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Appendicitis and its associated mortality and morbidity in infants up to 3 months of age: A systematic review

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Abstract

Background and Aims: Although appendicitis is rare in young infants, the reported mortality is high. Primary aim of this systematic review was to provide updated insights in the mortality and morbidity (postoperative complications, Clavien-Dindo grades I–IV) of appendicitis in infants ≤ 3 months of age. Secondary aims comprised the evaluation of patient characteristics, diagnostic work-up, treatment strategies, comorbidity, and factors associated with poor outcome.

Methods: This systematic review was reported according to the PRISMA statement with a search performed in Pubmed, Embase and Web of Science (up to September 5th 2022). Original articles (published in English ≥ 1980) reporting on infants ≤ 3 months of age with appendicitis were included. Both patients with abdominal appendicitis and herniated appendicitis (such as Amyand's hernia) were considered. Data were provided descriptively.

Results: In total, 131 articles were included encompassing 242 cases after identification of 4294 records. Overall, 184 (76%) of the 242 patients had abdominal and 58 (24%) had herniated appendicitis. Two-hundred (83%) of the patients were newborns (≤ 28 days) and 42 (17%) were infants between 29 days and ≤ 3 months of age. Either immediate, or after initial conservative treatment, 236 (98%) patients underwent surgical treatment. Some 168 (69%) patients had perforated appendicitis. Mortality was reported in 20 (8%) patients and morbidity in an additional 18 (8%). All fatal cases had abdominal appendicitis and fatal outcome was relatively more often reported in newborns, term patients, patients with relevant comorbidity, non-perforated appendicitis and those presented from home.

Conclusion: Mortality was reported in 20 (8%) infants ≤ 3 months of age and additional morbidity in 18 (8%). All patients with fatal outcome had abdominal appendicitis. Several patient characteristics were relatively more often reported in infants with poor outcome and adequate monitoring, early recognition and prompt treatment may favour the outcome.

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KEYWORDS

appendicitis, infants, morbidity, mortality, neonates, newborns

1 | BACKGROUND

Two phenotypes of appendicitis are recognized in newborns: abdominal and herniated appendicitis (such as Amyand's hernia, Garengeot's hernia and umbilical hernia containing the inflamed vermiform appendix).^{1,2} Although appendicitis is a rare entity in this frail population, awareness is of importance due to high mortality rates. Fortunately, previous studies have shown a decline of mortality over the years: Between 1901 and 1975 the mortality rate was up to 78%, while reported rates between 1985–2000 and 1990–2014 were 28% and 23%, respectively. This may be due to improvements over the past decades regarding availability of diagnostic modalities and perioperative and neonatal intensive care.^{1,3–5}

However, the lack of specific presenting symptoms and unfamiliarity with especially abdominal appendicitis commonly leads to a delay in diagnosis and surgical intervention.^{1,6} And, many aspects regarding diagnostic work-up, therapeutic strategies and factors of poor outcome of acute appendicitis in infants ≤ 3 months of age have to be largely clarified. For example, almost 75% of the affected newborns are diagnosed with perforated appendicitis, but whether this contributes to the high rate of mortality is still debated.^{1,3}

Taken together, we performed a systematic review with the primary aim to provide updated insights in the mortality and morbidity of appendicitis in infants ≤ 3 months of age. Since the development of the immune system, an essential factor in the pathogenesis of appendicitis, takes place beyond the newborn period (≤ 28 days), we have focused on infants ≤ 3 months of age.^{7,8} The secondary aims of this systematic review comprised the description of diagnostic modalities and treatment strategies in this population, and we aimed to identify patient characteristics and factors that may be associated with poor (fatal) outcome.

2 | METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.⁹ As data collection was started during an update of the registration site, this review was not registered after consultation of Prospero.

2.1 | Search strategy and selection procedure

A comprehensive search was performed in the databases PubMed, Embase.com and Web of Science, from inception to September 5th 2022 in collaboration with a medical information specialist (JCFK). The search included controlled terms and free text terms for synonyms of

“newborns” or “neonates” combined with synonyms for “appendicitis.” The search was performed without restrictions for methodology, date or language. The full search strategies are provided in Table S1. Duplicate articles were excluded using Endnote X20.0.1 (Clarivate™). Title and abstracts were screened by two independent reviewers (ST and AT) with full text assessment of selected articles thereafter. In case of disagreement, conflicts were resolved by plenary discussion and consultation of a third reviewer (RG). Reference lists of identified reviews and the included articles were screened for publications that were not detected with our search strategy.

2.2 | Inclusion and exclusion criteria

Articles reporting cases of infants ≤ 3 months (i.e., < 4 months, < 17 weeks and < 121 days) of age with appendicitis were eligible for inclusion. Suitable were randomized controlled trials (RCTs), prospective and historical cohort studies, cross-sectional studies, case reports and series (or retrospective chart reviews) and letters to the editor. Systematic and literature reviews, and comments or letters to the editor without sufficient data on cases were excluded. Studies were excluded if they were published in languages other than English. We chose to exclude articles published before 1980 as they would not be attentive to current insights due to advancements in medicine. Patients with a noninflamed appendix, prenatal appendicitis and appendicitis secondary to underlying malignancy were also excluded.

2.3 | Aims

The primary aim was to provide an overview of mortality and morbidity (postoperative complications Clavien-Dindo [CD] grades I–IV) in infants ≤ 3 months of age with appendicitis.¹⁰ Secondary aims were to assess patient characteristics, diagnostic work-up and treatment strategies, associated relevant comorbidities, the incidence of an ileo-/colostomy and bowel resections; previous exposure to antibiotics; use of formula feeding compared to breast feeding in the neonatal period; and duration of hospital stay.

2.4 | Used definitions

Appendicitis was defined as stated by the included article, including radiological, perioperative, or histopathological confirmation. In line with previously published articles, patients were divided into patients with abdominal appendicitis and patients with herniated appendicitis (such as Amyand's hernia, Garengeot's hernia and umbilical hernia containing the

inflamed vermiform appendix).^{1,2} In addition, subclassifications were made between nonperforated and perforated appendicitis, and between newborns (≤ 28 days) and infants (between 29 days and ≤ 3 months).

The mortality rate was calculated as follows: number of cases with fatal outcome/the total number of cases identified $\times 100$. Morbidity was defined as the presence of a postoperative complication with severity classified as CD grades I–IV. We divided minor (CD grades I–II) from major (CD grades III–IV) complications.¹⁰ There were no restrictions regarding the timing of the complication (both short-term complications of ≤ 30 days and long-term complications of >30 days). In case of fatal outcome (CD grade V), patients and potential postoperative complications of grades I–IV of the concerning patient, were not included in the list of morbidity, nor were complications of a(n) (initial) nonoperative treatment. Thus, the morbidity rate was calculated as follows: number of non-fatal cases with a postoperative complication of grades I–IV/the total number of cases that underwent surgical treatment (either immediate or after initial conservative treatment) $\times 100$.

Relevant comorbidity was defined as the presence of either Hirschsprung disease, congenital syndromes and cardiac, metabolic or anatomical abnormalities. Necrotizing enterocolitis (NEC) was only listed as a relevant comorbidity in case a separate admission or secondary surgical intervention was reported during the same admission. Data on additional findings during histopathology (such as cytomegalovirus or rotavirus) or co-existing findings (such as allergies) were not regarded as relevant comorbidity.

2.5 | Data extraction and outcomes

A predetermined dataset was used to extract information on study characteristics, population and patient characteristics, relevant comorbidity, clinical presentation, diagnostic work-up, initial treatment and course of treatment, intraoperative findings and interventions, post-operative course, complications and histopathological report (Table S2). All data was extracted and interpreted by two independent reviewers (ST and AT). In case of discrepancy a third reviewer was consulted (RG).

2.6 | Critical appraisal of the evidence and statistical analysis

The checklists for case reports and series for systematic reviews of the Joanna Briggs Institute (JBI) were used.¹¹ Regarding the primary and secondary aims, data of included articles were reported descriptively with calculation of the mortality and morbidity rate as provided above.

3 | RESULTS

3.1 | Systematic review

After a search in PubMed, Embase and Web of Science, 4294 articles were identified. One-hundred-ninety-four articles remained after

removal of duplicates and screening of title and abstract. With cross-referencing, eight additional eligible articles were identified. In total, 131 articles were included in this systematic review.^{3,6,12–140} Figure 1 provides the PRISMA flowchart. A pooled-analysis could not be provided due to heterogeneity of clinical data and as the majority of included articles were case reports/series.

3.2 | Critical appraisal

Figure 2 shows an overview of the critical appraisal of all case reports ($N = 121$) (A) and case series or retrospective chart reviews ($N = 10$) (B). Overall, for case reports the quality of data mainly lacked or was unclear for the current clinical condition, postintervention status and reporting of postoperative complications. For case series and retrospective chart reviews, data most often lacked regarding demographics and clinical outcome.

3.3 | Baseline characteristics

As stated, 131 articles were included, encompassing 242 infants ≤ 3 months of age with appendicitis: 11 (8%) of the articles were published between 1980 and 1989, 11 (8%) between 1990 and 1999, 24 (18%) between 2000 and 2009, 58 (44%) between 2010 and 2019, and 27 (21%) since 2020. Baseline characteristics of the patients are presented in Table 1. In total, 200 (83%) of the 242 patients were newborns (≤ 28 days) and 42 (17%) were infants between 29 days and ≤ 3 months of age; Some 184 (76%) of the patients had abdominal appendicitis and 58 (24%) herniated appendicitis ($N = 55$ right-sided Amyand's hernia, $N = 2$ left-sided Amyand's hernia, and $N = 1$ umbilical hernia). Data on previous exposure to antibiotics, feeding pattern, biochemical results and duration of hospital stay was either too limited and/or heterogeneous and will not be provided.

3.4 | Mortality

Mortality was reported in 20 (8%) of the 242 patients. The reported mortality over the last four decades was: Fatal outcome in four (31%) of the 13 reported patients in articles published between 1980 and 1989; Five (33%) of the 15 patients between 1990 and 2001: Three (9%) of the 32 patients between 2000 and 2009: Six (6%) of the 104 patients between 2010 and 2019: and two (3%) of the 78 patients since 2020. Importantly, all fatal cases concerned patients with abdominal appendicitis and 18 of the 20 patients with fatal outcome were newborns. Figure 3 provides an overview of characteristics for patients with abdominal appendicitis with an uncomplicated course, grades I–IV post-operative complication and fatal outcome separately.

Four of the patients with fatal outcome were diagnosed with appendicitis during autopsy: $N = 2$ clinical deterioration in patients with cardiac comorbidity (without evident abdominal catastrophe

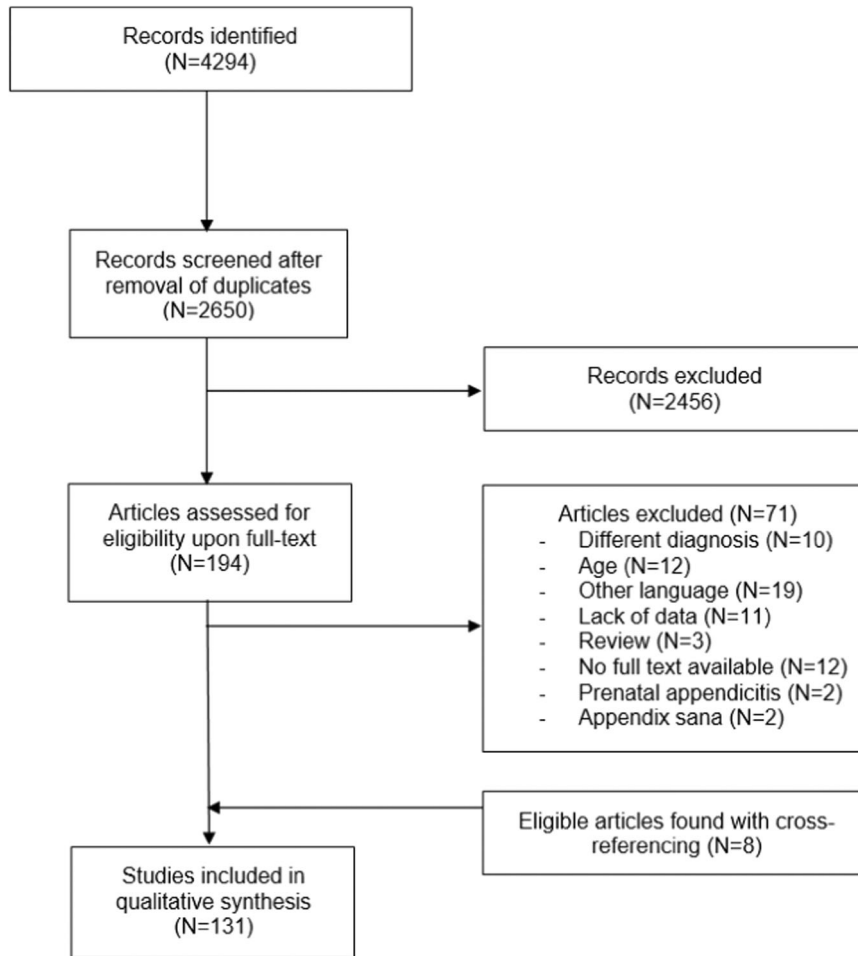


FIGURE 1 PRISMA flow-diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

reported), $N = 1$ patient seen several times, with abdominal catastrophe on last consultation but died before transfer to another hospital, $N = 1$ initial conservative treatment for primary peritonitis with surgery planned after clinical deterioration, but died of cardiac arrest beforehand.^{120,136,141} In the remaining 16 patients with fatal outcome, two died due to long-term complications and had relevant comorbidity: one patient had Patau syndrome, Fallot tetralogy and malrotation, and died of pneumonia 2 months after appendicitis; and one had Hirschsprung disease with multiple additional surgeries and died of Pseudomonas peritonitis and bilateral bronchopneumonia several months after treatment for appendicitis.^{104,129}

3.5 | Morbidity

In total, 236 (98%) of the 242 patients underwent surgical treatment, either immediate or after initial conservative treatment. Overall, in 18 (8%) of the 236 patients that underwent surgical treatment one or more postoperative complication(s) (CD grades I–IV) was or were reported. The majority of these complications was minor (CD grades I–II): $N = 5$ surgical site infection, and $N = 3$ (paralytic) ileus

or slow peristalsis, $N = 8$ other. The remainder of complications was major (CD grades III–IV): $N = 2$ adhesive ileus requiring secondary surgery, $N = 1$ wound dehiscence requiring surgery, $N = 1$ secondary surgery due to perforation with NEC as underlying pathology, $N = 1$ secondary surgery due to intestinal stricture requiring subtotal resection with NEC as underlying pathology, $N = 1$ secondary surgery with placement of a transverse colostomy with Hirschsprung disease as underlying pathology.^{22,25,98,118} An overview is provided in Table 2.

3.6 | Clinical presentation

Symptoms and/or findings of physical examination during either primary presentation or observation over time were reported in the majority of patients and are listed in Table 3. In all but one of the patients with herniated appendicitis, a local swelling was reported with most commonly accompanying symptoms of local erythema, tenderness or oedema. In patients with abdominal appendicitis, the predominant finding was abdominal distension with most commonly accompanying symptoms of vomiting or gastric residuals, abdominal tenderness, poor feeding, and fever.

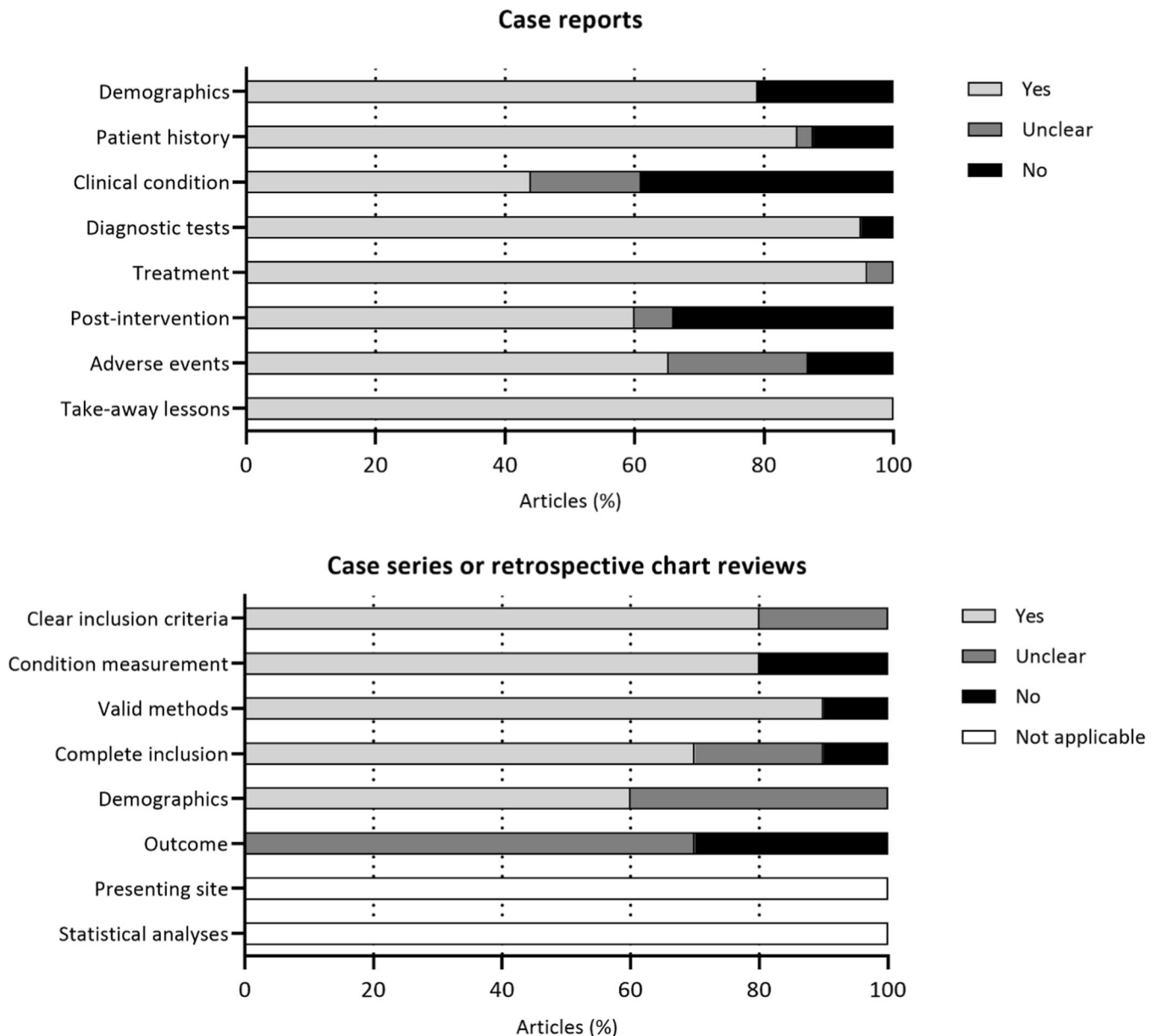


FIGURE 2 Summary of critical appraisal of the evidence. For case reports, main concerns were found for the current clinical condition due to lack of vitals and/or clinical impression of the patient. The majority, however, listed abdominal or inguinal physical examination. In addition, concerns were raised for postintervention status and information on adverse events (postoperative complications). For case series, data were mainly lacking for outcome, as statements were often only provided for mortality and not for morbidity.

3.7 | Imaging

In 181 (75%) of the 242 patients at least one abdominal X-ray was reported and in 28 patients at least one repeated X-ray. Imaging data retraceable to patients with either herniated or abdominal appendicitis was provided in a total of 159 patients: $N = 20$ patients with herniated appendicitis and $N = 139$ abdominal appendicitis. In patients with herniated appendicitis the most common findings on initial or repeated X-ray were: dilated bowel loops in 9 (45%) of the 20 patients and herniated bowel loops/scrotal gas in seven (35%). In patients with abdominal appendicitis the most common findings on

initial or repeated X-ray were: dilated bowel loops and/or signs of (partial) obstruction in 59 (42%) of the 139 patients, pneumoperitoneum in 46 (33%), pneumatosis or other signs of NEC in 30 (22%), portal venous gas in six (4%), wall oedema in six (4%) and ascites in four (3%). Notably, appendicitis was suspected in one patient upon plain X-ray.³⁴

In 125 (52%) of the 242 patients at least one ultrasound was performed with a repeated ultrasound in 14 patients. Imaging data retraceable to patients with either herniated or abdominal appendicitis was provided in 102 patients: $N = 21$ patients with herniated appendicitis and $N = 81$ abdominal appendicitis. In patients with

TABLE 1 Baseline characteristics.

	All Number (%)	Abdominal appendicitis Number (%)	Herniated appendicitis Number (%)
Total	242	161	50
Type of appendicitis			
Abdominal	184 (76)	n/a	n/a
Herniated	58 (24)		
Age at presentation			
Newborns (≤28 days)	200 (83)	140 (87)	29 (58)
Infants (≥29 days and ≤3 months)	42 (17)	21 (13)	21 (42)
Gestational maturity			
Unclear	43 (18)	20 (12)	20 (40)
Term	94 (39)	65 (40)	13 (26)
Preterm	105 (43)	76 (47)	17 (34)
Sex			
Unclear	7 (3)	3 (2)	4 (8)
Male	157 (65)	91 (57)	46 (92)
Female	78 (32)	67 (42)	0 (-)
Already admitted in hospital			
Unclear	108 (45)	64 (40)	13 (26)
No	79 (33)	51 (32)	28 (56)
Yes	55 (23)	46 (29)	9 (18)
Perforated appendicitis			
Perforated	168 (69)	129 (80)	19 (38)
Nonperforated	74 (31)	32 (20)	31 (62)

Note: All data is reported descriptively by number of patients with percentage. For subgroup results of patients with abdominal appendicitis and herniated appendicitis, the patients of the retrospective chart review of Xuxu et al. were not included as data could not be retraceable to patients with either abdominal or herniated appendicitis.

herniated appendicitis the most common findings on initial or repeated ultrasound were: herniated bowel loops in 15 (71%) of the 21 patients, hyperaemia or hypervascularity of the testis or epididymitis in seven (33%), free fluid/hydrocele in six (29%) and signs of testicular ischemia or torsion in three (14%). In patients with abdominal appendicitis the most common findings on initial or repeated ultrasound were: ascites or abscess in 26 (32%) of the 81 patients, a cystic lesion or abdominal mass in 12 (15%), appendicitis in 11 (14%), bowel dilatation in eight (10%), pneumatosis intestinalis in seven (9%), portal venous gas in six (7%), and pneumoperitoneum in six (7%).

Other diagnostic modalities reported were contrast enema studies, intravenous pyelogram studies, MRI-scans and CT-scans.

The latter was reported in 9 (4%) of the 242 patients, where in two cases the diagnosis of appendicitis was made (one of these cases was a complementary CT to an already suspected case of appendicitis on ultrasound).^{54,106}

3.8 | Treatment strategies

A(n) (initial) conservative treatment was reported in 78 (32%) of the 242 patients ($N = 13$ herniated appendicitis, $N = 65$ abdominal appendicitis). Immediate surgery was reported in 141 (58%) of the patients ($N = 34$ herniated appendicitis, $N = 107$ abdominal appendicitis). Of the remaining patients, the initial treatment strategy was unclear. Eventually, 236 (98%) of all 242 patients underwent surgical treatment, either immediate or after initial conservative treatment ($N = 58$ herniated appendicitis, $N = 178$ abdominal appendicitis).

In patients with herniated appendicitis, the main reasons to convert to a surgical approach were either an increase or persistence of the local swelling, erythema or tenderness or recurrence of swelling after initial reduction. In patients with abdominal appendicitis, the main reasons to convert to a surgical approach were evident clinical deterioration, increase of symptoms or lack of clinical improvement, and in two cases recurrence of intraperitoneal abscess. In 14 patients the presence of pneumoperitoneum on X-ray was the indication to convert treatment. And, as listed previously, appendicitis was suspected in only the minority of patients before surgery.

3.9 | Ileo- or colostomy and small bowel resections

An ileostomy/colostomy or additional bowel resection was only performed in patients with abdominal appendicitis (postoperative complications not included). In 36 (20%) of the 178 surgically treated patients with abdominal appendicitis an ileostomy or colostomy was placed. Reported indications were: $N = 5$ suspicion or confirmation of Hirschsprung disease, $N = 2$ ischemic distal ileum or necrotic patches, $N = 1$ segmental ileal loop volvulus with perforated appendicitis, $N = 1$ no specific reason mentioned, but preoperative treatment for NEC, $N = 26$ patients with presumed concurring NEC, and $N = 1$ unclear.^{13,45,53,59,80,115,129} A bowel resection with primary anastomosis was performed in an additional seven (4%) of the 178 surgically treated patients with abdominal appendicitis (postoperative complications not included). Reported indications were: $N = 2$ ileocaecal resection due to perforation of the caecum or fistula of the appendix into caecum, $N = 1$ resection of a part of ascending colon due to local lesion caused by adherent appendix, $N = 1$ resection terminal ileum due to adherent appendix and cystic lesion, $N = 1$ Meckel's diverticulum, $N = 1$ adherent ileal loop, $N = 1$ old perforation terminal ileum.^{44,45,69,98,124,131,135} In one patient a diverticulectomy of a Meckel's diverticulum was performed and in three patients a Ladd's procedure.^{20,24,104,134}

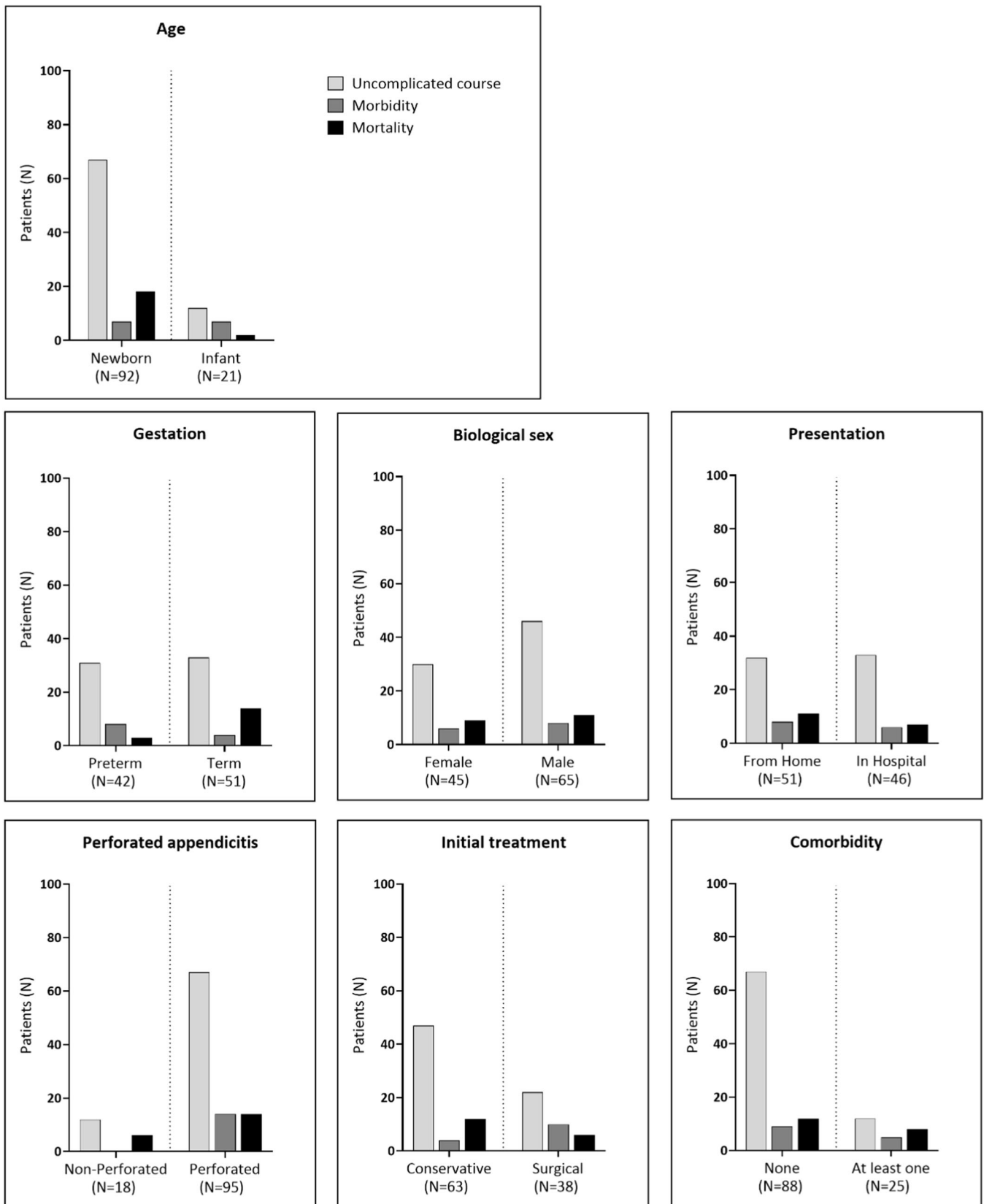


FIGURE 3 Patient characteristics and factors that may be associated with poor outcome in abdominal appendicitis. Each diagram represents the number of patients with an “Uncomplicated course” (light grey), “Morbidity” (postoperative complications grades I–IV) (dark grey) and “Mortality” (black). Unclear data, missing data or data that lacked the potential to be traced to individual patient characteristics was not included.

TABLE 2 Morbidity.

Grade	Description	Number
1–2	Surgical site infection (or seroma)	5
	(Paralytic) Ileus or slow postoperative peristalsis conservatively treated	3
	Recurrence of inguinal hernia ^a	1
	Postoperative viral infection	1
	Catheter sepsis requiring antibiotics	1
	Readmission and AB started for potential micro-perforation (and Rotavirus)	1
	Readmission for severe abdominal distension, spontaneously resolved	1
	Diaper dermatitis due to diarrhoea from AB use	1
	Bloody stools	1
Expanding subcapsular liver hematoma postoperative, conservatively treated	1	
3–4	Adhesive ileus requiring readmission and surgery	1
	Necrotic bowel due to adhesions and discoloured bowel with venous thrombosis of surrounding mesentery, requiring bowel resection with mucus fistula and ileostomy ^a	1
	Wound dehiscence requiring surgery	1
	Secondary surgery due to perforation near splenic flexure, resection of terminal ileum with ileostomy and resection of ascending/transverse and descending colon with Hartmann pouch (underlying pathology NEC)	1
	Secondary surgery with indication for transverse colostomy due to dilated bowel loops with transition point near mid-transverse colon. (Rectal) biopsies later confirmed Hirschsprung disease.	1
	Intestinal strictures postoperatively requiring secondary surgery with subtotal resection and anastomosis of the colon (underlying pathology NEC)	1

Note: Postoperative complications of grades I–IV according to the Clavien-Dindo scoring system. A total of 22 postoperative complications was reported in 18 patients. All but two were patients with abdominal appendicitis.

^aRepresents the patients with herniated appendicitis. The postoperative complications of patients with fatal outcome were not included in this overview.

3.10 | Comorbidity

Relevant comorbidity was reported in 29 (12%) of the 242 patients. Table 4 provides an overview of the identified relevant comorbidities. As demonstrated, Hirschsprung disease was found in eight (3%) of the patients.^{25,59,86,114,115,129} In all but one, it concerned perforated appendicitis. The length of the aganglionic segment was provided in five of the eight patients: $N=2$ total colon aganglionosis, $N=1$ transition point mid-transverse colon, $N=1$ aganglionic segment extending to descending colon, $N=1$ transition at rectosigmoid junction. Poor outcome was reported in six of the eight patients with Hirschsprung disease: in four mortality and in two morbidity. NEC was mentioned in 80 (43%) of the 184 patients with abdominal appendicitis: either as primary or differential diagnosis, concurring entity, or appendicitis was interpreted as a local form of NEC. Nonetheless, as stated previously, NEC was only registered as relevant comorbidity in this systematic review ($N=5$) in case a separate admission or secondary surgery was reported during the same admission.

4 | DISCUSSION

4.1 | Principal findings

In this systematic review, we have provided data on 242 infants ≤ 3 months of age with appendicitis. We demonstrate mortality in 20 (8%) of the 242 infants and morbidity in an additional 18 (8%). The four patients that were diagnosed with appendicitis at autopsy underline the challenge of adequate recognition. Findings of this systematic review may enhance this recognition as we provide insights on the clinical presentations and diagnostic work-up. In addition, we evaluated potential treatment strategies and patient characteristics that may be associated with poor outcome.

4.2 | Interpretation

We found mortality in 20 (8%) of the 242 infants ≤ 3 months of age with appendicitis (18 were newborns with abdominal appendicitis,

TABLE 3 Clinical symptoms and physical examination.

Abdominal appendicitis	N = 156 (%)	Herniated appendicitis	N = 49 (%)
Abdominal distension	123 (79)	Local swelling	48 (98)
Abdominal tenderness	67 (43)	Local erythema	29 (59)
Vomiting or gastric residual	63 (40)	Local tenderness	22 (45)
Poor feeding	43 (28)	Vomiting	17 (35)
Fever	37 (24)	Local oedema	15 (31)
Bloody stools	32 (21)	Fever	15 (31)
Respiratory distress	22 (14)	Irritability	14 (29)
Obstipation	21 (13)	Abdominal distension	8 (16)
Irritability	21 (13)	Poor feeding	6 (12)
Abdominal mass	19 (12)	Abdominal tenderness	4 (8)
Lethargy	17 (11)	Obstipation	3 (6)
Abdominal wall erythema	16 (10)	Abdominal wall erythema	3 (6)
Septic appearance or shock	14 (9)	Respiratory distress	2 (4)
Poor circulation or mottled	11 (7)	Septic/shock or mottled	2 (4)
Abdominal induration/oedema	11 (7)	Inguinal-scrotal fistula	1 (2)
Dehydration	10 (6)	Lethargy	1 (2)
Jaundice	9 (6)		
Diarrhoea	8 (5)		
Inguinal-scrotal swelling/erythema	4 (3)		
Abdominal wall shiny aspect	3 (2)		
Convulsions	2 (1)		
Swelling and redness of the leg (due to psoas abscess)	1 (1)		

Note: Overview of clinical symptoms and physical examination. Data is only provided in case symptoms and findings were provided and could be retraceable to patients with either abdominal or herniated appendicitis. All items were scored as they were either reported during (primary) presentation or noted during observation over time.

corrected mortality rate of this subgroup is 11%). The lowest number of fatal cases were demonstrated in the last two decades. This decline of the mortality rate is in line with previous literature in newborns with abdominal appendicitis: Karaman et al.³ reported a mortality rate of 78% between 1901 and 1975, 33% between 1976 and 1984, and 28% between 1985 and 2000. Raveenthiran et al.¹ report a mortality rate of 23% between 1990 and 2014.^{1,3} The

TABLE 4 Relevant comorbidity.

Comorbidity	Number
Congenital heart disease/defect	9
<ul style="list-style-type: none"> Congenital heart disease requiring Inderal 	1
<ul style="list-style-type: none"> (prenatal) functional single right ventricle, double-outlet right ventricle, small systemic flow, large ductus arteriosus 	1
<ul style="list-style-type: none"> Fallot tetralogy^{a,b} 	2
<ul style="list-style-type: none"> Patent ductus arteriosus 	3
<ul style="list-style-type: none"> Hypoplastic right ventricle with pulmonary valve atresia, atrial septal defect with right-to-left shunt and a patent ductus arteriosus 	1
<ul style="list-style-type: none"> Pulmonary atresia with ventricular septal defect^c 	1
Hirschsprung disease ^d	8
Necrotizing enterocolitis (NEC)	5
<ul style="list-style-type: none"> Previous hospital admission and treatment for NEC 	2
<ul style="list-style-type: none"> Secondary surgery as result of perforation, with additional resection required due to underlying NEC 	1
<ul style="list-style-type: none"> Perforation of distal ileum requiring surgery with bowel resection and anastomosis due to underlying NEC, prior to presentation with Amyand's hernia 	1
<ul style="list-style-type: none"> Intestinal stricture requiring subtotal resection, underlying NEC 	1
Malrotation ^b	3
Oesophageal atresia with distal tracheoesophageal fistula ^a	2
Cystic fibrosis	1
Mosaic Trisomy 13	1
Patau syndrome ^b	1
Down Syndrome ^c	1
Ureteropelvic junction obstruction ^d	1
Bilateral choanal atresia	1
Congenital hypothyroidism due to thyroid agenesis	1

Note: Overview of relevant comorbidities as reported by the original article. In total, 34 relevant comorbidities were reported in 29 patients. In four patients, multiple were reported:

^aPatient with Fallot tetralogy and oesophageal atresia with distal tracheoesophageal fistula.

^bPatient with Fallot tetralogy, Patau syndrome, and malrotation.

^cPatient with pulmonary atresia with ventricular septal defect and Down syndrome.

^dPatient with Hirschsprung disease and ureteropelvic junction obstruction.

decline may be due to the advances in broad-spectrum antibiotic therapies, developments in anaesthetics and surgical skills, and improvements of the perioperative care and neonatal intensive care units.^{1,3-5} Importantly, these findings may be affected by a potential publication bias and moreover, it should be questioned whether all

reported fatal cases were due to appendicitis itself or rather to the coinciding relevant comorbidity and/or long-term complications. Nevertheless, the overall reported mortality rate appears to be substantially higher compared to mortality rates in older infants and adults (0.04%–0.2%) and awareness of appendicitis in this patient group remains necessitated.^{142,143}

Regarding morbidity, postoperative complications of CD grades I–IV were reported in an additional 18 (8%) infants ≤ 3 months of age with appendicitis. All but two were patients with abdominal appendicitis. Morbidity was relatively more often reported in infants, preterm patients, patients with perforated appendicitis and those who underwent immediate surgical treatment. However, based upon results of this systematic review we cannot determine whether this is due to the treatment strategy or due to a more severe disease phenotype in these patients. Importantly, the majority of complications was minor (CD grades I–II) and the number of identified postoperative complications appears lower compared to rates in older children ($\sim 25\%$, 0–17 years old).¹⁴⁴ This may partially be due to missing data, as in approximately a third of the included articles a statement on adverse events was lacking/unclear, which may have led to under registration of postoperative complications.

Fatal outcome was only reported in patients with abdominal appendicitis and none among patients with herniated appendicitis; And, morbidity was reported in only two patients with herniated appendicitis. These findings may be attributed to two important factors.^{1,3} First, a local (irreducible) swelling as opposed to general (abdominal) symptoms allows for timely recognition and prompt treatment, more so as the differential diagnosis includes testicular torsion and incarcerated small bowel that both require immediate (surgical) treatment. Secondly, although several of the patients with Amyand's hernia presented with general symptoms and sepsis, the relative anatomically contained feature of an Amyand's hernia may be a protective factor against poor outcome. This hypothesis is supported by a review into Amyand's hernia (in adults), where mortality of Amyand's hernia was found to be related to the presence of peritoneal distribution of the inflammation.¹⁴⁵

In this systematic review, a perforation of the appendix was reported in 168 (69%) out of 242 infants ≤ 3 months of age with appendicitis. The perforation rate is unmistakably higher compared to the perforation rate of approximately 30% in older children and 15% in adults with abdominal appendicitis.^{146,147} Possible and often mentioned explanations for these high perforation rates are the relatively thin appendiceal wall, lack of a protecting well-developed omentum, and the underdeveloped immune system in newborns and infants.^{1,7,8,148,149} As a paradox, relatively more fatal cases were found among patients with nonperforated compared to perforated abdominal appendicitis (6/18, 33% and 14/95, 15%, respectively). These findings are supported by findings of Raveenthiran et al.¹ and may be explained by a potential delay in recognition and treatment of patients with nonperforated appendicitis.

Preterm patients are traditionally considered to be more vulnerable compared to term patients, and it was expected that this would be reflected in more fatal cases among preterm patients with

appendicitis. Contradictory, we found 14 (70%) of the 20 patients with fatal outcome to be born at term. This may be partially explained by the fact that preterm patients are usually admitted at the neonatal intensive care after birth, allowing for close monitoring and subsequently early detection and initiation of (targeted) treatment. Moreover, appendicitis and NEC mimic each other's symptoms which may increase awareness towards the potential need of surgical intervention in preterm patients.^{69,129,131} Taken together, our findings suggest that strict observation of patients with symptoms compatible with abdominal appendicitis, as well as early diagnosis and treatment of these patients may favour their outcome.

Diagnosing appendicitis in these young infants remains challenging. One of the reasons being the lack of communicational skills of neonates and young infants, as older children can express abdominal pain (in the right lower quadrant) as the most common symptom.^{4,150} In comparison, in infants ≤ 3 months of age with appendicitis, abdominal distension was the most common symptom. And, although abdominal distension and other identified symptoms may be nonspecific, it is of importance that the clinician looks for their presence to decrease the risk in delay of diagnosis and treatment. In addition, based on results of this systematic review, we strongly advise that in all patients with symptoms compatible with abdominal appendicitis a plain X-ray is performed (including lateral view) as has been suggested previously by Schwartz et al.¹²⁰ In case of pneumoperitoneum, a surgical treatment is warranted. In the absence of pneumoperitoneum or clear diagnosis other than appendicitis, an abdominal ultrasound is advised as well as the implementation of repeated plain X-rays.

A surgical treatment should at least be considered as ultimately 236 (98%) of the 242 identified patients underwent surgery, either immediate or after initial conservative treatment. However, conclusions on choice or timing of treatment cannot be exclusively made as this was not a comparative study on type of intervention, RCT's are lacking and cases of successful conservative treatment may have been potentially missed as a result of selection or publication bias.

4.3 | Study limitations

In this systematic review the majority of included articles was either a case report or case series. Consequently, this greatly affected the overall level of evidence, which needs to be regarded as low. Noteworthy, due to the fact that most articles were case reports/series and due to the fact that there was a large (clinical) heterogeneity among the identified cases (e.g., but not limited to, different phenotypes of appendicitis, geographical distribution, various patient characteristics and distribution in time) a formal pooled or meta-analysis could not be performed. And, since not all data could be retraceable to either abdominal or herniated appendicitis, due to missing data, and risk of publication bias, a potential skewing of baseline characteristics and outcomes could be present. We therefore recommend that definitive conclusions should be drawn with caution. Importantly, we did not address whether

appendicitis should be considered as a local form of NEC as this was outside the scope of this systematic review. Ideally, a large cohort study should be performed to evaluate all previously mentioned factors and to provide accurate rates of mortality and morbidity within the current period of developed medicine, but due to the heterogeneity of the patient group and low incidence this may not be feasible. Therefore, we would like to encourage the continued publication of case reports and case series.

5 | CONCLUSIONS

In conclusion, mortality was reported in 20 (8%) of the 242 identified infants ≤ 3 months of age with appendicitis and morbidity in an additional 18 (8%). All fatal cases had abdominal appendicitis and several patient characteristics were relatively more often reported in infants with poor (fatal) outcome. Adequate monitoring, early recognition and timely initiation of treatment may favour the outcome. The available evidence suggests to perform plain abdominal X-rays in all patients with abdominal symptoms compatible with appendicitis, and an ultrasound in case the X-ray is normal. A surgical approach in this patient group should be considered, but definitive conclusions regarding the optimal strategy need to be drawn with caution.

AUTHOR CONTRIBUTIONS

Sarah-May M. L. The, Anne-Fleur M. H. The, Joep P. M. Derikx, Tim G. J. de Meij, and Ramon R. Gorter conceived this systematic review. All authors provided expertise to the protocol of this systematic review. Johannes C. F. Ket performed the search. Sarah-May M. L. The and Anne-Fleur M. H. The performed the study selection, data extraction and draft of the manuscript. All authors contributed to the interpretation of data, refinement of the manuscript and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available via the referenced articles. Any further (summarized) data is available within this article and supplementary material of this article.

TRANSPARENCY STATEMENT

The lead author Sarah-May ML The affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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