Appendicitis in Low-Resource Settings

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Abstract

Background: Acute appendicitis is one of the most common surgical emergencies globally. Its incidence is increasing in low- and middle-Human Development Index countries (LMHDICs). Although a proportion of patients can be treated successfully with non-operative management consisting of antibiotics, supportive therapy, and close observation, current diagnostic algorithms lack the granularity to identify these patients accurately.

Methods: We reviewed published literature describing practice patterns and clinical outcomes for appendicitis in LMHDICs and compared them with studies from high-Human Development Index countries, as well as guidelines published by international surgical societies.

Results: We identified shortcomings in current diagnostic and therapeutic strategies used in LMHDICs. Delays in obtaining surgical care inherent in many LMHDIC healthcare systems make prompt surgical care the mainstay for the treatment of acute appendicitis. Laparoscopic appendectomy leads to better outcomes than open appendectomy in resource-constrained settings and when available should be the surgical technique of choice.

Conclusions: Acute appendicitis is common in LMHDICs, and if possible, laparoscopic appendectomy should be the procedure of choice.

Keywords: appendectomy; appendicitis; developing world; surgery

APPENDICITIS is one of the most common surgical emergencies globally. Despite its ubiquitous nature, epidemiologic understanding of the disease remains incomplete. The lifetime risk of acute appendicitis in the United States has been estimated at 8.6% in men and 6.7% in women [1]. Whereas the pooled incidence of the disease has been decreasing in the United States, Europe, and Oceania since the 1990s, it has increased in low- and middle-Human Development-Index countries (LMHDICs) [2]. Although the exact reason for this discrepancy is unknown, a number of factors may be responsible.

Dietary fiber content has been postulated to correlate with development of appendicitis [3,4]. At least one theory posits dietary patterns associated with urbanization contribute to the increasing incidence in LMHDICs [4]. Additionally, environmental pollutants correlate with a higher incidence of appendicitis [5,6], suggesting a connection between appendicitis and pollution from urban industrial development [7]. More recent work implicates intestinal dysbiosis, or changes in the human intestinal microbiome, as a driver of disease. Zhong et al. [8] noted a correlation between certain intestinal micro-organisms and appendicitis, and other work [9] demonstrated a correlation between disease incidence and invasion of the appendiceal mucosa by fusobacteria in a geographically diverse patient cohort.

Immune alterations also correlate with appendicitis. Differential expression of human genes, including paired like homeodomain 2 (*PITX2*), have been linked to appendicitis [10], while temporal and spatial clustering of appendicitis cases suggests an infectious etiology for the disease [11–13]. However, researchers have been unable to identify specific inciting agents [13]. Given clear temporal and geographical trends, and the presumed role of reactive lymphadenopathy in the pathophysiology of appendicitis, it is feasible that dense living conditions and suboptimal hygiene in developing countries facilitate spread of predisposing infections. Regardless of etiology, shifting trends in incidence highlight the need for an evidence-based approach to inform diagnosis and management of acute appendicitis in resource-constrained settings.

Pathophysiology of Appendicitis

Optimal management of appendicitis is further complicated by an incomplete grasp of the disease's pathophysiology. Appendicitis generally is believed to result from obstruction of the appendiceal lumen by a fecalith, hypertrophied lymphatic tissue, or, less commonly, carcinoid tumor or intestinal parasites [1]. This results in a spectrum of disease ranging from local inflammation (uncomplicated appendicitis) to

frank gangrene and appendiceal perforation (complicated appendicitis). Although classic teaching suggests appendicitis is a progressive disease that begins uncomplicated and evolves into complicated disease in the absence of treatment, there is evidence that these clinical outcomes represent separate disease entities entirely. The rate of uncomplicated appendicitis differs with a number of covariates, whereas that of perforated appendicitis does not [14], suggesting different etiologies of disease. Additionally, increases in perforated appendicitis cases despite a sustained decrease in uncomplicated cases [15] supports the entities having different natural histories. A retrospective review of 9,000 patients with acute appendicitis showed no correlation between elapsed time to appendectomy and the risk of appendiceal perforation [16], raising questions around the traditional model of time-dependent development of complicated appendicitis. Finally, genetic factors may play a role, as a single nucleotide polymorphism (SNP) in the interleukin-6 (*IL6*) gene may be protective against complicated appendicitis [17].

Clinical Management of Appendicitis: Non-Operative Procedures

Uncomplicated and complicated appendicitis may result in different clinical outcomes. The former is mainly self-resolving or can be treated effectively with antibiotics [18,19], whereas the latter carries a substantial risk of morbidity and death [20–22] if not treated expeditiously with surgical intervention. Consequently, it is not unreasonable to consider different clinical management algorithms for these diseases. Non-operative management in certain patients with uncomplicated appendicitis can reduce the risk of major and minor complications [18], leading to recommendations by the World Society of Emergency Surgery (WSES) for non-operative management in carefully selected patients [23]. However, the European Association of Endoscopic Surgery (EAES) does not recommend non-operative management of appendicitis with antibiotics, noting that “high quality evidence of superiority is still lacking” [24]. If non-operative management is pursued, *adequate follow-up is essential*, as these patients have a 13.9% [19] to 39% [25] risk of recurrence within five years. Nonetheless, non-operative management may help decrease the rate of negative appendectomy, which has been linked to higher complication rates than appendectomies carried out for histologically confirmed appendicitis [26,27]. Although clinical management differs according to where patients present on the clinical spectrum, there is little consensus as to which clinical, radiographic, pathologic, and operative findings differentiate uncomplicated from complicated appendicitis [28].

Diagnosis of Appendicitis

Appropriate clinical management of appendicitis hinges on accurate diagnosis and assessment of disease severity. A number of clinical prediction rules (CPRs) have been described [29–38] (Table 1). The Alvarado (MANTRELS) score [29] is the best known. The Alvarado system has been widely studied in high-Development Index countries (HDICs), and the results of a large meta-analysis [39] showed that it can rule out appendicitis accurately but lacks precision in ruling in appendectomy candidates. Other CPRs are the

Appendicitis Inflammatory Response (AIR) Score [30], the Ramathibodi Appendicitis Score (RAMA-AS) [37], and the pediatric appendicitis score (PAS) [34]. A recent meta-analysis by Kularatna et al. [40] identified 12 CPRs (inclusive of the Alvarado and AIR scores) for diagnosing adult appendicitis and concluded that the AIR was the most performant and pragmatic.

Although CPRs are helpful in establishing a diagnosis of appendicitis, they are less useful in determining disease severity [41,42]. This has led to the testing of additional biomarkers and refinement of CPRs aimed at differentiating complicated and uncomplicated disease. Laboratory values including the delta neutrophil index (DNI) [38], C-reactive protein, and white blood cell (WBC) count have been used as biomarkers in combination with clinical and imaging data for this purpose [38,43–46] (Table 2). The WSES has determined that although useful as triage tools, no current CPR achieves adequate performance reliably to identify patients who warrant appendectomy [23]. Nonetheless, both the WSES and EAES [24] recommend stratification of patients by CPR as a first step in management.

Applicability of Diagnostic Algorithms to LMHDICs

The generalizability of these tools to LMHDICs is unclear. The overwhelming majority of CPRs are based on data gathered in HDIC populations. Of the 12 CPRs identified by Kularatna et al. [40] in their meta-analysis, none was derived from an LMHDIC population. This is particularly important given that different CPRs exhibit variable performance when applied to different populations. For example, the Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score outperforms the Alvarado score in Asian [35] and Indian [47] populations. Additionally, in a retrospective review of 1,000 black South Africans [48], more than one quarter of patients with histologically confirmed appendicitis would have been classified as low or intermediate probability by the Alvarado score, and 5% of patients with confirmed appendicitis would have been discharged without treatment. However, the Modified Alvarado Scoring System (MASS; which differs from the Alvarado score in that it does not consider the presence of left shift) had a sensitivity of 94.1% and a specificity of 90.4% for acute appendicitis in a Tanzanian patient cohort [49]. A number of factors may help explain discrepancies in CPRs between patient populations. For example, unlike the Alvarado score, RIPASA incorporates age, gender, and duration of symptoms, suggesting differential weights of variables in specific populations. Moreover, LMHDICs have a greater proportion of pediatric patients [50], which may limit the value of extrapolation [51].

Other disease processes prevalent in LMHDIC settings may produce similar clinical prodromes, further complicating diagnosis. A range of pathologic agents, including *Trichuris trichuria*, amoebiasis, ascariis, and *Enterobius vermicularis*, have been identified in patients who underwent incidental appendectomy [52], demonstrating the ability of multiple tropical infections to masquerade as acute appendicitis. *Salmonella typhi* infection (typhoid fever) also may present with severe right lower-quadrant pain [53]. In areas with high rates of human immunodeficiency virus infection, abdominal tuberculosis may co-occur with, or mimic, the symptoms of

TABLE 1. CLINICAL PREDICTION RULES TO AID IN DIAGNOSIS OF APPENDICITIS

Scoring System	Citation	Criteria	Points	Interpretation
Alvarado Score (MANTRELS)	Alvarado 1986 [29]	Migration of pain to right lower quadrant	1	5 or 6 points: “compatible with the diagnosis of acute appendicitis” 7 or 8 points: “probable appendicitis” 9 or 10 points: “very probable appendicitis”
		Anorexia	1	
		Nausea/vomiting	1	
		Tenderness in right lower quadrant	2	
		Rebound pain	1	
		Elevated temperature ($>99.1^{\circ}\text{F}$; 37.3°C)	1	
		Leukocytosis ($>10,000$ WBC/ mm^3)	2	
Appendicitis Inflammatory Response Score	Andersson and Andersson 2008 [30]	Shift of WBC count to left ($>75\%$)	1	Score <5 : low probability Score 5–8: indeterminate result Score >8 : high probability
		Vomiting	1	
		Pain in right iliac fossa	1	
		Rebound tenderness	1	
		Light	1	
		Medium	2	
		Strong	3	
		Temperature $\geq 38.5^{\circ}\text{C}$	1	
		Proportion (%) of polymorphonuclear leukocytes		
		70–84	1	
		≥ 84	2	
APPEND Score	Mikaere et al. 2018 [31]	White blood cell count $10.0\text{--}14.9 \times 10^9/\text{L}$	1	≥ 5 Positive score predictive value 85%
		$\geq 15.0 \times 10^9/\text{L}$	2	
		Anorexia	1	
		Migratory pain	1	
		Localized peritonism	1	
Adult Appendicitis Score	Sammalkorpi et al. 2014 [32]	Elevated CRP (≥ 15 mg/L)	1	Score <11 : low probability of appendicitis Score ≥ 16 : high probability of appendicitis
		Neutrophilia ($>7.5 \times 10^9/\text{L}$)	1	
		Male gender	1	
		Pain in RLQ	2	
		Pain relocation	2	
		RLQ tenderness	2	
		Men and women >50 years old	3	
		Women <50 years old	1	
		Guarding	2	
		Mild	2	
		Moderate or severe	4	
		Blood leukocyte count ($\times 10^9$) ≥ 7.2 and <10.9	1	
		≥ 10.9 and <14.0	2	
		≥ 14.0	3	
		Proportion of neutrophils (%) ≥ 62 and <75	2	
		≥ 75 and <83	3	
		≥ 83	4	
		CRP (mg/L), symptoms <24 h ≥ 4 and <11	2	
		≥ 11 and <25	3	
		≥ 25 and <83	5	
		≥ 83	1	
		CRP (mg/L), symptoms >24 h ≥ 12 and <53	2	
		≥ 53 and <152	2	
		≥ 152	1	
New Approach to Accurate Diagnosis of Acute Appendicitis	Tzanakis et al. 2005 [33]	Ultrasound positive for acute appendicitis	6	≥ 8 points: 95.4% sensitive, 97.4% specific, and 96.5% accurate for acute appendicitis
		Tenderness in RLQ	4	
		Rebound tenderness	3	
		Leukocytosis ($>12,000$ WBC/ mL)	2	

(continued)

TABLE 1. (CONTINUED)

<i>Scoring System</i>	<i>Citation</i>	<i>Criteria</i>	<i>Points</i>	<i>Interpretation</i>
Peciatric Appendicitis Score	Samuel 2002 [34]	RLQ tenderness to cough, percussion, or hopping	2	Score of ≤ 5 is not compatible with the diagnosis of appendicitis; Score of ≥ 6 is
		Anorexia	1	
		Temperature ($\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$)	1	
		Nausea/vomiting	1	
		Tenderness over right iliac fossa	2	
		Leukocytosis ($>10,000 \times 10^9$ WBC/L)	1	
		Left shift (absolute neutrophil count $>7,500$)	1	
RIPASA Score	Chong et al. 2010 [35]	Male gender	1	Score of 7.5: sensitivity of 88.5%, specificity of 66.7%, and accuracy of 80.5%
		Female gender	0.5	
		Age <40	1	
		Age ≥ 40	0.5	
		Right iliac fossa pain	0.5	
		Migration of pain to RLQ	0.5	
		Anorexia	1	
		Nausea/vomiting	1	
		Duration of symptoms <48 hours	1	
		Duration of symptoms >48 h	0.5	
		Right iliac fossa tenderness	1	
		Right iliac fossa guarding	2	
		Rebound tenderness	1	
		Rosving's sign	2	
		Fever	1	
		Raised white blood cell count	1	
		Negative urinalysis	1	
Modified Alvarado Scoring System	Kalan et al. 1994 [36]	Foreign national registration identity card	1	Patients with a score of <7 were not considered for surgery unless there were compelling reasons to do otherwise Patients with a score of 7–9 underwent appendectomy
		Migration of pain to RLQ	1	
		Anorexia	1	
		Nausea/vomiting	1	
		Tenderness in RLQ	2	
		Rebound pain	1	
		Elevated temperature ($>99.1^{\circ}\text{F}; 37.3^{\circ}$)	1	
Ramathibodi Appendicitis Score (RAMA-AS)	Wilasrusmee et al. 2017 [37]	Leukocytosis ($>10,000$ WBC/ mm^3)	2	Score <0.64 : very low risk Score 0.64–0.84: low risk Score 0.85–1.74: moderate risk Score >1.74 : high risk
		Progression of pain	1.04	
		Aggravation of pain by cough or movement	0.78	
		Migration of pain to RLQ	0.77	
		Body temperature $\geq 37.8^{\circ}\text{C}$	1.64	
		Rebound tenderness	1.53	
		Leukocytosis ($>10,000$ WBC/ mm^3)	0.91	
		Neutrophil $>75\%$	0.69	
Delta neutrophil index	Shin et al. 2017 [38]	Delta neutrophil index >0.2		Sensitivity 59.8%; specificity 77.1%

CRP=C-reactive protein; RLQ=right lower quadrant; WBC=white blood cells.

appendicitis [54,55]. Finally, patients from LMHDICs who have appendicitis may present with a different constellation of symptoms. For example, studies of black South African patients [56,57] have shown that most individuals with histologically proved appendicitis describe non-specific abdominal pain, whereas only a minority report classic migratory pain patterns. Application and assessment of CPRs in LMHDIC settings represent a considerable unmet need and potential for impactful clinical research.

Diagnostic Adjuncts: Imaging and Laboratory Investigations

Diagnosis of appendicitis remains challenging for physicians throughout the world, even more so in LMHDICs. Although CPRs are useful in diagnosis, no algorithm is sufficiently accurate to identify acute appendicitis or stratify disease severity reliably. Although the addition of ultrasound scanning to diagnostic algorithms is useful in resolving

TABLE 2. ESTABLISHED CLINICAL PREDICTION RULES FOR GRADING SEVERITY OF APPENDICITIS

Scoring System	Citation	Criteria	Points	Interpretation	
Accuracy of WBC count and CRP for assessing severity of pediatric appendicitis	Siddique et al. 2011 [43]	CRP >10 mg/dL WBC count $\geq 11 \times 10^9/\text{dL}$		Sensitivity 100%; specificity 20%	
Ruptured Appendicitis Scoring System	Williams et al. 2009 [44]	Generalized abdominal tenderness	4	Score ≥ 9 carries post-test probability of 92% for acute appendicitis	
		Presences of abscess on CT	3		
		Duration of symptoms >48 h	3		
		WBC count >19,400 cells/mcL	2		
		Presence of abscess on CT	1		
Logistic regression model to predict acute uncomplicated and complicated appendicitis	Eddama et al. 2019 [45]	CRP WBC count Gender Age		Logistic regression correctly classified 80.8% of cases Calculator available at www.appendistat.com	
Scoring system to distinguish uncomplicated from complicated acute appendicitis	Atema et al. 2015 [46]		With CT imaging	With US imaging	
		Age ≥ 45 y	2	2	Score ≥ 7 with CT imaging (22 possible): Sensitivity 90.2%; specificity 70.3%
		Body temperature $^{\circ}\text{C}$ ≤ 37	0	0	
		37.1–37.9	2	2	
		≥ 38.0	4	4	
		Duration of symptoms ≥ 48 h	2	2	Score of ≥ 6 with US imaging (19 possible): Sensitivity 96.6%; specificity 45.7%
		WBC count $>13 \times 10^9/\text{L}$	2	2	
		CRP (mg/L) ≤ 50	0	0	
		51–100	2	4	
		>100	3	5	
		Extraluminal air on CT	5		
		Periappendiceal fluid on CT or US	2	2	
		Appendicolith on CT or US	2	2	
		Delta neutrophil index	Shin et al. 2017 [38]	Delta neutrophil index >0.6	

CRP=C-reactive protein; CT=computed tomography; US=ultrasonography; WBC=white blood cells.

diagnoses in intermediate-risk patients in resource-constrained settings [58,59], the technique is operator dependent, requiring a well-trained evaluator, and is less accurate than cross-sectional imaging [24,60,61]. Computed tomography (CT) decreased the rate of incidental appendectomy by nearly 50% compared with ultrasonography (from 8.1% to 4.5%) in a retrospective study of 3,540 patients [62].

Unfortunately, cross-sectional imaging remains scarce in many LMHDICs. A recent survey of imaging capability revealed only 84 magnetic resonance imaging (MRI) machines for the whole of the West African sub-region [63], and a four-state, 15-million patient catchment area in Nigeria had only six CT scanners [64]. Another study, in Tanzania, showed that the country had only 5.7 general radiology units per 1 million people (far below the 20 units/1 million people recommended by the World Health Organization) [65]. Even when cross-sectional imaging is available in resource-constrained settings, its use often is limited in appendicitis because of demands on it for more critical conditions. A review of more than 1,000 appendicitis cases at a tertiary hospital in Nigeria showed only one patient underwent a CT scan [66]. Even in high Human Development-Index Countries (HHDICs), use of CT to diagnose appendicitis differs substantially. A study of 89 centers in the United Kingdom,

two in Spain, and one each in Japan, Hong Kong, Australia, and New Zealand revealed that only 12.9% of patients underwent pre-operative CT [67]. This variation seems to come at a cost of more common incidental appendectomy, as this international cohort had a 20.6% incidental appendectomy rate [67] compared with an American cohort that had an overall incidental appendectomy rate of 6% [62]. Finally, although laboratory markers improve diagnosis, reliable pathology and laboratory medical services often are limited in rural areas because of lack of availability and the high associated costs, which many patients cannot afford [68,69]. So, despite advances in imaging and laboratory markers, the diagnosis of acute appendicitis relies heavily on presentation and clinical examination, which can be difficult even for experienced physicians.

Sub-Optimal Diagnosis Leads to Worse Outcomes

Lack of readily accessible and reliable adjuncts for the diagnosis of appendicitis may result in delays in escalation of care for patients with acute appendicitis. These diagnostic delays translate into worse clinical outcomes in a number of studies in LMHDIC populations [70–73]. Delays in diagnosis are further compounded by geographical factors, as patients

who hail from rural areas often are subject to additional delays before being referred to centers with surgical capabilities. This may help explain disparities in outcomes between rural and urban patients noted in a number of LMHDICs including Nepal [71], Nigeria [72], Pakistan [74], South Africa [75,76], and Ethiopia [77]. One such study [75] noted a higher rate of intensive care unit admission (17% vs 3%), longer median length of hospital stay (9 vs. 3 days), and a higher rate of perforation (86% vs. 39%) in rural patients than in urban dwellers who presented to a South African hospital with acute appendicitis. These CPRs hold promise as a tool to help rural clinicians triage and refer patients efficiently for definitive surgical care [48] with the goal of closing these gaps in outcomes. However, none of the existing diagnostic algorithms is sufficiently simple or performant for widespread use in highly resource-constrained areas.

Appendectomy

The rate of complicated appendicitis differs significantly across studies in LMHDIC populations. In South Africa, the complicated appendicitis rate ranges from 11% [78] to 60% [75], and a recent systematic review placed the rate of perforation at 36% [79]. Although non-operative management can be considered in carefully selected patients [23], the risk of failure of antibiotic therapy for uncomplicated appendicitis resulting in appendectomy during index hospitalization has been as high as 5.8% [80]. Concerningly, the risk of recurrence at one and five years was 27.3% and 39.1%, respectively [25]. The high risk of antibiotic failure and disease recurrence is compounded by the high rate of complicated appendicitis in LMHDIC populations. Given diagnostic shortcomings and delays in escalation of care, surgical therapy remains an attractive, indeed recommended, option for the treatment of suspected acute appendicitis in LMHDIC populations.

Since its description by Charles McBurney in the 1890s [81], appendectomy has become the most commonly performed emergency abdominal operation globally [82]. Open appendectomy continues to be a mainstay of treatment in LMHDICs. However, laparoscopic appendectomy [83] has become the procedure of choice for definitive treatment of acute appendicitis in HHDIC populations. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) [84], WSES [23], and EAES [24] all recommend laparoscopic appendectomy for the treatment of uncomplicated appendicitis. This recommendation extends to complicated appendicitis, although this view is based on weaker evidence. Laparoscopic appendectomy results in a shorter hospital stay, a lower incidence of surgical site infection (SSI), less pain, and lower overall costs [23,24] than open appendectomy. Laparoscopic appendectomy also is recommended by these groups over open appendectomy in more complicated cases including the obese, the elderly, and patients with other comorbidities [23,24,84].

Laparoscopic appendectomy is a safe and effective strategy for definitive management of appendicitis in LMHDICs [52,55,71,75,78,85,86]. Studies in resource-constrained settings have replicated findings from HHDIC cohorts that show a lower rate of SSI with laparoscopic than with open appendectomy [87,88]. Additionally, laparoscopic appendectomy

proved superior to open appendectomy for the management of complicated appendicitis in LMHDICs [89,90]. Unlike open appendectomy, laparoscopic appendectomy offers the chance to evaluate the entire abdomen for alternative or additional pathology [24,91,92], making it a valuable addition to the LMHDIC surgeon's armamentarium when cross-sectional imaging may not be available and the risk of concurrent pathology may be high.

Laparoscopic Appendectomy Improves Outcomes

A recent international, multicenter, observational cohort study was undertaken by the GlobalSurg Collaborative with the goal of describing surgical approaches to appendectomy and frequencies of post-operative complications in a geographically and socioeconomically diverse population [93]. The study gathered patient-level data from 4,546 patients (2,499 from HHDICs, 1,540 from MHDICs, and 507 from LHDICs) from 52 countries and showed only 8.6% and 8.1% of appendectomies performed in MHDIC and LHDICs, respectively, were performed laparoscopically. The study demonstrated a higher risk of complications associated with appendectomy in LHDICs (odds ratio [OR] 1.55; 95% confidence interval [CI] 1.19–1.99; $p=0.001$) and MHDICs (OR 1.24; 95% CI 1.03–1.49; $p=0.020$) compared with HHDICs. The authors also found a significant association between the risk of SSI and development status. Patients from LHDICs had an OR of 3.81 (95% CI 2.78–5.1; $p<0.001$) of developing an SSI whereas those from MHDICs had an OR of 2.99 (95% CI 2.34–3.84; $p<0.001$) compared with those from HHDICs. A recent meta-analysis [94] also showed an elevated rate of SSI (17.9/100 appendectomies; 95% CI 10.4–25.3 infections/100 appendectomies) associated with open appendectomy in LMHDICs. These findings illustrate the importance of targeted interventions to decrease SSIs associated with appendectomy.

Research suggests appendectomy-associated SSI prevention is possible in LMHDIC settings. A randomized trial showed that a single pre-operative dose of cefuroxime sodium and metronidazole prevented 92.2% of SSIs [95], while another study [96] in Pakistan showed pre-operative antibiotics prevented infection in 94% of patients. Laparoscopic appendectomy appears to lower the rates of SSI and of complications in general. Although likely underpowered to obtain statistical significance, a retrospective cohort study in Nepal [88] showed a trend toward a lower rate of SSI (1.8% vs. 9.8%; $p=0.13$) similar to the aforementioned meta-analysis, which revealed a decrease in the pooled SSI rate to 8.8/100 laparoscopic appendectomies (95% CI 4.5–13.2/100 operations). The GlobalSurg Collaborative study found laparoscopic appendectomy to be associated with a lower rate of SSI (OR 0.22; 95% CI 0.14–0.33; $p<0.001$) and fewer overall complications (OR 0.55; 95% CI 0.42–0.71; $p<0.001$) compared with open appendectomy. These data translate into an absolute risk reduction of any complication of 6% (number needed to treat [NNT] of 16) for laparoscopic appendectomy for uncomplicated appendicitis and an absolute risk reduction of 17% (NNT of 8) in the case of perforated appendicitis [93]. These data underscore the utility of laparoscopic appendectomy in improving outcomes in resource-constrained settings.

Adoption of Laparoscopic Appendectomy in LMHDICs

Although data support the use of laparoscopic appendectomy in LMHDICs to reduce complications and improve clinical outcomes, adoption of this procedure in these settings remains slow [93]. This is likely a result of the legacy of a number of obstacles including unfamiliarity with laparoscopic techniques by senior surgeons, lack of training, and high costs associated with capital and disposable equipment [92]. Recent publications by authors from LMHDICs outlining clinical, economic, and systemic advantages of laparoscopy in resource-constrained settings [97] suggest a change in attitudes toward laparoscopy by surgeons in these countries. Additionally, a multitude of low-cost, high-fidelity trainers and simulators are now available to help increase comfort with basic laparoscopic skills [92].

Laparoscopy affords diagnostic advantages that have proved useful in identifying concurrent or alternative pathology [64]; and when compared with ultrasonography, CT, and MRI, diagnostic laparoscopy is cost effective (equipment cost ratio of 1:500:2500:4500) with a low complication rate (0.09%) [98]. Laparoscopic appendectomy was cost-effective compared with open appendectomy in a Colombian cohort with an incremental cost-effectiveness ratio (ICER) of US\$25.86 [99]. Moreover, in a Nigerian population, the approach decreased the rate of incidental appendectomy and the length of the post-operative hospital stay [72]. These findings illustrate the urgent need for a comprehensive cost-benefit analysis of laparoscopic appendectomy across LMHDICs.

A number of interesting modifications to laparoscopic appendectomy have been proposed to facilitate wider adoption in resource-constrained settings. A gasless technique utilizing modified, reusable open surgical instruments through gel ports eliminates the need for costly insufflators, disposable instruments, and bottled gases [100]. The procedure can be performed under spinal anesthesia, and as of 2016, the authors had performed 113 appendectomies using this approach. Other surgeons [101] conducted a randomized trial of 72 patients comparing open appendectomy ($n=36$) and laparoscopic intra-corporeal ligation with 2-0 silk suture ($n=36$) and specimen extraction using a bag fashioned from a glove in the operating room. The authors reported one SSI (1.3%) in the laparoscopy group and five SSIs (13.9%) in the open surgery group and reported a lower overall cost, although specific figures were not provided. Finally, another group of surgeons [102] used an autoclavable, reusable endoring applicator (ERA) to apply Falope rings to the appendix after skeletonization of the mesoappendix with diathermy. The appendix was then divided and removed through the inner lumen of the ERA, obviating specimen containment on withdrawal. The procedure is inexpensive (Falope rings were Rs. 50 [US \$0.70] at the time of publication), but the procedure cannot be performed on appendices >8 mm in diameter nor on friable or perforated organs.

Some of these cost-saving methods have been evaluated by surgical societies. Based on low-grade evidence (evidence level 3), the WSES recommends (grade of recommendation B) that electrocoagulation or bipolar energy be used for mesoappendiceal dissection, as this is the most cost-effective, and there are no differences in outcomes between them and other dissection techniques. The group also recommends that

the use of endoloops be considered as an additional cost-lowering method (evidence level 3; grade of recommendation B) [23]. On the contrary, the EAES recommends the use of a stapler or suture over clips or endoloops when the base of the appendix is inflamed, necrotic, or perforated [24].

Conclusions

Acute appendicitis remains one of the leading causes of abdominal surgical emergencies globally. The incidence of appendicitis is increasing in LMHDICs. Although a proportion of patients can be treated successfully with non-operative management consisting of antibiotics, supportive therapy, and close observation, current diagnostic algorithms lack the granularity to identify these patients accurately. Shortcomings in current diagnostic strategies, combined with delays in obtaining surgical care inherent in many LMHDIC healthcare systems, make prompt surgical

TABLE 3. RESEARCH DEFICITS IN UNDERSTANDING OF APPENDICITIS IN LOW- AND MIDDLE-HUMAN DEVELOPMENT-INDEX COUNTRIES (LMHDICs)

Characterization of appendicitis	Disease incidence and stratification Clinical presentation Incidence of non-appendicitis causes of right lower quadrant abdominal pain Epidemiology
Improved diagnostics	Evaluation of performance of existing CPRs in LMHDIC populations Development of new CPRs based on data collected from large cohorts Development and validation of simple, effective triage tools to facilitate rapid identification and referral of rural patients to hospitals with surgical capacity
Needs assessments	Identify critical deficiencies in imaging and laboratory medical services Identify critical deficiencies in laparoscopic surgical infrastructure for both capital and consumable equipment Identify training gaps in senior surgeons and trainees preventing adoption of laparoscopic techniques Identify supply chain obstacles to widespread adoption of laparoscopic surgery
Surgical outcomes	Detailed understanding of current surgical complication rates in order to target interventions Understanding of benefits and challenges associated with early adoption of laparoscopic appendectomy Evaluation of the safety of cost saving modifications to laparoscopic appendectomy
Cost efficacy	Comprehensive regional and global cost-effectiveness studies examining the widespread implementation of laparoscopic appendectomy Impact of cost-saving modifications to laparoscopic appendectomy on overall cost

CPR = clinical prediction rules.

care the mainstay of the treatment of acute appendicitis. Laparoscopic appendectomy leads to better outcomes than open appendectomy for these patients and when available should be the surgical technique of choice in resource-constrained settings. Table 3 identifies areas of focus for additional research aimed at improving the diagnosis and treatment of appendicitis in a cost-effective manner in order to optimize outcomes in LMHDICs.

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