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Acute Appendicitis in Pediatric Patients: An Updated Narrative Review

Abigail B Podany, Anthony Y Tsai* and Peter W Dillon

Division of Pediatric Surgery, Department of Surgery, The Pennsylvania State University College of Medicine, USA

***Corresponding author:** *Anthony Y Tsai, Division of Pediatric Surgery, Department of Surgery, The Pennsylvania State University College of Medicine, 500 University Drive, Hershey, PA 17033-0850, USA, Tel: 717-531-8342, Fax: 717-531-4185, E-mail: atsai1@hmc.psu.edu*

Abstract

Acute appendicitis is the most common pediatric surgical emergency worldwide. The diagnosis and management in children involves a unique set of challenges for clinicians. While the diagnosis is primarily clinical, utilization of imaging and laboratory studies can aid practitioners in making a more prompt diagnosis, preventing complications from appendiceal perforation and limiting the rate of negative appendectomies. In children special emphasis has been placed on minimizing ionizing radiation exposure, and thus multiple imaging modalities have been employed to aid in diagnosis including MRI and ultrasound. Additionally, several algorithms have been developed to stratify patients into low, intermediate, and high-risk categories for acute appendicitis. Once diagnosed, treatment of acute appendicitis is distinguished between simple appendicitis which is most often treated with laparoscopic removal, and complex appendicitis with perforation which may be treated with primary surgical resection or percutaneous drainage with interval appendectomy. Recently, there is a resurgent interest in treating simple appendicitis with antibiotics. We will examine the evidence for all and discuss potential future directions.

Keywords

Appendicitis, Pediatric, Diagnosis, Imaging, Scoring systems, Appendectomy, Outcomes

Introduction

Acute appendicitis is the most common pediatric surgical emergency worldwide. Prompt evaluation and management is essential to minimizing complications. Despite its prevalence, controversy continues regarding management strategies for appendicitis with continued emergence of newer surgical techniques, a recent interest in potential non-operative therapy as an alternative in select cases, and ongoing debate about the best management for complicated appendicitis. The aim of this review is to provide an update about our current understanding of appendicitis in the pediatric population, with particular focus on pathogenesis, diagnosis, and current management strategies.

Reference sources were identified in PubMed using search terms including appendicitis, acute appendicitis, pediatric appendicitis, and appendix. Articles were selected for inclusion on the basis of relevance and consensus between other articles on the same subject.

Epidemiology

The annual rate of acute appendicitis increases from one to six per 10,000 from birth to four years of age up to 19-28 per 10,000 for children under the age of 14 with an overall lifetime risk of nine percent for males and seven percent for females and a peak incidence between the ages of 11 and 12 years [1-3]. Appendicitis is rare under the age of five years and accounts for less than five percent of cases [4]. The relative rarity increases the diagnostic difficulty in these younger children, which is evident by an increased rate of perforated appendicitis. The rate of perforation declines as age increases, with rates of nearly 100% at the age of one year, 50-69% at the age of five, and more variably reported but generally less than 30% in older children [1,4-6].

There are not current known genetic mutations that directly confer increased risk of appendicitis, although it has been suggested that differential regulation of the local immune system within the intestine due to genetic variation may play a role in the pathogenesis of appendi-

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citis [7,8]. Studies of twins have shown that while genetic effects may explain up to 30% of the variation in lifetime risk for appendicitis, the largest risk is attributable to environmental factors [9-11]. In the United States, recent studies have found higher rates of perforated appendicitis in African-American and Hispanic children. Although racial disparities in the delivery of care may exist, these different rates were not entirely attributable to delays of care, and could suggest heterogeneity in the path to perforation in different populations [12-14].

Seasonal variation in the incidence of acute appendicitis has been noted in multiple studies from diverse geographic locations. Rates of appendicitis increase in the summer months when temperatures are warmer and there is increased humidity [15-19]. It is still unclear whether direct effects of temperature and humidity may play a role in the pathogenesis of appendicitis or if the association is related to seasonal variation of air pollutants or increased gastrointestinal infections in summer months [20].

Neonatal Appendicitis

Appendicitis is rare in the neonate with only 100 cases reported in the last 100 years [21]. It has been postulated that neonatal appendicitis may represent a different entity, such as a localized form of necrotizing enterocolitis, but this diagnosis continues to be a topic of debate due to its rarity [22,23]. The neonatal appendix is less susceptible to developing appendicitis because of its funnel shape, which gradually takes on its adult form between the age of one to two years [24,25]. There is still a high mortality (28%) associated with the diagnosis of neonatal appendicitis, and a high index of suspicion is critical in the approach to the neonate presenting with abdominal symptoms-most commonly abdominal distension or bilious emesis [24].

Etiology

Appendicitis most commonly results from luminal obstruction and associated infection. Causes of luminal obstruction can be highly variable and most commonly include a fecalith, lymphoid follicle hyperplasia, or inflammation of the local lymphatic tissues in response to infectious pathogens such as those noted in table 1 [26]. Tumors, such as appendiceal carcinoid can also rarely result in acute appendicitis [27], and the diagnosis is most commonly made postoperatively. Thus careful examination of pathologic specimens is recommended. The obstructed appendiceal lumen harbors trapped bacteria which subsequently overgrow causing luminal distension, lymphatic and venous obstruction, and finally tissue ischemia and gangrene. Once perforation has occurred, a walled-off abscess or free peritonitis may develop. There is a greater risk of generalized peritonitis in younger children who have a less developed omentum [25].

The classic teaching holds that prompt diagnosis and management is necessary to prevent progression to perforation. Recent studies have attempted to delineate a reliable timeline from initiation of symptoms to perforation of the appendix. In one prospective study, patients with symptoms lasting longer than 48 hours had a 4.9 times increased odds of perforation [28]. Others have reported that the risk of perforation in the first 24 hours approaches 10% and increases in a linear fashion thereafter [29]. However, these studies note that acute appendicitis remains a heterogeneous condition that does not always progress to perforation.

The Role of the Microbiota in Appendicitis

The appendix harbors a population of microbes distinct from the rest of the gastrointestinal tract [30]. It has long been hypothesized that the appendix serves as a microbial reservoir possibly for replenishment of colonic bacterial species [31,32]. Although the role of microbiota in the pathogenesis of appendicitis is unclear, increased abundance of anaerobic bacteria from the phylum *Fusobacteria* and a reduced abundance of *Bacteroides* species was found by 16 s ribosomal RNA sequencing in appendiceal specimens from cases of pediatric appendicitis [33] in accordance with what has been reported in adult specimens [32,34]. Further large-scale studies are necessary to corroborate this data, but identification of consistently present microbes may eventually aid in antibiotic selection for cases of complicated appendicitis or abscess formation.

Diagnosis

The diagnosis of abdominal pathology in young children can be challenging. Utilization of imaging and lab-

Table 1: Causes of Acute Appendicitis. Infectious etiologies can cause acute appendicitis by direct luminal obstruction, or indirectly through enlargement of lymphoid tissues [58-60].

Causes of Acute Appendicitis			
Luminal obstruction	**Viral infections**	**Bacteria**	**Parasites**
Fecalith	Measles	Salmonella	Entamoeba
Lymphoid hyperplasia	Adenovirus	Shigella	Strongyloides
Foreign body obstruction	Cytomegalovirus	Actinomyces	Enterobius vermicularis
Tumors:			
Carcinoid	Epstein-Barr virus	Campylobacter	Schistosoma
Adenocarcinoma			Ascaris
Lymphoma			
Serous cystadenoma			

oratory studies can aid practitioners in making a more prompt diagnosis, preventing complications from appendiceal perforation and limiting the rate of negative appendectomies. There is not one test with a high sensitivity and specificity for diagnosing acute appendicitis, and thus imaging and laboratory studies must always be considered in the context of patient history and physical exam findings.

Laboratory markers

Laboratory markers are useful to supplement clinical findings in children. Most thoroughly studied have been the white blood cell (WBC) count, C-reactive protein level, and procalcitonin level. WBC count varies with age, and may be elevated in gastroenteritis, mesenteric adenitis, and other infectious conditions. WBC count is elevated in up to 96% of children with appendicitis with variable sensitivities (68-79%) and specificities (80-96%) reported [6,35,36]. In one recent study, pediatric patients with the combination of a C-reactive protein level greater than 3 mg/dL (normal levels less than 3 mg/dL) and a WBC count greater than 12,000/mm^3 (normal between 4,500 and 10,000/mm^3) had an odds ratio of 7.75 predictive of acute appendicitis [37]. Procalcitonin, a precursor of calcitonin secreted by K cells in the lung and C cells of the thyroid gland is rarely detectable in serum, but rises in response to endotoxin and inflammatory cytokines. Procalcitonin level is not routinely used in most centers. Studies have shown that it is specific (97%) but not sensitive (80%) with a positive predictive value of 72% for perforated appendicitis, suggesting that it may have utility in differentiating complicated from uncomplicated appendicitis [38,39].

Imaging modalities

The goals of imaging studies are two-fold: the first goal is to confirm or reject the diagnosis of acute appendicitis, and the second is to differentiate simple, non-perforated appendicitis from perforated or complex disease, which may alter management strategies. In children, special emphasis has been placed on minimizing ionizing radiation exposure, and thus different imaging modalities have been extensively studied.

Trans-abdominal ultrasound

In children, ultrasound is a useful first-line modality. It is a rapidly available tool with no risk of ionizing radiation and can easily be followed by other diagnostic imaging modalities if necessary. Accuracy of ultrasound is dependent upon visualization of the appendix, which may be difficult due to operator factors, patient body habitus, and overlying bowel gas. In a recent multicenter study, the sensitivity and specificity of ultrasound in the diagnosis of appendicitis when the appendix was visualized were 98% and 92% respectively and lower if the appendix was unable to be identified [40]. A non-diagnostic ultrasound in the clinical context of a patient without leukocytosis may be equivalent to a negative ultrasound in its ability to rule out appendicitis [41], highlighting the increased accuracy of combining diagnostic tools.

Computed tomography

Computed tomography (CT) scan has been widely adopted as the imaging modality of choice in North America. Implementation of routine imaging has helped to decrease perforation rate form 38% to 10% overall by enhancing earlier diagnosis [42]. Advantages of CT include operator independence, relative speed and availability, and accuracy, with reported sensitivities of 95-100% and specificities of 93-100% (highest with administration rectal contrast) for acute appendicitis [42]. However, increasing concern have been raised regarding the risks of ionizing radiation from CT scans and associated cancer risks [43,44], and steps have been taken to reduce radiation by decreasing the radiation dose per scan as well as the overall utilization of CT scans [42]. Alternative imaging modalities have been studied and used with increasing frequency.

Magnetic resonance imaging (MRI)

Magnetic Resonance Imaging (MRI) has gained recent attention as a viable alternative diagnostic modality for pediatric appendicitis. Its diagnostic accuracy has been demonstrated to be extremely high with a sensitivity of 97% and specificity 97% and an acquisition time of 11 minutes [45]. The sensitivity and specificity of MRI is comparable to that of CT in both simple appendicitis as well as perforated appendicitis [46]. Given the benefit of no radiation exposure, reduction of the acquisition time, and the improvement in image acquisition software, MRI has the potential to become the primary radiographic modality to assist in the diagnosis of appendicitis. The current limitations of this modality include cost considerations and lack of clinician familiarity with MRI interpretation for those who do not use it routinely.

Clinical risk scores

To aid clinicians in making the diagnosis of acute appendicitis, several algorithms have been developed to calculate its likelihood by stratifying groups into low, intermediate, and high-risk categories as shown in table 2 [47,48]. The Alvarado score, also known as MANTRELS, is the most widely used scoring model in pediatric and adult populations. The sensitivity and specificity of an Alvarado score ≥ 7 for acute appendicitis is quite variable in the literature and reported to be 72-93% and 79-81% respectively in pediatric populations [25]. The Pediatric Appendicitis Score (PAS) has likewise variable accuracy with a reported sensitivity of 61-100% and specificity of 92-96% for a score ≥ 7 [47-49]. This scoring system was developed to address clinical findings specific to pediatric patients, including "hopping" pain as a surrogate for rebound tenderness and a temperature cut off of 38 °C (37.5 °C in the Alvarado score). An additional clini-

Table 2: Clinical risk scores for suspected acute appendicitis [47,48]. PAS = pediatric appendicitis score. Elevation in temperature for the Alvarado score is defined at temperature ≥ 37.5 °C, and for the PAS as ≥ 38 °C. The ruptured appendicitis score [50] has a sensitivity is 47 and specificity 98 for ruptured appendicitis at a score of 9.

	Alvarado score	Pediatric Appendicitis Score (PAS)
Symptoms		
Migration of pain to the right lower quadrant	1	1
Nausea/vomiting	1	1
Anorexia	1	1
Signs		
Right lower quadrant tenderness	2	2
Rebound tenderness	1	
Elevation in temperature	1	1
Cough/hopping/percussion tenderness in the right lower quadrant		2
Laboratory tests		
Leukocytes ≥ 10,000/μl	2	1
Polymorphonuclear neutrophilia ≥ 75%	1	1
Total score	**10**	**10**

Risk of appendicitis

Low risk:	Intermediate risk:	High risk:
Alvarado score 0-4	Alvarado score 5-6	Alvarado score 7-10
PAS score 0-3	PAS score 4-6	PAS score 7-10

Ruptured appendicitis score	
Variable	**Points**
Generalized tenderness	4
Abscess on imaging	3
Duration > 48 hours	3
WBC > 19,400 cells/μl	2
Fecalith on imaging	1
Total	**13**

cal risk score formulated to aid clinicians in determining whether patients have complicated appendicitis has also been proposed (Table 2) [50]. This Ruptured Appendicitis Score may be a useful tool for preoperatively identifying patients with the highest risk of ruptured appendicitis so that alternate management (e.g. abscess drainage or antibiotics) can be considered. The sensitivity and specificity are variable depending on the cut-off used, and further validation of this tool is warranted in broader populations. The wide range of sensitivity is one reason these scoring systems have not gained acceptance in the pediatric population.

Treatment strategies

The availability of ancillary radiological studies such as ultrasound, CT, and MRI varies from region to region and may impact both the decision-making and the surgical outcome of acute appendicitis [51]. Even with access to ultrasound, more than half of the children presenting with abdominal pain may have equivocal findings for acute appendicitis [52]. In cases of suspected appendicitis with equivocal findings, active observation in the hospital is a safe and effective strategy that can decrease the negative appendectomy rate without impacting the complication rate [52]. It is recommended that these patients should be observed without antibiotic treatment in order to avoid confusion in decision-making and prevent therapeutic delay [53]. Approximately half of the observed patients will eventually be discharged without the need for any additional intervention [52].

Once the diagnosis of appendicitis has been made, the management is determined based on whether it is simple appendicitis (appendix intact), advanced or complicated appendicitis with free perforation, or advanced appendicitis with phlegmon or abscesses. Each one will be discussed separately below. Fluid resuscitation, intravenous antibiotics, and analgesia are required in all patients.

Antibiotic prophylaxis for simple appendicitis

Single dose antibiotic prophylaxis should be given preoperatively once the diagnosis of acute appendicitis has been made [54]. Although there are two pediatric studies demonstrating no difference in surgical site infection (SSI) rates between placebo and various antimicrobials, a meta-analysis including both adult and pediatric studies found that for pediatric patients antimicrobial prophylaxis trended toward being beneficial without statistical significance [55]. Given the morbidity associated with the infectious complications such as prolonged hospitalization, readmission, and reoperation, most authors recommend antibiotic prophylaxis.

In terms of specific antimicrobial agents, wide-spectrum coverage including anaerobes should be administered. No single agent has been found to be superior to others in the adult population. A second-generation cephalosporin with anaerobic activity or third-generation cephalosporin with partial anaerobic activity is usually recommended with or without the addition of metronidazole [54]. Local biograms should also factor into the selection of antibiotics. Additional antibiotic administration after appendectomy does not decrease SSI rate [56].

Appendectomy for early appendicitis

The mainstay of the treatment for early or simple appendicitis is timely removal of the inflamed appendix to prevent progression to rupture with peritonitis. Surgery has been the standard approach since the 1890s [57]. Since the standardization of prompt appendectomy combined with antibiotic prophylaxis, mortality following appendectomy is a very rare event [57]. Appendectomy affords the ability for direct pathological examination of the appendix and diagnosis of coexisting or alternate diagnoses such as carcinoids. Other tumors such as adenocarcinoma and serous cystadenomas have been found as well as unusual parasitic and actinomycotic in-

fections [58-60]. Occasionally, the pathological findings will help direct the course of care postoperatively (e.g. perforation).

Timing of operation

Whether appendectomy is an emergent or an urgent procedure has been debated for some time. There is evidence to suggest that adverse outcomes such as perforation, complications, or operating time are not increased for children undergoing appendectomy more than six hours versus less than six hours after diagnosis [61]. In a multicenter cohort study and subsequent meta-analysis, the rate of complex appendicitis also does not seem to be increased in patients who waited 12 to 24 hours after admission to have the surgery [62]. A delay of more than 48 hours after admission does carry an increased risk of SSI and 30-day complications.

Operative approach

The choice of laparoscopic versus open surgery is based largely on availability of laparoscopic tools and surgeon experience. Outcomes of open and laparoscopic appendectomies are essentially equivalent in uncomplicated appendicitis. However, in complicated appendicitis laparoscopy was associated with lower superficial wound infections, shorter length of hospital stay, decreased risk of postoperative bowel obstruction, but longer operative time and higher risk of intra-abdominal infection in a meta-analysis of studies over a recent 12 year period [63]. In the rare case of neonatal appendicitis, an open approach is recommended due to the potential for the presence of other diagnoses (e.g. necrotizing enterocolitis) [21].

More recently, variations on single-incision laparoscopy have gained acceptance and increased utilization. For simple appendicitis with a non-perforated appendix, outcomes are comparable to standard laparoscopic management [64], and depending on the specific technique used, may be more cost-effective [65]. A variety of wound protective measures have been introduced and may be of benefit [66], as the overall wound infection rate of single incision appendectomies has been found to be slightly higher compared to standard 3-port laparoscopy in several series [64,67].

Non-operative approach

There is recent interest in treating simple appendicitis with only antimicrobial therapy. This treatment strategy stems from evidence in the adult literature, most notably the NOTA (Non Operative Treatment for Acute Appendicitis) study, where non-operative management of early appendicitis had a success rate of approximately 60% percent. Those patients with early failure had an increased risk of complicated appendicitis [68-70]. In the pediatric literature, there is insufficient evidence to suggest if non-operative management is a safe option. Preliminary data have shown that up to 75% of patients were successfully treated with antibiotic therapy without evidence of recurrence within a year after discharge [71,72]. The length of stay of initial hospital admission with medical management is longer than the operative approach. There is no long-term data currently available for the pediatric population.

Complicated appendicitis

Perforated appendicitis can be determined preoperatively and can be discovered intraoperatively during surgery for presumed early appendicitis. According to American Academy of Pediatrics (AAP) guidelines, infants (zero-one year) and children (two-12 years) with perforated appendicitis should be handled by a pediatric surgeon even if diagnosed by a non-pediatric surgeon [73].

If there is no appendiceal mass or abscess present, immediate appendectomy is recommended. There is no increased morbidity when the procedure is performed in children compared to adults [74]. Immediate appendectomy was found to have shorter time to return to normal activities and reduced adverse events such as abscess formation, small bowel obstruction, or unplanned admission than interval appendectomy six to eight weeks later [75]. Hospital charges and costs were significantly lower as well [76]. When compared to open appendectomy, laparoscopic appendectomy was associated with shorter hospital length of stay, lower risk of wound infection, reduced chance of small bowel obstruction, increased operative time, and slightly higher chance of intra-abdominal infection in a systematic meta-analysis [63].

If an appendiceal mass or abscess is present, ill-appearing patients should undergo appendectomy. In well-appearing patients presenting five to seven days after the onset of symptoms, initial antimicrobial treatment with interval appendectomy versus immediate appendectomy is debated among the experts. One meta-analysis including adult and pediatric patients showed morbidity as high as 36% in 886 patients with abscess or phlegmon who had immediate surgery. This result is compared to 14% of 895 patients who were managed non-operatively (OR = 3.4; 95% CI 2.0-5.6; $P < 0.001$) [77].

Preoperative care of patients with complicated appendicitis

In patients who are initially being managed non-operatively, rehydration, nutrition optimization, and antibiotics are key components. Nutritional supplementation may include temporary total parenteral nutrition if oral intake has been poor for an extended period of time. Nasogastric decompression may be necessary for persistent vomiting although routine use of nasogastric tube drainage does not appear to improve post-operative course [78].

Antibiotic choices include piperacillin and tazobact-

am as recommended by the American Pediatric Surgical Association guidelines [79] or broad-spectrum coverage similar to the ones used for early appendicitis. St Peter, et al. demonstrated that in a perforated appendicitis population a once daily dosing of ceftriaxone and metronidazole was just as effective as the more traditional three-drug combination of ampicillin, gentamycin, and clindamycin with faster defervescence, shorter length of stay, and substantial savings in administration and medication-related expense [80]. A more recent study had similar findings when comparing once-daily ceftriaxone and metronidazole to ertapenem and/or cefoxitin in all acute appendicitis patients including non perforated, perforated, and appendicitis with abscess, and had a comparable complication rate between the two study groups [81].

Interval appendectomy

In stable patients who present late in their course with perforated appendicitis and are found to have an abscess or phlegmon, some people will choose to treat with immediate surgery while others will choose interval appendectomy. Weiner reported no significant differences in the lengths of stay, cost of treatment, or overall complication rate in patients treated with interval appendectomy [82]. Another study, however, found that 22% of the patients intended for interval appendectomy required conversion to appendectomy because of the subsequent development of a small bowel obstruction [83].

In these cases, a solitary abscess or multiple abscesses should be drained percutaneously under image guidance [84]. There is some debate whether interval appendectomy is necessary after successful percutaneous abscess drainage and non-operative management as some experts argue that the frequency of morbidity associated with interval appendectomy is not substantially different from the recurrence rate in patients not undergoing interval appendectomy (11% versus 7%, respectively in one systemic review) [77]. Other systemic reviews have morbidity rates of 3.4% [85], and recurrence rates as high as 21% in children not undergoing appendectomy [86]. The counter-argument for interval appendectomy is the lifelong risk of recurrence, the need for additional procedures as 20% of recurrence required percutaneous abscess drainage, and delayed diagnosis of concurrent conditions such as carcinoid tumors. In all cases, appendectomy is required after nonoperative treatment of pediatric ruptured appendicitis with inflammatory mass or abscess as there is a 43% chance of recurrence within two years at an average of three months [87].

Outcomes

Postoperative infectious complications including wound infections and abscesses occur in approximately one to five percent of children with simple appendicitis and two to nine percent of those with advanced appendicitis [88-91]. Intra-abdominal or pelvic abscesses occur in about five percent of all cases [92,93]. Factors that increase infections include older age, higher body mass index, history of diarrhea at presentation, fever after postoperative day two, and leukocytosis after postoperative day five [94,95]. Overall, mortality for appendicitis in children is very rare and occurs in less than 0.1% of cases. Mortality occurs in very young children, under-resuscitated patients undergoing surgery, and postoperative sepsis [96].

Small bowel obstruction from adhesions occurs in one percent of patients with complicated appendicitis and may require operative adhesiolysis [97,98]. In rare cases, an inverted appendiceal stump can indirectly cause a bowel obstruction with small bowel to small bowel or ceco-colic intussusception [99]. Other rare adverse events include stump appendicitis, which results from a long remaining stump and may occur months to years after appendectomy in about 0.1% of the cases [100-102].

Data from the multi-center Pediatric National Surgical Quality Improvement Project (NSQIP) study from January 2012 to June 2015 include 28,181 cases after and show an overall morbidity rate of 4.6% and mortality rate of zero percent or two cases overall within 30 days of surgery. Infectious complications occurred in 4.1% of cases with a wound infection rate of 1.1%. Postoperative systemic sepsis affected 0.4% of the patients with 10 of the 123 reported cases developing septic shock resulting in only two deaths.

Conclusions

Acute appendicitis is a common disorder of childhood that clinicians of a variety of disciplines will encounter in clinical practice. Diagnostic accuracy may be aided by imaging and laboratory findings, though diagnosis based solely on clinical history and physical exam is possible in straightforward cases. The management is based on diagnosis whether it is simple appendicitis, complicated appendicitis with free perforation, or with phlegmon or abscesses. Surgical management remains the mainstay of therapy, and surgical options continue to evolve. Importantly, care for children diagnosed with acute appendicitis should continue to be provided by pediatric surgeons, and outcomes can be improved with standardization of management strategies and continued research into emerging technologies.

Author Contributions

ABP and AYT planned and wrote the manuscript; ABP, AYT, and PWD critically revised the manuscript; all authors edited and approved the final version.

Disclosures

The authors have nothing to disclose.

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