgery (WJES), 2015; 10: 51-015-0046-1. eCollection 2015.

[200] Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B *et al*. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: An open-label, noninferiority, randomised controlled trial. Lancet (London, England), 2011; 377(9777): 1573-1579.

[201] Bixby SD, Lucey BC, Soto JA, Theysohn JM, Ozonoff A, Varghese JC. Perforated versus non-perforated acute appendicitis: Accuracy of multi-detector CT detection. Radiology 2006; 241(3): 780-786.

[202] Jones AE, Phillips AW, Jarvis JR, Sargen K. The value of routine histopathological examination of appendicectomy specimens. BMC Surgery 2007; 7: 17

[203] Emre A, Akbulut S, Bozdag Z, Yilmaz M, Kanlioz M, Emre R *et al.* Routine histopathologic examination of appendectomy specimens: Retrospective analysis of 1255 patients. International Surgery 2013; 98(4): 354-362.

[204] Lai HW, Loong CC, Chiu JH, Chau GY, Wu CW, Lui WY. Interval appendectomy after conservative treatment of an appendiceal mass. World Journal of Surgery 2006; 30(3):352357.

[205] Hartwich J, Luks FI, Watson-Smith D, Kurkchubasche AG, Muratore CS, Wills HE *et al.* Nonoperative treatment of acute appendicitis in children: A feasibility study. Journal of Pediatric Surgery 2015; 51(1): 111-116.

[206] Steiner Z, Buklan G, Stackievicz R, Gutermacher M, Erez I. A role for conservative antibiotic treatment in early appendicitis in children. Journal of Pediatric Surgery 2015; 50(9): 1566-1568.

[207] Ademola TO, Oludayo SA, Samuel OA, Amarachukwu EC, Akinwunmi KO, Olusanya A *et al.* Clinicopathological review of 156 appendicectomies for acute appendicitis in children in Ile-Ife, Nigeria: A retrospective analysis. BMC Emerg Med 2015; 15:7.

[208] Bickell NA, Aufses AH Jr. Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. J Am Coll Surg 2006; 202:401-6.

[209] Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: Modern understanding of pathogenesis, diagnosis, and management. Lancet 2015; 386(10000): 12781287.

[210] Mentula P, Sammalkorpi H, Leppaniemi A. Laparoscopic surgery or conservative treatment for appendiceal abscess in adults? A randomized controlled trial. Annals of Surgery 2015; 262(2): 237-242.

[211] Okafor PI, Orakwe JC, Chianakwana GU. Management of appendiceal masses in a peripheral hospital in Nigeria: review of thirty cases. World J Surg.2003; 27(7):800–803

[212] Tannoury J, Abboud B. Treatment options of inflammatory appendiceal masses in adults. World Journal of Gastroenterology 2013; 19(25): 3942-3950

[213] Ein SH, Langer JC, Daneman A. Nonoperative management of pediatric ruptured appendix with inflammatory mass or abscess: Presence of an appendicolith predicts recurrent appendicitis. Journal of Pediatric Surgery 2005; 40(10): 1612-1615

[214] Carpenter SG, Chapital AB, Merritt MV, Johnson DJ. Increased risk of neoplasm in appendicitis treated with interval appendectomy: Single-institution experience and literature review. The American Surgeon 2012; 78(3): 339-343.

[215] Wright GP, Mater ME, Carroll JT, Choy JS, Chung MH. Is there truly an oncologic indication for interval appendectomy? American Journal of Surgery 2015; 209(3): 442-446.

[216] Deelder JD, Richir MC, Schoorl T, Schreurs WH. How to treat an appendiceal inflammatory mass: Operatively or non-operatively? Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract, 2014; 18(4): 641-645.

[217] Meshikhe AW. Management of appendiceal mass; controversial issues revisited. Journal of gastrointestinal surgery 2008; 12(4): 767-775.

[218] Chen CC, Ting CT, Tsai MJ, Hsu WC, Chen PC, Lee MD *et al.* Appendectomy timing: Will delayed surgery increase the complications? Journal of the Chinese Medical Association 2015; 78(7): 395-399.

[219] Fair BA, Kubasiak JC, Janssen I, Myers JA, Millikan KW, Deziel DJ. The impact of operative timing on outcomes of appendicitis: A national surgical quality improvement project analysis. American Journal of Surgery 2015; 209(3), 498-502

[220] Saar S, Talving P, Laos J, Podramagi T, Sokirjanski M, Lustenberger T *et al.* Delay between onset of symptoms and surgery in acute appendicitis increases perioperative morbidity: A prospective study. World Journal of Surgery 2016; 40(6):1308-1314.

[221] Qian D, He Z, Hua J, Song Z. Stump invagination versus simple ligation in open appendicectomy: A systematic review and meta-analysis. International Surgery 2015; 100(7-8): 1199-1206

[222] Pauniaho SL, Lahdes-Vasama T, Helminen MT, Iber T, Makela E, Pajulo O. Non-absorbable interrupted versus absorbable continuous skin closure in pediatric appendectomies. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society 2010; 99(3): 142-146.

[223] Serour F, Efrati Y, Klin B, Barr J, Gorenstein A, Vinograd I. Subcuticular skin closure as a standard approach to emergency appendectomy in children: Prospective clinical trial. World Journal of Surgery 1996; 20(1): 38-42.

[224] Xu B, Xu B, Wang L, Chen C, Yilmaz TU, Zheng W *et al.* Absorbable versus non-absorbable sutures for skin closure: A meta-analysis of randomized controlled trials. Annals of Plastic Surgery 2016; 76(5): 598-606.

[225] Tzovaras G, Liakou P, Baloyiannis I, Spyridakis M, Mantzos F, Tepetes K., *et al.* Laparoscopic appendectomy: Differences between male and female patients with suspected acute appendicitis. World Journal of Surgery 2007; 31(2): 409413.

[226] Adisa AO, Arowolo OA, Salako AA, Lawal OO. Preliminary experience with laparoscopic surgery in Ile-Ife, Nigeria. Afr J Med Med Sc. 2009;38:351–356

[227] Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. The Cochrane Database of Systematic Reviews 2010; (10): CD001546.

[228] Woodham BL, Cox MR, Eslick GD. Evidence to support the use of laparoscopic over open appendicectomy for obese individuals: A meta-analysis. Surgical Endoscopy 2012; 26(9): 2566-2570.

[229] Jaschinski T, Mosch C, Eikermann M, Neugebauer EA. Laparoscopic versus open appendectomy in patients with suspected appendicitis: A systematic review of meta-analyses of randomized controlled trials. BMC Gastroenterology 2015; 15, 48-015-0277-3. doi:10.1186/ s12876-015-0277-3

[230] Nataraja RM, Loukogeorgakis SP, Sherwood WJ, Clarke SA, Haddad MJ. The incidence of intraabdominal abscess formation following laparoscopic appendicectomy in children: A systematic review and meta-analysis. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2013 Part A, 23(9): 795-802.

[231] Wilson DG, Bond AK, Ladwa N, Sajid MS, Baig MK, Sains P. Intra-abdominal collections following laparoscopic versus open appendicectomy: An experience of 516 consecutive cases at a district general hospital. Surgical Endoscopy, 2013; 27(7): 2351-2356.

[232] Hansen JB, Smithers BM, Schache D, Wall DR, Miller BJ, Menzies BL. Laparoscopic versus open appendectomy: Prospective randomized trial. World Journal of Surgery 1996; 20(1): 17-20; discussion 21.

[233] Emmanuel A, Byrne J, Wilson I, Balfe P. Is laparoscopic appendicectomy a safe procedure for trainees in the peripheral hospital setting? Irish medical journal. 2011 Oct; 104(9):276-278.

[234] Osifo OD, Ogiemwonyi SO. Peritonitis in children: our experience in Benin-City, Nigeria. Surg Infect (Larchmt). 2011; 12(2):127–130

[235] Cheng HT, Wang YC, Lo HC, Su LT, Soh KS, Tzeng CW *et al.* Laparoscopic appendectomy versus open appendectomy in pregnancy: A population-based analysis of maternal outcome. Surgical Endoscopy 2015; 29(6): 1394-1399.

[236] Chung JC, Cho GS, Shin EJ, Kim HC, Song OP. Clinical outcomes compared between laparoscopic and open appendectomy in pregnant women. Canadian Journal of Surgery. Journal Canadien De Chirurgie 2013; 56(5): 341-346.

[237] Sahm M, Kube R, Schmidt S, Ritter C, Pross M, Lippert H. Current analysis of endoloops in appendiceal stump closure. Surgical Endoscopy 2011; 25(1): 124-129

[238] Partecke LI, Kessler W, Patrzyk M, Heidecke CD, Bernstorff WV. Comparison among different closure methods of the appendicular stump in laparoscopic appendectomy. Surgical Technology International 2011; 21:85-91

[239] Strzalka M, Matyja M, Rembiasz K. Comparison of the results of laparoscopic appendectomies with application of different techniques for closure of the appendicular stump. World Journal of Emergency Surgery: WJES, 2016; 11, 4-015-0060-3. eCollection 2016.

[240] Suh HH. A minimally invasive technique of appendectomy using a minimal skin incision and laparoscopic instruments. Surgical Laparoscopy & Endoscopy 1998; 8(2): 149-152.

[241] Zhao L, Liao Z, Feng S, Wu P, Chen G. Single-incision versus conventional laparoscopic appendicectomy in children: A systematic review and meta-analysis. Pediatric Surgery International, 2015; 31(4): 347-353.

[242] Carter JT, Kaplan JA, Nguyen JN, Lin MY, Rogers SJ, Harris HW. A prospective, randomized controlled trial of single-incision laparoscopic vs conventional 3-port laparoscopic appendectomy for treatment of acute appendicitis. Journal of the American College of Surgeons 2014; 218(5): 950-959.

[243] Knuth J, Heiss MM, Bulian DR. Transvaginal hybrid-NOTES appendectomy in routine clinical use: Prospective analysis of 13 cases and description of the procedure. Surgical Endoscopy 2014; 28(9): 2661-2665

[244] Wood SG, Panait L, Duffy AJ, Bell RL, Roberts KE. Complications of transvaginal natural orifice trans-luminal endoscopic surgery: A series of 102 patients. Annals of Surgery 2014; 259(4): 744-749.

[245] Yagci MA, Kayaalp C. Transvaginal appendectomy: A systematic review. Minimally Invasive Surgery, 2014, 384706.

[246] Brugger L, Rosella L, Candinas D, Guller U. Improving outcomes after laparoscopic appendectomy: A population-based, 12-year trend analysis of 7446 patients. Annals of Surgery 2011; 253(2): 309-313.

[247] Andersson RE. Short-term complications and long-term morbidity of laparoscopic and open appendicectomy in a national cohort. The British Journal of Surgery 2014; 101(9): 11351142

[248] Xiao Y, Shi G, Zhang J, Cao JG, Liu LJ, Chen TH *et al.* Surgical site infection after laparoscopic and open appendectomy: A multicenter large consecutive cohort study. Surgical Endoscopy 2015; 29(6): 1384-1393.

[249] Grosfeld JL, Solit RW. Prevention of wound infection in perforated appendicitis: Experience with delayed primary wound closure. Annals of Surgery 1968; 168(5): 891-895.

[250] Pettigrew RA. Delayed primary wound closure in gangrenous and perforated appendicitis. British Journal of Surgery 1981; 68(9): 635-638

[251] Siribumrungwong B, Noorit P, Wilasrusmee C, Thakkinstian A. A systematic review and meta-analysis of randomised controlled trials of delayed primary wound closure in contaminated abdominal wounds. World Journal of Emergency Surgery (WJES): 2014; 9(1): 497922-9-49. eCollection 2014.

[252] Daskalakis K, Juhlin C, Pahlman L. The use of pre- or postoperative antibiotics in surgery for appendicitis: A systematic review. Scandinavian Journal of Surgery (SJS): 2014; 103(1): 14-20.

[253] van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA & Snapshot Appendicitis Collaborative Study Group. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surgery 2016, (1); 151(4): 323-329.

[254] Asarias JR, Schlussel AT, Cafasso DE, Carlson TL, Kasprenski MC, Washington EN *et al.* Incidence of postoperative intraabdominal abscesses in open versus laparoscopic appendectomies. Surgical Endoscopy 2011; 25(8): 2678-2683

[255] Markides G, Subar D, Riyad K. Laparoscopic versus open appendectomy in adults with complicated appendicitis: Systematic review and meta-analysis. World Journal of Surgery 2010; 34(9): 2026-2040.

[256] Swank HA, Eshuis EJ, van Berge Henegouwen MI & Bemelman WA. Short- and long-term results of open versus laparoscopic appendectomy. World Journal of Surgery 2011; 35(6): 1221-6; discussion 1227-8.

[257] Hendahewa R, Shekhar A, Ratnayake S. The dilemma of stump appendicitis – A case report and literature review. International Journal of Surgery Case Reports 2015; 14: 101-103.

[258] Ali N, Aliyu S. Appendicitis and its surgical management experience at the university of Maiduguri teaching hospital Nigeria. Nigerian Journal of Medicine: Journal of the National Association of Resident Doctors of Nigeria 2012; 21(2): 223-226.

[259] Bliss LA, Yang CJ, Kent TS, Ng SC, Critchlow JF, Tseng JF. Appendicitis in the modern era: Universal problem and variable treatment. Surgical Endoscopy 2015; 29(7): 18971902

[260] Faiz O, Clark J, Brown T, Bottle A, Antoniou A, Farrands P *et al.* Traditional and laparoscopic appendectomy in adults: Outcomes in English NHS hospitals between 1996 and 2006. Annals of Surgery 2008; 248(5): 800-806.

[261] Andersson MN, Andersson RE. Causes of short-term mortality after appendectomy: A population-based case-controlled study. Annals of Surgery 2011; 254(1): 103-107.

[262] Blomqvist P, Andersson R, Granath F, Lambe M, Ekbom A. Mortality after appendectomy in Sweden, 1987–1996. Annals of Surgery 2001; 233(4): 455-60.

[263] Margenthaler JA, Longo WE, Virgo KS, Johnson FE, Oprian CA, Henderson WG *et al.* Risk factors for adverse outcomes after the surgical treatment of appendicitis in adults. Annals of Surgery 2003; 238(1): 59-66.

[264] Orlova E, Yeh A, Shi M, Firek B, Ranganathan S, Whitcomb DC *et al.* Genetic association and differential expression of PITX2 with acute appendicitis. Human Genetics (2019) 138:37–47

[265] Murphy CG, Glickman JN, Tomczak K, Wang YY, Beggs AH, Shannon MW *et al*. Acute appendicitis is characterized by a uniform and highly selective pattern of inflammatory gene expression. Mucosal Immunol 2008; 1(4):297–308.

[266] Duffy DL, Martin NG, Mathews JD. Appendectomy in Australian twins. Am J Hum Genet 1990. 47(3):590–592 (Elsevier)

[267] Oldmeadow C, Mengersen K, Martin N, Duffy DL. Heritability and linkage analysis of appendicitis utilizing age at onset. Twin Res Hum Genet 2009; 12(2):150–157.

[268] Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M *et al*. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res 2012; 22(9):1790–1797.

[269] Kristjansson RP, Benonisdottir S, Oddsson A, Galesloot TE, Thorleifsson G, Aben KK, *et al.* Sequence variant at 4q25 near PITX2 associates with appendicitis. Sci Rep 2017; 7(1):3119.

[270] Falush D, Stephens M, Jonathan KP. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics 2003; 164(4):1567–1587

[271] Chang ALynnS, Raber I, Xu J, Li R, Spitale R, Chen J *et al.* Assessment of the genetic basis of rosacea by GenomeWide Association Study. J Investig Dermatol 2015; 135(6):1548–1555.

[272] Ferreira MA, Matheson MC, Tang CS, Granell R, Ang W, Hui J *et al.* Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. J Allergy Clin Immunol 2014; 133(6):1564–1571.

[273] Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP *et al.* Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth 2012; 109(5):742–753.

[274] Essner JJ, Branford WW, Zhang J, Yost HJ. Mesendoderm and left-right brain, heart and gut development are differentially regulated by pitx2 isoforms. Development 2000; 127(5):1081–1093

[275] Logan M, Pagán-Westphal SM, Smith DM, Paganessi L, Tabin CJ. The transcription factor Pitx2 mediates situs-specific morphogenesis in response to left–right asymmetric signals. Cell 1998; 94(3):307–317