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Review Article

The Changing Spectrum of Acute Appendicitis in Nigeria: A Systematic Review

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Abstract

Background

Appendicitis is one of the leading causes of general surgical emergency admission worldwide. Available clinical research has produced conflicting reports about best practice, delivery and, a possible variation in outcome in the sub-Saharan Africa. Accordingly, the disease represents an important burden on modern health systems with severe emerging atypical presentations. So far, there has not been any systematic review of the literature on appendicitis research in Nigeria.

Aim

To examine the literature critically for possible changes in the pattern of appendicitis and to determine the impact of emerging atypical presentations in contemporary Nigerian settings.

Method

Published articles discussing appendicitis in Nigeria up to November 2019 were obtained for review from Medline search, medical libraries, and Google.

Results

Fourteen articles were included in the quantitative analysis. Some were excluded from the subgroup analyses. The current estimated incidence of appendicitis is 22.1-49.8 new cases per 100,000 per annum from Nigeria. The result reflects a rising incidence of similar studies over the last decades. Negative appendicectomies occurred at a rate of 10.5% (457/4566). The perforation rate for appendicectomy patients was 19% (868/4566), and the overall mortality rate was 0.4% (18/4566). Research efforts focused on disease patterns and management outcome measures within the country.

Conclusion

Laparoscopic surgery is emerging in Nigeria. The overall negative appendicectomy, perforation, and mortality rates are substantially low, suggesting improving health systems and quality metrics. Clinicians in the rural settings of tropical sub-Saharan Africa require a high index of suspicion. There is a critical need to consider differential diagnoses such as abdominal tuberculosis, amoebiasis, helminthiasis, and schistosomiasis when treating patients with acute abdomen. Finally, an aggressive healthcare financing in the form of Community -Based Health Insurance Scheme, will be highly beneficial at this stage to all Nigerians.

Key Messages

• Acute Appendicitis remains a significant health challenge in Nigeria

• Emerging atypical presentations of Acute Appendicitis is a dilemma to clinicians such as abdominal Tuberculosis, Schistosomiasis and Amoebiasis, etc.

• Laparoscopic Appendectomy is gradually gaining momentum.

• Elaboration of specific gene-expression on-going worldwide, but Nigeria is seriously lagging behind.

Introduction

Acute Appendicitis (AA) is one of the leading causes of general surgical emergency admission worldwide. It accounts for about 15-40% of all emergency surgery done in Nigeria [1,2]. The disease of the appendix is equally remarked to be as old as man with historical links to several developmental milestones as discussed below [3-7].

In a related development, some authors submitted that AA is a rare but changing entity in the rural Africa [1,2]. From the hustle and bustle city of Lagos, in the southwest to the whistling city of Maiduguri in the far northwest, AA continues to rattle the surgeons and permeates with such intriguing audacity that contrary to the earlier assertion, Onuigbo WIB opined that AA is relatively common among his kin- the Ibos, a major ethnic group in Nigeria, West Africa [8,9]. Interestingly, "there has been a steady decline in the incidence of AA since the late 1940s worldwide [10-12]. Variation in incidence of AA has been observed among countries, geographical regions, races, sex, age groups, and seasons" [13,14].

Furthermore, Nigeria is the largest black nation in the world and according to Organization for Economic Cooperation and Development (OECD), one out of every four Africans and more than one out of every five persons of West African origin is a Nigerian [15]. Therefore, the preceding submissions provide the catalyst for embarking on a meta-analysis of AA studies in Nigeria. Accordingly, appendectomy (AE) is one of the most commonly performed surgical procedures and represents an important burden on modern health systems due to attendant high morbidities and mortalities [16,17]. Meanwhile, the disease continues to generate interest among clinicians worldwide and especially in the tropical sub-Saharan Africa because of severe emerging atypical presentations. So far, there has not been any systematic review of the literature on AA research in Nigeria.

Objective

The study aimed to examine the literature critically for possible changes in the pattern of appendicitis and to determine the impact of emerging atypical presentations in contemporary Nigerian settings.

Methods

All peer-reviewed, published, original research studies in which appendicitis was addressed in Nigeria 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 (01/01/2000-01/10/2019) for current trials in AA. Research themes of relevant references were collected and analyzed. Consequently, a structured presentation detailing historical background, epidemiology, appendicitis audits, featured atypical presentations and emerging new trends were extracted from the materials.

Results

Historical Background

The appendix was first described in 1521, and inflammation of the appendix has been known to be a clinical problem since 1759 [3]. Interestingly, Reginald Fitz in 1886 was reported to have described 'appendicitis' and the natural history of the disease [4]. The disease of the appendix is equally remarked to be as old as man. During the Byzantine era, an Egyptian mummy was found with histopathological features of right lower quadrant adhesion, which was suggestive of previous AA [5-7].

Medical historians in Nigeria to date are unable to provide justification for grossly neglecting the much sorted historical development of surgery covering AA and AE. Obviously, there is a lack of data on the history of AA in Nigeria.

Really, Ajayi OO *et al.* (1999) [18] deserve much kudos for documenting "Surgery in Nigeria" that provided the catalyst for writing this section. Ajayi and Adebamowo [18] submitted that "The University College Hospital (UCH), Ibadan, is the premier teaching hospital in Nigeria. The hospital was established in 1948 as an affiliate of the University of London; but, it was not until 1961 that the first phase of medical training was completed. The first graduating sets were awarded MBBS in 1962" [18].

Professor WW Davey was the first Head of the Department of Surgery, UCH, Ibadan, from 1958 to 1964. Davey WW laid a very solid foundation for surgical training which culminated in the publication of the first edition of Davey's Companion to Surgery in Africa. Accordingly, the presumed first published work on 'appendicitis in West African' was by Ude FN in 1962 [19,20]. By injecting barium sulfate suspensions into the superior mesenteric artery of 100 cadavers at the UCH, Ibadan, Solanke TF (1968) [21] demonstrated a rich blood supply to the vermiform appendix of the Nigerian African. Also, in over 80 percent of cases, there were more than one appendicular artery rich anastomoses with adjourning vessels [21]. Other early contributors to AA research in Nigeria include Omo-dare P *et al.* in Lagos (1966) [22], Onuigbo WB (1977) [23], Ajao OG (1979) [24], Adekunle OO *et al.* (1986) [25]; and Adeloye A (1987) [26], etc. These early publications laid the solid groundwork and direction for the further study of AA in Nigeria over the next 50 years.

Epidemiology

Incidence of Appendicitis

The current incidence of AA in Nigeria is estimated at 22.1-49.8 new cases per 100,000 per annum [10,11]. However, findings from other tropical sub-Saharan Africa countries showed an estimate of 2.5-25.9 new cases per 100,000 per annum. The current figures from Nigeria reflect a rising incidence of similar studies over the last decades [24-26]. There have been reports of increasing incidence of AA in African countries by some authors in the previous few decades [14,27-29]. The findings from this series further concurred with this earlier assertion implying that AA incidence rates estimates from Nigeria as equally seen in a larger part of sub-Saharan Africa showed increasing incidence [14,27-29].

Gender Variation

A closer look at the studies emanating from Nigeria showed that relatively higher numbers of women are regularly treated for AA than men. The total numbers of women to men ratio is estimated at (2332/ 2224) as shown on Tables 1, 2, and 3. This observation is in sharp contrast with the findings of some other African studies [14,22,30,31]. The lifetime risk of AA in developed countries is about 6.7% for females and 8.6% for males worldwide [12]. However, the lifetime chances of undergoing AE are much higher, i.e., 9.89% for males and 9.61% for females [13]. The discrepancy between the frequency of surgery AE and the disease AA reveals the magnitude of the incidence of unnecessary AEs. The consensus on the timing of the operation is in favor of early intervention. The consequence of this approach of semi-emergency surgery for AA is a high rate of unnecessary AE, otherwise referred to as "negative AE" [14,32]. The probability of negative AA is over two times higher for women than that for men [14,22]. Moreover, the possibility for perforated AA has been reported to be 0.82 times lower in women than in men [14,33].

Infection

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

Viral Infection

There are studies evaluating the role of viral etiology of AA [14,34,35]. So far, such studies are rare in Nigerian settings. However, other authors reported that seasonal outbreaks of lymphotropic enteric viral or microbial infections might be the reason for a seasonal variation in AA. Even-though we are yet to get a substantial level of evidence, but some proofs thus exist [14,35,36], which are awaiting confirmation from further studies in that connection.

Bacterial Infection

Abdurrazzaaq and colleagues in 2018 from the UCH, Ibadan, Nigeria, submitted after an exhaustive study that the most prevalent aerobic and anaerobic bacteria isolated from inflamed appendices were *Escherichia coli* and *Clostridium perfringes* respectively [37]. The aerobes are sensitive to fluoroquinolones and a third-generation cephalosporin. Anaerobes are sensitive to metronidazole. A combination of Ciprofloxacin and Metronidazole as prophylactic antibiotics or as an eventual treatment for catarrhal appendicitis is recommended [37]. The finding is corroborated by other authors suggesting that 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* [37]. A small yet novel study using next-generation sequencing found a more significant number and the more considerable variation of (up to 15) bacterial phylae than expected in patients with AA [38]. 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 [39]. 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.

Parasitic Infection

Several authors have reported AA caused by parasitic infestation from different regions of Nigeria, Badmus *et al.* [40], Adebamowo *et al.* [41], Adisa *et al.* [42] and Ajao OG [24] from the Southwestern region; Duduyemi from North-central region [11], and Ahmed SA from the Northern region [14,35,43]. The commonly encountered parasites are *Schistosoma mansoni, Schistosoma haematobium, Enterobius vermicularis, Ascaris lumbricoides, Entamoeba histolytica,* and pin-worm, among others [11,14,24,40-42]. The parasitic infection was found in an estimated 2.1% of cases with AA in Nigeria. Similar findings have been reported from South Africa; the parasitic infection was found in 8.6% of cases with AA [14,35,44]. The role of parasitic infestation as the causative agent of AA cannot be overemphasized because these parasites are endemic to sub-Saharan tropical Africa. Some of these studies report is associated with a reduced incidence of inflammatory changes or chronic infection of the appendix, especially in patients with appendiceal pinworms [14,35,45,46].

Appendiceal Tumors

Primary tumors of the appendix are a relatively rare cause of AA. The global incidence of appendiceal tumors varies between the 0.4-1.7percent for all AEs [35,47-49]. Afuwape *et al.* study showed that the prevalence of Tumor-associated appendicitis constituted 2.2% (24/1081) of overall cases [10].

Carcinoid tumor is the most frequently encountered primary appendiceal neoplasm. The overall incidence of appendiceal carcinoid tumors varies from 0.4% to 1% [50], and it accounts for up to two-thirds of all appendiceal tumors [51,52]. "Primary adenocarcinoma of the appendix is rare with an incidence of 0.08-0.2% of all AEs and accounts for 4-6% of primary malignant appendiceal neoplasms," [53]. Nonetheless, the malignancy risk for patients undergoing interval AE after conservative treatment of complicated AA is 28-29% [54]. "Mucocele of the appendix is characterized by dilatation of the obstructed appendicular lumen by mucinous secretions and it is encountered in 0.1-0.4% of all AEs with a female predominance" [55,56]. "The etiology can be either benign (simple mucocele or retention cyst, mucosal hyperplasia, mucinous cystadenoma), or malignant (mucinous cystadenocarcinoma)" [57]. Of all mucoceles, 23-50% is incidental findings at surgery and should be carefully removed to prevent perforation, peritoneal contamination, and the development of pseudomyxoma peritonei [55]. The extent of resection depends on the histology of the mucocele [56].

Appendicitis Audits

General Overview

We reviewed fourteen papers that met the inclusion criteria. The initial diagnosis of AA was based on clinical and radiological features, subsequently confirmed by histopathological findings. The summary of the studied articles is found in Table 1, Table 2, Table 3, and Table 4. The majority of these papers examined had histopathology reports. Negative AEs were estimated at 10.5% (457/4566) of the total operations, and some other lesions constituted 4.2% (187/4566) of the cases, including Ascaris lumbricoides, Schistosoma haematobium, Enterobius vermicularis, etc. After excluding Adisa *et al.* [42] and Akhator A [58] studies, etc., that reported specified studies like 'schistosomiasis' and 'appendicitis in the elderly patients only' respectively.

Table 1: *Audits of Acute Appendicitis in Nigeria*

Ref	Year	City of study	Study period	Age criteria (years)	N	Male	Female	Normal	Appendicitis	Other	Death
Adeyanju AM *et al.*	2009	FMC Lagos	January 1989 to December 2006	All	180	106	74	7	158	22	NA
Adi AJ	2011	MH Lagos	January 2005 to December 2008	>16 years	132	74	58	NA	132	20	NA
Afuwape OO *et al.*	2018	UCH Ibadan	September 2011 to February 2013	>12 years	1081	619	452	100	741	24	NA
Ahmed SA *et al.*	2014	ABUTH Zaria	January 2001 to December 2010.	All	382	195	187	9	373	22	NA

Ajao OG	1977	UCH Ibadan	June 1975 to June 1977	All	47	30	17	12	30	5	5
Duduyemi BM	2014	DH Abuja	November 2009 to October 2012	All	293	128	165	12	281	7	NA
Edino ST *et al.*	2004	BUK Kano	July 1997 to July 2002	> 10 years	142	95	47	20	122	13	1
Dodi-yi-Manuel A *et al.*	2012	UPTH Port- H/ court	January 2008 to December 2009	All	130	62	68	12	118	13	NA
Oguntola AS *et al.*	2010	LAU-TEC & AMC Osogbo	January 2003 to December 2008	All	311	158	153	12	299	NA	NA
Onuigbo WIB	2019	Enugu	June 1973 to Febru-ary 1974	All	79	36	43	NA	79	1	NA
Talabi OA *et al.*	2015	OAUTH Ile-Ife	January 1995 to December 2012	< 15 years	156	76	80	17	139	NA	NA
Balogun OS *et al.*	2019	LUTH Lagos	July 2010 to June 2017	>16 years	224	134	90	NA	219	NA	NA
Ali N *et al.*	2012	UMTH Maidu-guri	January 2000 to December 2009	>15 years	1257	426	831	200	762	NA	12
Njeze GE *et al.*	2011	UNTH Enugu	January 2000 to December 2009	All	152	85	67	56	82	60	NA
TOTAL					4566	2224	2332	457	3535	187	18

NA = Not reported

Table 2: *Classification of Appendectomies*

Reference	Year	N	Male	Female	Normal	Acute	Ruptured	Other Pathology
Adeyanju AM *et al.*	2009	180	106	74	7	74	15	NA
Adi AJ	2011	132	74	58	NA	130	2	NA
Afuwape OO *et al.*	2018	1081	619	452	100	741	216	24
Ahmed SA *et al.*	2014	382	195	187	9	351	22	22

Ajao OG	1977	47	30	17	12	15	15	5
Duduyemi BM	2014	293	128	165	12	207	67	7
Edino ST *et al.*	2004	142	95	47	20	89	33	NA
Dodiyi-Manuel A *et al.*	2012	130	62	68	12	100	18	NA
Oguntola AS *et al.*	2010	311	158	153	12	259	40	NA
Onuigbo WIB	2019	79	36	43	NA	78	1	2
Talabi OA *et al.*	2015	156	76	80	17	64	75	NA
Balogun OS *et al.*	2019	224	134	90	NA	160	59	NA
Ali N *et al.*	2012	1257	426	831	200	762	295	NA
Njeze GE *et al.*	2011	152	85	67	56	82	10	6
Total		4566	2224	2332	457	3112	868	66

NA = Not reported

Table 3: *Gender Distribution*

Table 3a: *Normal Appendix by Gender*

			TOTAL		NORMAL	
Reference	**Year**	**N**	**Male**	**Female**	**Male**	**Female**
Adeyanju AM *et al.*	2009	180	106	74	4	3
Afuwape OO *et al.*	2018	1081	619	452	58	42
Ahmed SA *et al.*	2014	382	195	187	5	4
Ajao OG	1977	47	30	17	4	8
Edino ST *et al.*	2004	142	95	47	13	7
Dodiyi-Manuel A *et al.*	2012	130	62	68	6	6
Oguntola AS *et al.*	2010	311	158	153	4	8
Ali N *et al.*	2012	1257	426	831	80	120
Njeze GE *et al.*	2011	152	85	67	26	30
TOTAL		3582	1776	1896	264	228

Table 3b: *Perforated Appendicitis by Gender*

			TOTAL		RUPTURED	
Reference	**Year**	**N**	**Male**	**Female**	**Male**	**Female**
Adeyanju AM *et al.*	2009	180	106	74	8	7
Afuwape OO *et al.*	2018	1081	619	452	126	90
Ahmed SA *et al.*	2014	382	195	187	14	8

Ajao OG	1977	47	30	17	8	7
Edino ST *et al.*	2004	142	95	47	20	13
Dodiyi-Manuel A *et al.*	2012	130	62	68	12	8
Oguntola AS *et al.*	2010	311	158	153	18	22
Ali N *et al.*	2012	1257	426	831	80	120
Njeze GE *et al.*	2011	152	85	67	26	30
Total		3582	1776	1896	332	276

Table 4: *Prolife Of Post Appendectomy Mortality*

Reference	Year Of Study	Location	N	Mortality	Comments
Ajao OG	1977	UCH Ibadan	47	5	1- with pulmonary emboli 4- overwhelming septicemia from perforated appendicitis
Edino ST *et al.*	2004	BUK Kano	142	1	1 - overwhelming septicemia from perforated appendicitis
Ali N *et al.*	2012	UMTH Maiduguri	1257	12	12- overwhelming septicemia from perforated appendicitis
Total			1446	18	Rate=0.4%(18/4556)

Other details are as follows: The overall parasitic infection rate was 1.5% (50/4566). There are two reports from Nigeria on appendiceal neoplasms, primarily comprised of a carcinoid tumor estimated at 0.5% (23/4566) from 22 cases reported by Afuwape *et al.* [10] and a 27 years female patient reported by Njeze GE *et al.* [59]. Besides, TB appendicitis constitutes 0.024% (1/4566), which was reported in a 33 years male patient equally reported by Njeze GE *et al.*, both from the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria [59]. The overall appendiceal perforation rate in all the cases studied was 19% (868/4566), which appears relatively high but comparable to figures from Ghana, South Africa, etc. [33]. In this review, the incidence of the fecolith was estimated at 13.5% (621/4566), and the overall mortality rate was estimated at 0.4% (18/4566) for the AE cases considered.

Time to Presentation

The time to presentation is defined as that between the onset of symptoms and presentation in any health facility. The majority of the patients in this series do not seek medical treatment within the initial 24 hour period. According to some authors, the time to presentation is a significant risk factor for appendiceal perforation [60]. Edino *et al.*, found a perforation rate of 23.2%, which is comparable to other reported

perforation rates from Nigeria [60-63]. Moreover, it is equally essential to understand various factors that play a critical contributory role to high perforation rates in our contemporary settings in Nigeria. Such factors as i) delayed presentation, ii) fulminant disease, iii) misdiagnosis, and iv) failure to accept medical treatment [60-63].

Adeyanju *et al.* [64] reported that the interval between admission and surgery ranged from 1h to 198h with a mean of 22.06 h. An estimated 50% of AE cases were performed between 19-24 hour intervals. Complications were highest relatively after 24 hours period; Most of the patients had their surgeries at 19 hours and above or that the delay increased morbidity. Adeyanju and Adebiyi [64] reported a perforation rate of 13 (7.2%) of 180 AEs. In sharp contrast to the previous opinion, other authors have suggested that delaying surgery in AA does not necessarily increase morbidity or mortality (Mangete and Kombo, 2004) [65]; (Sack *et al.,* 2006) [66]. Balogun *et al.* submitted a perforation rate of 28.5% from their study. Nonetheless, another retrospective study by Edino *et al.* [60] reported a perforation rate of 23.2%, which constitutes 33 cases of appendiceal perforation from 142 AEs. This is far higher than the values observed by some researchers in Nigeria and smaller than the quoted figure from Ghana [60,64,67,68]. This difference may reflect a varying pattern of referral and also because these studies are retrospective.

Etiopathogenesis of Appendicitis

The study is first to appropriate definitive terminologies for the various etiological factor for AA and the details follow an exhaustive review of elaborate work of literature subsequently summarized in the sections below:

Sanctuary-Site Theory

Sanctuary-Site is defined as a hidden body part notorious for recrudescence or early relapsing of diseases. The great question in the mind of all is why the sanctuary site is an acceptable term for this theory. The term has been appropriately used for ovaries and testes previously. In this series, a conceptual review of the appendix shows that structurally, the appendix is a finger-like projection located at the base of the caecum whose definitive function is unknown but thought to play a role in immune reaction [69]. Current postulation suggests that it may be a 'bank house' or 'storage tank' for commensal bacteria (Bollinger *et al.*, 2007) [69]. However, its removal leaves no apparent functional deficit. Notwithstanding, inflammation of the appendix can occur following luminal obstruction. The obstruction is caused mainly by fecolith, worms, adhesions, tumors, and lymphoid hyperplasia, etc. [69].

Ajao OG, in his series, found Ascaris worms in the ileum in three cases, and one patient had ova of Schistosoma in the appendiceal wall [24]. In a study of the appendices of some cadavers, Solanke [70] and others [71] have also found and ova of parasites in the lumen of appendix [24,43,64,70].

Consequentially, appendix may be a storage tank or a hidden body part notorious for recrudescence of parasites, ova of parasites or any other microbes. Thus, it is serving the "sanctuary-site" role in this regard as documented [24,43,64,70]. The resulting appendiceal obstruction leads to the accumulation of intraluminal secretions with increased pressure, reduced lymphatic, venous drainage, and proliferation of bacteria growth

in the appendiceal wall, causing inflammation. In advanced cases, there could be perforation and leakage of pus into the peritoneal cavity [24,43,64,70].

Tampered Immune Hypothesis

The hypothesis suggests the endemicity of water-borne gastrointestinal pathogens, including *poliomyelitis, hepatitis viruses, shigellosis, cholera, typhoid enteritis, giardiasis,* and *amoebiasis* with prevalent infections in our population setting like Nigeria [35]. Moreover, some authors rationalized that these pathogens tampered with the overall immune response of the patients resulting in a less vigorous immune response that does not lead to sufficient hypertrophy of the lymphoid follicles. The resulting obstruction in the wall of the appendiceal lumen is insufficient enough to occlude it [35].

Consequently, the relatively high ratio of fecoliths in the appendiceal specimens is explained by that mechanical contribution. Moreover, that does not yield to immune modulation or runs a relentless course to AA [35]. The tampered immune response is the one logical explanation for the finding of fecoliths in the overwhelming majority of our cases of AA examined [35].

Fecolith Hypothesis

Fecolith is one of the most important causative agents of mechanical obstruction. Rendle Short first hypothesized it in 1920. The fecolith hypothesis was spurred by the observation of an upsurge of AA in Britain at the beginning of the twentieth century [35,72]. Short 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 [35,73-75]. The fecolith hypothesis implicates two factors in the etiology of AA, which consists essentially of fecoliths and high intra-colonic pressure.

In the first instance, Burkitt and his team demonstrated a significant difference in the incidence of fecoliths in AA and non-pathological specimens of the vermiform appendix in a comparative study of patients in Toronto and Johannesburg [35,76]. Several other authors worldwide have corroborated these findings. The incidence of fecolith is 11-52% in patients operated on for AA [35,77-80].

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 [35,81]. In a study from China, the incidence of the fecolith was 9.6% in normal appendices [35,82]. After the occlusion occurs, appendiceal intraluminal high pressure tends to return material into the caecum. Therefore, a shred of evidence for a just cause of AA is missing [35,83]. Consequently, it is possible, therefore, that the real incidence of fecoliths in cases of AA is much higher.

Stump Appendicitis

Stump appendicitis is described as an inflammation of the remnant of the Vermiform appendix after a previous surgical AE. Rarely, residual appendix stump after surgery may contain a trapped mass of fecolith, which may subsequently cause inflammation and perforation [84,85]. However, the entity "stump appendicitis" was

first described and reported in 1945 by Rose in Australia. He reported stump appendicitis in two patients who had surgery for AA, and they later presented with appendiceal abscess [84,85]. In recent times, there were sporadic reports on stump appendicitis following traditional open and laparoscopic appendectomies (LAs). To date, stump appendicitis appears to have remained a rare clinical entity and may be considered an infrequent cause of recurrent iliac fossa pain following AE [84,85].

Balogun OS *et al.* reported stump appendicitis due to retained fecolith after laparoscopic surgery in a 49-year-old male Nigerian who presented to us with recurrent right iliac fossa pain and abdominal distension of 2 weeks' duration [84,85]. The patient had a LA one year before the onset of fresh AA symptoms. A diagnosis of stump appendicitis with small-bowel obstruction was made with an abdominal computed tomography scan. He subsequently had an open stump appendectomy and small-bowel adhesiolysis with a good postoperative outcome [84,85].

Glasgow Western Infirmary Based Theory

This classification was verified personally by Onuigbo WIB (2019) with a consecutive series of AEs performed by three German doctors on 79 Ibo patients at a Mission Hospital in Nigeria [8]. The study was carried out at the Glasgow Western Infirmary, which postulated that AA is classifiable histologically into "limited" and "complete" types. In the Ibo-ethnic group, the proportion of limited AA was found to be higher than the Glasgow findings [8]. Now, the Ibos are aware of and dread AA, which they call "etuto afo," i.e., an intra-abdominal abscess. Therefore, awareness of the patients themselves is another factor that affects the proportion of limited AA diagnosed in a hospital [8].

Atypical Presentations

The body of literature on AA in Nigeria is skewed towards the discovery of a few clinical entities, which are public health concerns. In this section, the author mainly describes these atypical presentations of AA, also emphasizing the rarity of the conditions.

Situs Inversus Totalis Theory

Situs Inversus is a rare congenital anomaly which occurs in 1:20,000 of the general population. Left-sided AA is associated with two types of congenital abnormalities, Situs Inversus, and malrotation [86]. This condition is often diagnosed incidentally while investigating or treating a patient for some other conditions as in our index patient. Ngim O *et al.* [86] in 2013 presented a case report of a 22-year-old Nigerian male who was admitted through the emergency unit of a military hospital in South Nigeria on account of an acute abdomen. A diagnosis of AA was made after clinical evaluation, but at surgery, the inflamed appendix and cecum were found in the left iliac fossa. At the time of his presentation, an abdominal ultrasound scan could not be done for logistic reasons. However, an abdominal ultrasound scan and a chest X-ray done after surgery confirmed Situs Inversus Totalis [86]. This case is presented to highlight the rarity of this condition and the first reported case in Calabar, Nigeria. The author emphasized the need to do an abdominal ultrasound scan routinely in matters of the acute abdomen where indicated.

The reason is to avoid making a wrong incision at the surgery with its attendant morbidity and poor cosmesis. Laparoscopic surgery, where possible, is of immense benefit in this condition [86].

Amyand Hernia

The first description of an appendix in an inguinal hernia is attributed to Amyand (sergeant surgeon to King George I and II). Who, in 1735, found a perforated appendix in an 11-year-old boy who presented with a right inguinal hernia and fecal fistula [87,88]. Amyand's operation was also one of the first documented descriptions of an AE being performed [87,89]. Four years before this, French surgeon René Jacques Croissent de Garengeot described the presence of an appendix within the femoral hernia sac, the so-called de Garengeot hernia [87,88].

Dienye and Jebbin in 2011 presented a case report of AA masquerading as the acute scrotum. Atypical presentations of AA are not uncommon, but the association with acute scrotum is an extreme rarity [87]. A 30-year old fisherman presented at a rural medical facility with a 2-day complaint of severe pain at the right hemiscrotum followed about 24 hours later with mild diffuse abdominal pain. He was admitted as a case of the acute abdomen for close observation. An abdominal and scrotal ultrasound scan was normal. By the second day of admission, the pain became marked at the right lower abdomen with associated vomiting. There was also marked tenderness at the right lower quadrant with a rebound. A diagnosis of AA was thus made, and AE was done after proper workup [87]. The abdominal and scrotal pain stopped after surgery, and the patient was discharged on the seventh postoperative day. Patients with unusual abdominal and scrotal pain should be admitted, initially given close observation, and subsequently re-evaluated to prevent unnecessary scrotal exploration of negative AE [87].

Amoebic Appendicitis

Globally, cases of amoebiasis presenting as AA is a rarity [90]. The literature report revealed only very few examples from Japan, India, Egypt, and Kuwait [90-94]. Therefore, a case was equally reported of a 30-year-old male Nigerian of the Igbo ethnic group. Who attended the Oko Community Hospital complaining of pain in the abdomen with nausea for about two days to presentation [90]. The physical examination revealed classical tenderness in the right iliac fossa, and Rovsing's sign was positive. At the operation, the appendix showed adhesions and was removed. On microscopy, there were luminal pus cells as well as typical *Entamoeba histolytica* parasites showing ingested red blood corpuscles. Histopathology examination revealed the unexpected presence of *Entamoeba histolytica* instead of the ordinary inflammation. This case increases the awareness of surgeons in Nigeria that appendix may be a primary site for amoebiasis. Therefore, confirming cases of amoebiasis presenting as AA in the tropical sub-Saharan African settings [90].

Lassa Fever

Dongo AE *et al.* submitted that Lassa fever is rarely considered as a differential diagnosis of acute abdomen and AA even in endemic areas. Lassa fever is a zoonotic viral infection that is endemic to the West Africa sub-region [95,96]. In a majority of cases, the diagnosis of Lassa fever is suspected only after surgical intervention. Therefore, such patients often undergo unnecessary surgery with resultant delay in the

commencement of ribavirin therapy. Thus increases morbidity and mortality and the risk of nosocomial transmission to hospital staff [95,96].

Dongo AE and colleagues reported seven cases in patients who underwent a surgical operation for suspected AA, perforated typhoid ileitis, intussusception, and ruptured ectopic pregnancy after routine investigations. All seven were post-operatively confirmed as Lassa fever cases. Four patients died postoperatively, most before the commencement of ribavirin, while the other three patients eventually recovered with appropriate antibiotic treatment, including intravenous ribavirin [95].

Akpede *et al.* reported the case of a 7-year-old girl who was admitted with typical signs and symptoms of AA, the diagnosis of which was supported by her Ultrasonographic scan (USS) results. AE, however, was deferred on admission because the anesthetic team believed that her high-grade fever made AA unlikely and requested a Lassa virus specific RNA (LASV) PCR tests instead. Results of the PCR assay were indeed positive, but the child responded poorly to intravenous ribavirin and ceftriaxone; her condition deteriorated until she underwent surgery on the sixth day of admission [96]. The intraoperative findings included a ruptured appendix with pyoperitoneum. She improved rapidly after surgery. The diagnosis of AA was confirmed histologically. Surgeons working in West Africa should include Lassa fever in the differential diagnosis of acute abdomen, especially AA. The presence of high-grade fever, proteinuria, and thrombocytopenia in patients with acute abdomen should heighten the suspicion of Lassa fever. Prolonged intra-operative bleeding should not only raise suspicion of the disease but also serve to initiate precautions to prevent nosocomial transmission [95,96].

Tuberculous (TB) Appendicitis

Tuberculosis is still a common infection in the Sub-Saharan African nations like Nigeria [97-99]. The emerging facts, according to Ofoegbu OS *et al.*, showed that there are alarming HIV positive TB mortality rates in African countries, including Nigeria, which are said to be 29.9 times higher than non-African countries [97,98,100]. TB or extrapulmonary TB [97,98] and not having a treatment supporter [99,100], the presence of other morbidities like neoplastic diseases [98], respiratory, and cardiovascular diseases [100] as well as diabetes mellitus [99] in HIV positive TB patients, have also been implicated in the increased mortality in these patients. Although the ileocecal region is the most affected part of intestinal tuberculosis, acute tuberculous appendicitis is quite a rare entity. Primary TB of the appendix presenting as the appendicular abscess is even more unique, with the incidence of 0.1-0.6% [97-100]. Due to the rarity of acute tuberculous appendicitis and the absence of any specific clinical and radiological findings, diagnosis is made only after histopathological examination of the appendectomy specimen. In our Nigerian setting, a nation where TB is still endemic, there is a need for a high index of suspicion. Clinicians still need to consider the diagnosis, especially when treating patients with an acute abdomen in the background of HIV infection [97-100].

Schistosomal Appendicitis

Globally, *Schistosoma haematobium, Schistosoma mansoni,* and *Schistosoma japonicum* have been implicated as a species of pathological importance with respect to AA; mainly, because these three species commonly deposit their eggs in the appendix [101,102]. Surprisingly, Schistosomiasis causes AA as a rarity,

even though Schistosomiasis of the appendix is a well-recognized disease [101,103,104]. Some other reports have implicated *S. haematobium, S. mansoni,* and *S. japonicum* species in having a preference for the appendix [40,41,101,105,106]. Ahmed SA *et al.*, in a 2014 study, reported 30 cases of schistosomal appendicitis seen in a tertiary hospital in Northern Nigeria, from 1464 AE specimens received over a 22-year study period [101]. However, fecoliths were identified in 24 cases. Microscopic examinations showed that all the appendices had Schistosoma ova in the mucosa and different parts of the wall. The egg was morphologically consistent with *S. haematobium* in 29 cases, while one example was consistent with *S. mansoni*.

The implication of Ahmed SA *et al.* (2014) submission is that Schistosomiasis is endemic in many parts of Nigeria [101]. The incidence of schistosomal appendicitis from Ahmed SA *et al.* study is 2.1% (30/1464). Many Nigerian authors have documented similar findings for the incidence of schistosomal appendicitis, in which 2.3% was reported by Gali *et al.* [101,107] in Maiduguri and 2.4% was observed by Adebamowo *et al.* [41,101] in Ibadan.

Adisa AO *et al.* in 2009 reported 2.3% (22/956) as the incidence of schistosomal appendicitis in their study at the Obafemi Awolowo University Teaching Hospital Ile-Ife [42,101].

However, the incidence of schistosomal appendicitis figure reported by Ahmed SA *et al.* was higher than that reported by Ojo *et al.* [101,106]. Ahmed SA *et al.* estimate values of 0.9%, but lower than the 4.15% value observed by Badmos *et al.* [40,101] and 9% value observed by Attah *et al.* [101,108] in Ibadan. The reason for the fall in the incidence is probably due to the improvement of the provision of social and medical amenities and treatment with effective trematodecidal drugs in Nigeria. For instance, a complete cure is achievable with a single 60mg/kg dose of oral praziquantel, which is also readily available. Conclusively, the symptomatology of Schistosomal appendicitis is similar to other traditional AA. The diagnosis is only reliably made at histopathological examination. So much need to be done in the area of prevention of schistosomiasis to reduce the bizarre attendant morbidity, and adequate follow-up is however required to ascertain long-term outcome [101,108].

Biomarkers

Biomarkers Utilization

Biomarkers are used to supplement patient history and clinical examination, especially in children, women of fertile age, and elderly patients when the diagnosis is difficult [109]. No inflammatory marker alone, such as white blood cell count, C-reactive protein (CRP), or other novel tests, including pro-calcitonin, can identify appendicitis with high specificity and sensitivity [109,110]. However, the white blood cell count is obtained in virtually all patients who are assessed for AA, when available. A range of novel biomarkers has been suggested during the past decade, including bilirubin, but yet to gain full external validity and often suffer from low sensitivity, awaiting general acceptance within clinical practice [109,111].

Bilirubin as Marker for Acute Appendicitis

Recent studies suggest that bilirubin is a potential marker for AA [112-114]. Raised Serum bilirubin from 20.52μmol/L to 143.64μmol/L in acute inflammation of the appendix has been observed [112-114]. The

underlying mechanism for hyperbilirubinemia is thought to be due to compromised appendix wall integrity that leads to translocation of bacteria and endotoxin into the portal system. Interestingly, the mechanism captures the disruption of the excretion of bile into the biliary ducts. Serum total bilirubin increases as the infection become more severe [114,115]. Pro-inflammatory cytokine and nitric oxide also play a role in triggering intrahepatic cholestasis [116]. In the Kolanjiappan B *et al.* [112] study, mean serum bilirubin levels were 1.65±0.83 among subjects diagnosed having a perforated appendix, whereas it was 0.82±0.36 among subjects having a non-perforated appendix. Thus, it can be stated that mean serum bilirubin levels were quite higher in patients with perforated AA compared to non-perforated. This finding is similar to a retrospective study conducted by USC Medical Center, Los Angeles, that found patients with gangrene and perforation were significantly more likely to have hyperbilirubinemia than those with AA [117]. Many studies looked at the level of 17μmol/l as the cut-off value to predict perforated appendix, [117,118]. Given the multiple findings on sensitivity and specificity, hyperbilirubinemia gave some value as a predictor of a perforated appendix. Researchers suggested that the bilirubin level should be assessed together with clinical signs and symptoms [119]. Bilirubin is an emerging potential marker for AA, and related studies are yet to commence in Nigeria.

Antibiotic Therapy

Some literature suggested that delaying surgery in AA does not necessarily increase morbidity or mortality, but in sharp contrast to the previously held viewpoint [64,65]. Adeyanju *et al.* reported that most surgeons in Nigeria are now undertaking active in-patient management and observation with antibiotic therapy; as against emergency surgery without necessarily increasing the rate of rupture [64]. This emerging approach is contrary to the popular and earlier submission that clinicians in the African settings are generally opposed to antibiotic therapy and so reject it as a non-option [14]. However, as a general rule, this non-surgical management approach does not apply to ruptured cases and tends to lead to the increasing occurrence of recurrent appendicitis. Besides, the majority of patients managed using this method tend to refuse surgery once the acute episodes have subsided, consequentially leading to recurrence and rupture at a later date [120]. Bickell *et al.* [121], in his study of 219 adults with AA had documented a minimal perforation risk in the first 36 h of symptom onset and remained at 5% after that. However, a study has shown that in many patients treated with antibiotics, AA symptoms resolve without ensuing perforation. Therefore, antibiotic therapy is proven to be credible as a treatment option in uncomplicated AA for a selected group of patients worldwide [122].

Laparoscopic Appendicectomy

LA is the gold standard in developed countries. Laparoscopic surgery offers many proven advantages over conventional open surgery for many procedures [123]. The benefits include: i) minimal surgical trauma, ii) less postoperative pain, iii) rapid postoperative recovery, iv) exploration of the entire abdominal cavity, v) management of unexpected findings, vi) better cosmetic outcomes, and vii) rapid return to normal activities [123-129]. These advantages have increased the utilization and acceptability of laparoscopy. Moreover, it has significantly impacted on other forms of minimally invasive procedures over the past few decades.

Expectedly in Nigeria, the overwhelming interest in laparoscopic surgery is rising exponentially among surgeons in general. The emerging fact to date is that many private and public hospitals are adopting the technique for different conditions. Still, there exist some worries about the safety and overall outcome of laparoscopy for various circumstances in our developing setting [123-126]. In many developing countries like Nigeria, the challenges posed by the burden of infectious diseases and other primary healthcare concerns have limited government support for the development of modern tertiary healthcare facilities. Indeed, laparoscopic surgery is practiced in only a few tertiary hospitals across the country. Especially for those surgeons that share similar enthusiasm and now able to sustain the routine practice of laparoscopy in general surgery [123-126].

In a related development, Afuwape *et al.* submitted that the challenges experienced in developing countries apart from the cost of instrumentation include: a) lack of government support, and, b) a low acceptance level among patients [130]. The consequent low volume of surgical cases debars cost reduction for surgery. Consequently, there is a need for public health education in Nigeria to drive this relatively new frontier of surgery to improve our practice and encourage indigenous innovations within the country [130].

Outcome Measures

Complications Post Appendectomy

Adesunkanmi AR in 1993 reported surgical site infection (SSI) and wound dehiscence in 20.4% and 7.4% of the 54 cases, respectively. In his submission, AA is commonly encountered in private and tertiary health institutions in Nigeria and that the clinical course and postoperative outcome are relatively independent of the clinical settings [131].

Ajao OG in 1979 found relatively high rates of perforation, which were closely related to delay in surgical intervention. The delay which ultimately contributed significantly to the high morbidity and mortality in the cases studied. He, therefore, recommended that urgent surgical management is required in other to avoid serious complications like portal pyemia that can result from appendiceal mass or abscess [24].

Balogun OS *et al.*, in 2019, documented pelvic abscess in 8 (13.5%) of the patients and submitted that, "routine use of peritoneal drain for perforated AA did not significantly reduce the incidence of pelvic abscess in the clinical setting in Nigeria" [84]. A recent Cochrane review reported that "the beneficial role of abdominal drainage on the prevention of intra-peritoneal abscess or wound infection after open AE is uncertain for patients with complicated AA" [84,132]. Interestingly, the overall complication rate in Balogun OS *et al.* study was 43.1%. However, "we recorded more than one type of complication from some patients in this series. Preoperative ASA score was associated with the incidence of post-op AE complications for perforated AA ($\chi^2 = 11.22$; $P < 0.05$). The study also showed some association between the frequency of SSI and the male gender ($P = 0.041$), comorbidity ($P = 0.037$), and ASA (0.03) at a 95% confidence interval." However, there is no statistically significant association between SSI and age (age group), previous attacks, total white blood cell count at presentation, and time to surgical intervention [84,132].

Adeyanju MA *et al.*, in 2015, submitted that "post-AE complications occurred more in males, but this was not statistically significant (0.321 at 5% significance). The correlation between sex and complexity in this

study shows a positive index of 0.074, which revealed that men are more likely to have complications than women" [84]. Accordingly, complications were more likely to occur in patients with perforated than non-perforated AA. "The perforation rates can be explained by the presence of pus in the peritoneal cavity before surgery. The positive correlation of 0.70 between BMI and complications at a 5% level of significance could be due to poor wound healing in obese people" [84].

Adisa *et al.*, in 2012, contributed post-LA complications in their study to include superficial SSI, which involved the umbilical wounds [123]. Hypertrophic and keloidal scars were reasonably common complications of abdominal wounds seen in their practice [123,124]. Surprisingly, they recorded no incisional hernias in their study. Nonetheless, the majority of these post-LA complications occurred in the first year.

The overall findings are similar to other previous studies [133-135].

Mortality Post Appendectomy

In 1920 the mortality was very high, ranging up to 22% for AA [136-138]. This figure, however, has subsequently declined enormously, which is estimated at 0.1% for uncomplicated AA. The estimate is higher, i.e., 0.6%, for gangrenous, and much higher at 5% for perforated AA [136-138]. "Among African populations, although AA has now become the most frequent abdominal emergency, it still presents a far less frequent surgical problem than is the case among whites. Mortality is low in contemporary African settings. For instance, from 1984-1986, in patients hospitalized in Benin City, Nigeria, death was 0.3%" [136-138]. For the same period at Baragwanath Hospital, Soweto, it was also 0.3%. Surprisingly, "AA causes low mortality in general, in both developed and developing populations, mortality increases steeply if the appendix becomes gangrenous and gives rise to diffuse peritonitis; Moreover, in this respect, the danger is particularly severe in the very young and the very old" [136-138] .

In this series, the overall mortality rate for AE patients was estimated at 0.4% (18/4556). As shown in Table 4, this is similar to estimates from other studies in African settings.

Other details from this series are as follows.

In the study by Ajao OG [24], one patient died five days postoperatively as a result of pulmonary embolism diagnosed only at autopsy. The four other deaths were due to septicemia, and all the fatalities had perforated appendices [24]. Also, in the Edino *et al.* study, there was one fatality from overwhelming sepsis estimated at 0.7% of all the cases reviewed [60]. From Ali N *et al.* study in Maiduguri [139], there were 12 deaths recorded. The cause of death in all the cases is from overwhelming septicemia due to perforated AA. In the majority of the articles reviewed, the mortality rates were not mentioned. It is not very clear as to whether we are under-estimating the mortality rate reports. Or that the present figure is genuinely representative of the statistics from the entire nation of Nigeria.

Health Systems and Quality Metrics

Conceptually, the healthcare system in Nigeria has notable challenges, which include i) under investment in health systems, ii) poor healthcare infrastructure, iii) inadequate funding, iv) insufficient policy frameworks, and v) inappropriate implementations of Public-Private-Partnerships (PPPs) [140]. These, among other challenges, may contribute to poor universal health care (UHC) delivery being experienced by most

government and private health facilities in Nigerian [141,142]. Today, many Nigerian patients are still experiencing severe dissatisfaction to the prevailing quality of healthcare services. Due to the mounting inadequacies being experienced, and especially those who can afford it, now receive medical treatment abroad through medical tourism. The rich-patients seek health-care elsewhere, especially for general surgeries, as well as for Medicare in cardiology, neurology, and oncology in India, etc. [140-142]. Surprisingly, there are very few indigenous high-profile private hospitals also mopping such rich-patients but such services are significantly beyond the reach of the low and middle class socio-economic Nigerian-patients like Lagoon hospitals, and EKO-corps hospitals, etc.

Besides, there exist to date pulses of Community-Based Health Insurance (CBHIS) for workers in the informal sector and rural areas. Interestingly, states such as Lagos, Anambra, Ogun, and Kwara are currently implementing CBHIS. A good example is Lagos State, which is newly establishing a Lagos State Health Insurance Scheme [140,143]. The slow pace of implementing universal health insurance coverage is unfortunate because countries such as Ghana, Rwanda, and Kenya- which started several years after Nigeria- have hit over 50% coverage in the meantime [140,144].

However, many of the State and General hospitals have been able to perform very few AEs, laparotomies, and other general surgery procedures either by experienced Medical Officers or General Surgeons in-house. There are Federal Medical Centers in all the States of the Federation with multi-disciplinary teams of specialists at about 25 to 50Kilometers from the rural communities that tend to serve as referral centers in Nigeria. In all, the delivery system is improving, but much still needs to be done [145].

Discussion

Epidemiology

The current figures from Nigeria reflect a rising incidence compared to similar studies over the last decades [20,24,106]. There are reports of the increasing prevalence of AA in African countries by some authors in the previous few decades [14,27,28]. The findings from this series further concurred with this earlier assertion implying that AA incidence rates estimates from Nigeria showed increasing incidence [14,27,28]. Especially when compared with other countries in tropical sub-Saharan Africa [14,27,28].

Furthermore, AA was regarded as the disease of the rich. Mainly because in the UK the general public was made aware of AA in 1901, especially when Sir Frederick Treves operated on Edward VII for the disease [136,146,147]. The King's coronation had to be postponed. The frequency of AA rose rapidly from the turn of the century until about 1940-1950. Since then, it has fallen to about half of its peak level [136,148,149]. In 1980, in the UK, the incidence figure for Anglesey was about 200, for England and Wales, 100, and Scotland, also 100, per 100000 populations. The rate for Scotland had fallen tremendously, from about 550 in 1930 to 100 in 1980 [136,150]. In Sweden, at Jonkoping County, with a population of 302,475, the incidence rate of AA from 1984 to 1989 was estimated at averaged 116/100000 per annual [30,136]. In the UK, reports from the North Tees Hospital, suggest that the incidence of AA declined from about 100 to 52 per 100000 populations from 1975 to 1991 [136,151]. In the USA, from 1979 to 1984, the annual AA incidence rate from some regions of the nation varied from 94 to 154 per 100 000. The rate was about 1.5

times higher for whites compared with that of Afro-Americans [136,152]. In South Africa, "AA remains rare in rural Africans. At Murchison Hospital, South Natal, in 1986, there were seven patients with the disease in about 8000 admissions, drawn from a semi-rural population of about 200 000" [136,153]. At Baragwanath Hospital, Soweto, in 1987, there were 210 patients in 24 000 admissions from a population of about 2.5 million, i.e., constituting a rate of about 8.2 per 100000 [136,153]. In 1993 and 1994, the rate was calculated to be 9.5 per 100000 [136,153].

Njeze GE *et al.* [59] submitted that significantly acute or chronic appendicitis, which was the most common lesion seen presented at a mean age of 19.9 years SD 9.12. This observation agrees with existing literature, which depicts "AA as a disease of adolescents and young adults [154], One report by Zulfikar *et al.*, and Ojo *et al.*, suggests that the AA commonly present in the second and third decades of life" [59,106,155].

Dietary Fiber Hypothesis

"There has been a considerable report of the epidemiology of AA covering incidences, gender, and age from Nigeria [14,35,156-158]. We are truly experiencing a modern trend of increasing incidence of AA in some African countries in the last few decades," [14,35]. "The gradual adoption of a western lifestyle, including diets, has been considered to be responsible for this situation [14,35,45,46,159,160]. One hypothesis that holds- sway suggests that the high fiber content of diet in these groups of people in tropical Africa allows for a reduced fecal transit time" [63,75,136,161]. Invariably," the high fiber content of diet is responsible for a low frequency of occurrence of fecoliths in the lumen of the appendix as a causal agent for AA in people living in these parts of the world" [14,35,45,46]. "The fecolith hypothesis has been discussed extensively in the preceding sections; Patients with Mediterranean or African diet that is very rich in dietary fibers like the Bantus tribe in Africa has a significantly low incidence of AA" [63,75,136,161].

Lymphoid Hypertrophy Hypothesis

Lymphoid hypertrophy hypothesis suggests that AA is an immune disorder. That tends to be prevalent, especially in settings where housing and public health indices have improved significantly [14,156,157]. "The implication of this attendant theory is that for AA to occur, the rural communities dwellers must be exposed to some infections resulting in hypertrophy of the lymphoid follicles that abound in the wall of the appendix." Consequentially, these hypertrophied lymphoid follicles lead to luminal obstruction of the appendix leading to AA after all," [14,152,157,158,160]. "This hypothesis attempts to bring to our understanding the higher incidence of AA in the developed countries when compared with developing countries. In a related development, some authors overwhelmingly submitted that AA tends to occur more frequently in males while others have suggested a significantly higher incidence in females" [14,152,157,158,160].

Nonetheless, "AA most frequent peak age incidence is the age range of 10 to 30 years. However, historical happenings or events post the Second World War, such as a lower domestic overcrowding and reduced birth rate, might have contributed to the epidemics as narrated by a study" [14,161]. Interestingly, "some authors are of the opinion that overcrowding may play a favorable role in the prevalence of AA; which may express the contribution of poor hygiene in the low occurrence of AA in developing countries indirectly" [14,152,157,158,160].

Intestinal Parasites

The parasite infection rate estimate is two percent in this study as shown in Table 2 represented as other pathology. But, there is a relatively high prevalence of intestinal parasites to date, especially in the rural community of Nigeria, accounting for a few cases of AA in this review [14]. "The frequently encountered parasites are S*chistosoma mansoni, Schistosoma haematobium, Enterobius vermicularis, Ascaris lumbricoides, Entamoeba histolytica,* and pin-worm, among others. Badmus *et al.* [40], Adebamowo *et al.* [41], Adisa *et al.* [42], and Ajao OG [24] from the Southwestern region; Duduyemi from North-central region [11], and Ahmed SA from the Northern region of Nigeria" [43]. These parasites continue to be a significant health challenge to clinicians, mainly in the rural communities of Nigeria.

Perforation Rates

The appendiceal perforation rate estimate from this series is 19% for overall cases as shown in Tables 2 and Table 3. Balogun *et al.* reported that delay in the surgical intervention had not impacted significantly on the increased rate of perforation 84. Yang *et al.* submitted that perforation rates were high in South Africa, and associated with a delay in seeking medical care [162]. However, obviously, from this review, all fatalities recorded in AA patients were attributable to overwhelming septicemia due to perforated AA. Afuwape *et al.* argued that there is a causal relationship between appendiceal perforation and delay in presentation for intervention [10]. "Women undergoing AE were more likely to have a negative operation than men, but men were more likely to have more severe disease" [10,163]. The disease severity in men has been shown in previous studies with an underlying explanation of differences in health-seeking behavior, whereas no differences by gender have been reported in other large-scale studies [162].

Laparoscopic Appendectomy

LA is gradually gaining momentum, especially in some tertiary hospitals in Nigeria, from this series [124,164-166]. It was obvious that the "laparoscopic approach for an AE is at least as safe and effective as its open counterpart; Interestingly, open AEs remain popular among surgeons in Nigeria as the first-line option of care" [124,130,133]. "Exploring further on frequent use of LA ultimately will culminate in the reduction of operating time and hospital costs for our patients. Analysis of our data demonstrated that despite the availability of the equipment and expertise for both techniques, at such centers, a large number of patients underwent open AE as compared to a laparoscopic procedure; Thus reflects the personal preference of the staff surgeon in the settings, probably because of the lesser cost for the patient" [124,130,133]. The issue of residents training resulting in increased overhead healthcare costs remains an area of great concern in academic institutions [124,130,133]. The overall healthcare costs are particularly relevant in developing countries without proper healthcare support like ours, where it has a direct impact on the whole patient care [124].

New Trends in Appendicitis

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 [167,168]. 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)" [167,168]. "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 AA derived from linkage genes, complex segregation, and twin studies range between 27% and 56%" [167-169]. Interestingly, "there are newer reports that represent milestone developments in our understanding of the role of familial genes and heredity in AA" [170,171]; nonetheless, further studies to elucidate the distinctive role of PITX2 in AA are now being warranted and highly recommended by clinicians in general. Notwithstanding the ongoing global elaborate effort at genome-wide association study (GWAS), Nigeria is yet to catch up with the genome mapping project on AA [172].

Panel: Key Messages

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

2. The incidence of perforated AA remains significantly high in Nigeria 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 a few cases reported emerged as 'atypical presentations', which is a challenging dilemma to clinicians.

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 Nigerian clinicians due to high overhead cost or limited skills of such health-workers, particularly in the contemporary rural settings in Nigeria.

5. The open AE technique continues to be popular in Nigerian healthcare settings. Nonetheless, LA is gradually gaining momentum and at the developmental stage.

6. The latest research focus is the elaboration of specific gene-expression in AA from the results of a genome-wide association study (GWAS) of AE worldwide, but Nigeria is seriously lagging behind in this recent global research effort in general.

Future Trends in Appendicitis

1. A strong call for the adoption of scoring systems, endoscopic tools, laparoscopy so as 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 Nigerian rural 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 appendectomy, especially in most rural settings of Nigeria 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.

7. There is an urgent need for the implementation of the Community -Based Health Insurance Scheme (CBHIS) which will be highly beneficial in the following ways:

a) Augment government expenditure on health, which is quite low in Nigeria.

b) The pooling of health resources creates equity and equality in healthcare provision for society.

c) Regular income to health care facilities encourages progressive improvement in quality standards within the health facilities.

d) Data generated for claims processing allow for disease profiling and provides useful information for public health plans.

e) Increase the utilization of health care facilities at all levels due to the elimination of payment at the point of service.

f) Increase efficiency in the healthcare delivery system.

g) Provide massive scale-up of health insurance, especially to rural populated who have the highest disease burden in the population.

h) The clarion call is to encourage the stage holders to support the commencement of the CBHIS in Nigeria to make the Millennium Development Goal of the WHO attainable; one such is accessible and affordable Healthcare for all by the year 2020.

Conclusion

The diagnosis of AA in the developing world may still be made with acceptable levels of accuracy based on in-depth medical history and clinical examination. The majority of the patients do not seek medical treatment within the initial 24 hour period. The Alvarado and RIPASA scoring system may be utilized. However, the clinical accuracy of the surgeon has a superior pick-up rate for AA. Laparoscopic surgery is emerging. The overall negative AE and perforation rates are 10.5% and 19%, respectively, while the mortality remains essentially low. These indices all fall below the range reported in other studies suggesting improving health systems and quality metrics.

Clinicians in the rural settings of tropical sub-Saharan Africa require a high index of suspicion. There is a critical need to consider differential diagnoses such as abdominal tuberculosis, amoebiasis, helminthiasis, and schistosomiasis when treating patients with acute abdomen. Finally, AE poses an important modern health challenge due to the attendant high morbidities and mortalities and, AA continues to generate interest

among clinicians worldwide. Therefore, an aggressive healthcare financing in the form of CBHIS, will be highly beneficial at this stage to all Nigerians.

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Not Applicable

Competing Interests

The Author declares that there is no conflict of interest.

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