

Association of Gangrenous, Suppurative, and Exudative Findings With Outcomes and Resource Utilization in Children With Nonperforated Appendicitis

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IMPORTANCE The clinical significance of gangrenous, suppurative, or exudative (GSE) findings is poorly characterized in children with nonperforated appendicitis.

OBJECTIVE To evaluate whether GSE findings in children with nonperforated appendicitis are associated with increased risk of surgical site infections and resource utilization.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study used data from the Appendectomy Targeted Database of the American College of Surgeons Pediatric National Surgical Quality Improvement Program, which were augmented with operative report data obtained by supplemental medical record review. Data were obtained from 15 hospitals participating in the Eastern Pediatric Surgery Network (EPSN) research consortium. The study cohort comprised children (aged ≤ 18 years) with nonperforated appendicitis who underwent appendectomy from July 1, 2015, to June 30, 2020.

EXPOSURES The presence of GSE findings was established through standardized, keyword-based audits of operative reports by EPSN surgeons. Interrater agreement for the presence or absence of GSE findings was evaluated in a random sample of 900 operative reports.

MAIN OUTCOMES AND MEASURES The primary outcome was 30-day postoperative surgical site infections (incisional and organ space infections). Secondary outcomes included rates of hospital revisits, postoperative abdominal imaging, and postoperative length of stay. Multivariable mixed-effects regression was used to adjust measures of association for patient characteristics and clustering within hospitals.

RESULTS Among 6133 children with nonperforated appendicitis, 867 (14.1%) had GSE findings identified from operative report review (hospital range, 4.2%-30.2%; $P < .001$). Reviewers agreed on presence or absence of GSE findings in 93.3% of cases (weighted κ , 0.89; 95% CI, 0.86-0.92). In multivariable analysis, GSE findings were associated with increased odds of any surgical site infection (4.3% vs 2.2%; odds ratio [OR], 1.91; 95% CI, 1.35-2.71; $P < .001$), organ space infection (2.8% vs 1.1%; OR, 2.18; 95% CI, 1.30-3.67; $P = .003$), postoperative imaging (5.8% vs 3.7%; OR, 1.70; 95% CI, 1.23-2.36; $P = .002$), and prolonged mean postoperative length of stay (1.6 vs 0.9 days; rate ratio, 1.43; 95% CI, 1.32-1.54; $P < .001$).

CONCLUSIONS AND RELEVANCE In children with nonperforated appendicitis, findings of gangrene, suppuration, or exudate are associated with increased surgical site infections and resource utilization. Further investigation is needed to establish the role and duration of postoperative antibiotics and inpatient management to optimize outcomes in this cohort of children.

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← Invited Commentary
page 692

+ Supplemental content

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Appendicitis is the most common abdominal surgical emergency in childhood.^{1,2} Disease severity of appendicitis spans from mild appendiceal inflammation to frank perforation with diffuse fecopurulent peritonitis. Management, including determining the duration of postoperative antibiotic treatment and inpatient observation, is typically based on assessment of disease severity as nonperforated or perforated, the latter defined by direct or indirect evidence of appendiceal perforation.³⁻⁶ Children with nonperforated appendicitis may be managed without postoperative antibiotics while those with perforated appendicitis may require extended postoperative antibiotics and are at a higher risk for adverse outcomes and increased resource utilization.⁴⁻¹¹

Nonperforated appendicitis with findings of advanced disease such as gangrenous, suppurative, or exudative (GSE) changes represents up to 20% of cases and can present a management dilemma for pediatric surgeons.^{9,12-15} Existing studies have provided conflicting data regarding outcomes and the benefit of postoperative antibiotics in this subset of patients with appendicitis. In a large multicenter analysis of adult patients with nonperforated appendicitis, gangrenous changes were associated with higher risk of organ space infection; however, other studies have not demonstrated this association.¹²⁻¹⁵ Existing data in the pediatric population are currently limited to small, single-center studies using nonstandardized definitions for both GSE findings and study outcomes.^{12,13} The paucity of high-quality data is reflected in variation in both postoperative management and outcomes associated with GSE findings in the published literature.^{9,12,13,16-19}

With the above considerations, the goal of this multicenter study was to evaluate whether the presence of GSE findings in patients with nonperforated appendicitis is associated with increased risk of surgical site infections (SSIs) and resource utilization. Furthermore, the study sought to develop and assess the reliability of a standardized definition for GSE findings based on operative report review. Understanding how GSE findings are associated with postoperative outcomes may be important for refining clinical management, including antibiotic treatment duration and need for additional inpatient care. Such insight could have implications for severity adjustment in comparative performance reporting programs like the American College of Surgeons Pediatric National Surgical Quality Improvement Program (NSQIP-Pediatric).

Methods

Data Source

This was a retrospective, multicenter cohort study using clinical and outcomes data from NSQIP-Pediatric augmented with operative report data obtained through supplemental medical record review. This study was approved by the local institutional review boards of all participating Eastern Pediatric Surgery Network (EPSN) research consortium hospitals with Boston Children's Hospital serving as the data coordinating center (IRB-P00039632). Reporting followed guidelines from

Key Points

Question In children with nonperforated appendicitis, do findings of gangrene, suppuration, or fibrinous exudate increase the risk of infectious complications and resource utilization?

Findings In this cohort study of children with nonperforated appendicitis, the presence of gangrene, suppuration, or exudate was associated with increased organ space infection rates and postoperative length of stay.

Meaning Further investigation is needed to establish the role and duration of postoperative antibiotics in this cohort of children with nonperforated appendicitis.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

All children with acute appendicitis in NSQIP-Pediatric who were managed at 1 of 15 tertiary pediatric hospitals associated with the EPSN were identified. The NSQIP-Pediatric database includes a wide array of disease-specific clinical data for children undergoing appendectomy for acute appendicitis for the purpose of comparing risk-adjusted adverse event and resource utilization data among its 152 member hospitals.²⁰ Data are collected through a rigorous medical record review process by dedicated surgical clinical reviewers using standardized criteria and definitions. The accuracy of NSQIP-Pediatric data is facilitated through periodic auditing, mandatory recertification for data abstractors, and availability of American College of Surgeons clinical support to address questions regarding definitions and data abstraction protocol.²¹

Each participating site downloaded their respective NSQIP-Pediatric data used in this analysis and collected full operative report text via supplemental medical record review. The data were uploaded to the data coordinating center using a secure transfer process. The American College of Surgeons was not involved in the management or transfer of any study data. NSQIP-Pediatric data and operative report text for each patient were reviewed by primary study staff to ensure data quality and completeness of the operative reports provided.

Study Cohort

The study cohort included children (aged ≤ 18 years) undergoing appendectomy for acute appendicitis identified from the NSQIP-Pediatric database from July 1, 2015, to June 30, 2020. Patients were excluded if the operative report data were incomplete, if the appendectomy represented an interval appendectomy (not performed for management of acute appendicitis), or if additional procedures were performed during the appendectomy (eg, resection of a Meckel diverticulum).

Definition of Gangrenous, Suppurative, or Exudative Appendicitis

Complete operative reports were reviewed by a subcommittee of EPSN surgeons to establish the presence or absence of GSE findings. Disease severity was based only on operative report text, and the process was blinded to the original assessment of the operating surgeon. Surgeon reviewers received

standardized video-based training prior to operative report auditing, which described the background for the project and the process for identifying cases of perforated appendicitis and nonperforated appendicitis with and without GSE findings from operative reports. Perforated appendicitis was defined using validated NSQIP-Pediatric criteria.^{3,4,22} These criteria include presence of at least 1 of the following intraoperative findings: visible hole in the appendix, abscess, extraluminal fecalith, or diffuse fibrinopurulent exudate extending outside the right lower quadrant and pelvis.^{3,4}

Remaining operative reports of patients without perforated appendicitis were reviewed and categorized as nonperforated with or without GSE findings. To be categorized as having GSE findings, the operative report had to contain keywords describing any of the following directly involving the appendix: gangrene (or gangrenous), necrosis (or necrotic), exudate (or exudative), rind, peel, suppuration (or suppurative), purulence (or purulent), and/or mucopurulence (or mucopurulent). Furthermore, nonperforated cases were categorized as having GSE findings if a hole or leakage of pus or stool from the appendix occurred as result of operative manipulation (eg, it was not present at the start of the operation). Cases with any GSE findings were further stratified as those with and without gangrenous (or necrotic) changes to assess the relative association of gangrene vs suppurative/exudative changes with outcomes. Patients with perforated appendicitis were excluded from further analysis.

Classification of Outcomes

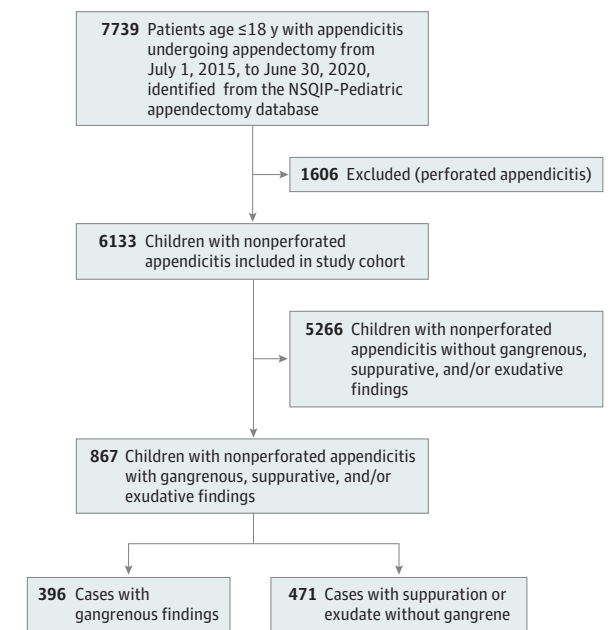
The primary outcome of this study was 30-day postoperative composite SSIs (incisional and/or organ space infection based on percutaneous drainage procedures or NSQIP-Pediatric-defined radiographic criteria). Secondary outcomes included rates of incisional SSI and organ space infection (OSI) individually, postoperative abdominal imaging, revisits (emergency department visits or inpatient readmissions), and postoperative length of stay (LOS). Outcomes were compared between patients with and without GSE findings. As a sensitivity analysis, patients with GSE findings were further stratified into those with and without gangrenous changes.

Statistical Analysis

To assess interrater reliability of the above operative severity assessment of GSE findings, a random sample of 900 operative reports was reviewed by different combinations of 2 EPSN surgeons, with each surgeon reviewing at least 50 operative reports. Interrater reliability in distinguishing perforated vs nonperforated disease and the presence or absence of GSE findings in nonperforated appendicitis was measured as rate of reviewer agreement and with the weighted κ statistic.

To evaluate associations between operative report findings and outcomes of interest, multivariable, mixed-effects regression models were used to compare patients who had 1 or more of the above intraoperative findings with patients who did not have the finding. Models were adjusted for hospital-level clustering with random effects and for patient characteristics, including sex, race and ethnicity, and insurer type. Race and ethnicity data were provided by NSQIP-Pediatric as

Figure 1. Assembly of the Study Cohort



NSQIP-Pediatric indicates the Pediatric National Surgical Quality Improvement Program.

reported by participant family or caregiver and combined into the categories Black, Hispanic, and White for use in the study.

A logistic link was used for binary outcomes (SSI, postoperative abdominal imaging, revisits). A gamma link was used for continuous outcomes (postoperative LOS) given rightward skewed distribution. Measures of association were reported as adjusted odds ratios (ORs) and rate ratios (RRs), accordingly. Analyses were performed with SAS version 9.4 (SAS Institute). The statistical significance threshold was a 2-sided $P < .05$.

Results

In total, 7739 children undergoing appendectomy for acute appendicitis from 15 children's hospitals were identified from the NSQIP-Pediatric data. After excluding perforated appendicitis cases, 6133 (79.2%) with nonperforated appendicitis were included in the analysis (Figure 1). In the final cohort, 39.6% were female, and 34.5% had public insurance while 43.9% had private insurance. The racial and ethnic makeup of the cohort was 5.4% Black, 21.5% Hispanic, and 36.1% White, and 35.4% had missing race. GSE findings were present in 14.1% of cases and ranged from 4.2% to 30.2% across hospitals ($P < .001$) (Figure 2). Gangrenous findings were present in 6.5% of cases, while suppurative or exudative changes without gangrene were present in 7.7%.

Interrater Reliability of GSE Definition Criteria

A total of 900 operative reports were doubly reviewed by 20 EPSN surgeons. Two reports were excluded because they described procedures other than appendectomy. Surgeon re-

Figure 2. Variation in Rates of Gangrenous, Suppurative, and Exudative Changes in Nonperforated Appendicitis Cases at 15 Hospitals in the Pediatric National Surgical Quality Improvement Program

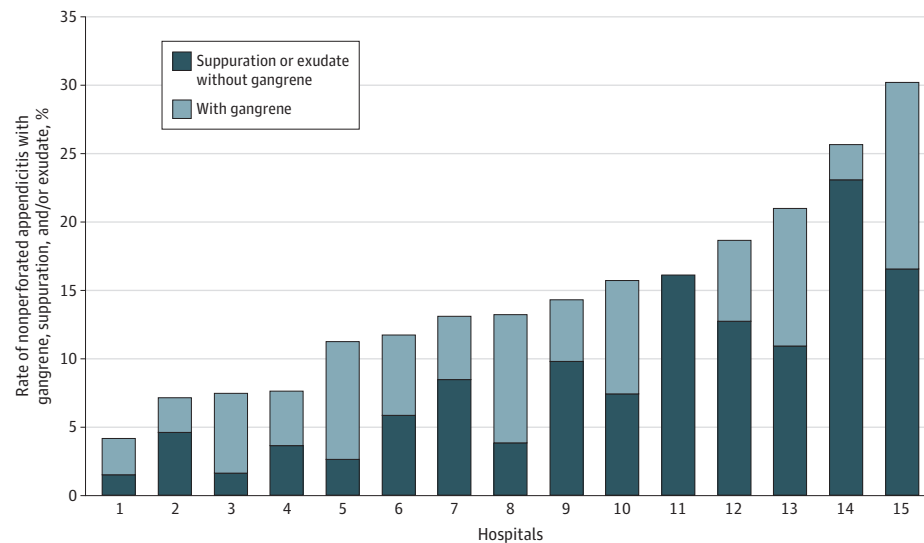
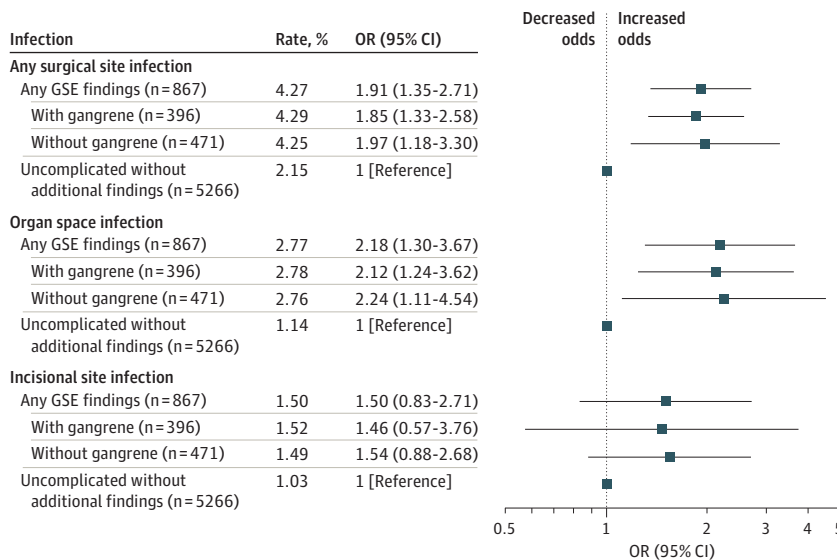


Figure 3. Association of Gangrenous, Suppurative, and Exudative (GSE) Findings With Surgical Site Infections in Children With Nonperforated Appendicitis



OR indicates odds ratio.

viewers agreed on severity classification (perforated, nonperforated with GSE findings, nonperforated without GSE findings) in 93.3% of cases, corresponding to a weighted κ of 0.89 (95% CI, 0.86-0.92), indicating excellent agreement.²³

Association of GSE Findings With Surgical Site Infections

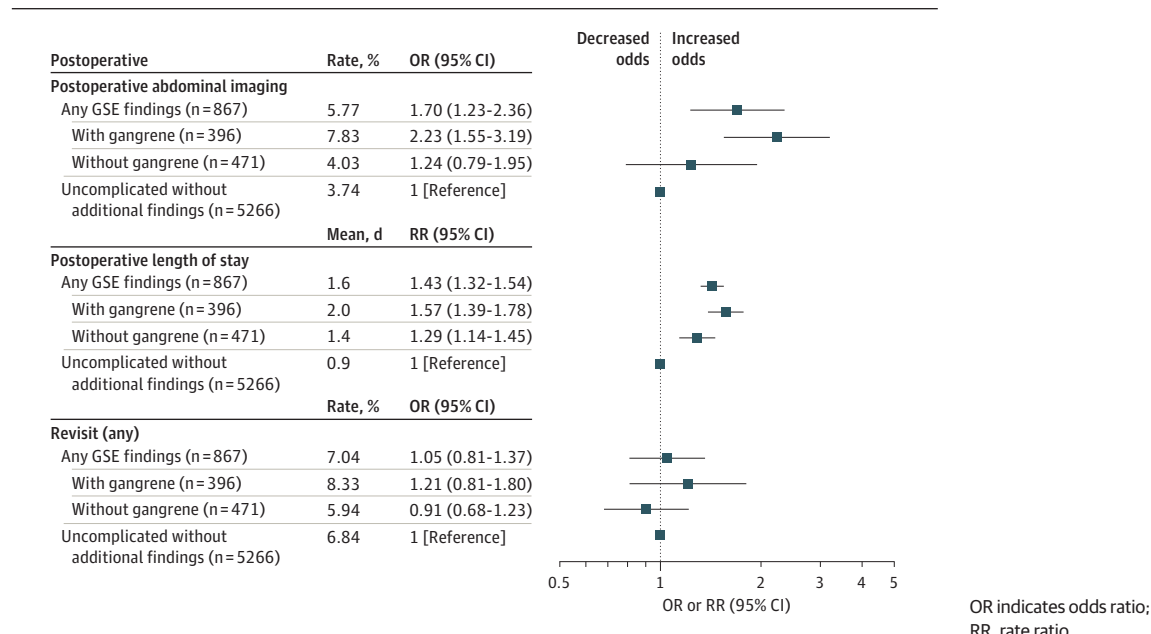
The overall rate of any SSI was 2.4%, and patients with GSE findings had a higher rate of any SSI compared with those without GSE findings (4.3% vs 2.2%; $P < .001$). When stratified by SSI type, patients with GSE findings had higher rates of OSI (overall, 1.4%; GSE, 2.8%, vs non-GSE, 1.1%; $P = .001$). There were no differences in rates of incisional SSI between pa-

tients with and without GSE findings (overall, 1.1%; GSE, 1.5%, vs non-GSE, 1.0%; $P = .22$).

In the multivariable analysis, presence of GSE findings was associated with 91% increased odds of any SSI (OR, 1.91; 95% CI, 1.35-2.71; $P < .001$) and 2.2-fold increased odds of OSI (OR, 2.18; 95% CI, 1.30-3.67; $P = .003$) (Figure 3). There were no differences in odds of incisional SSI between patients with or without GSE findings (OR, 1.50; 95% CI, 0.83-2.71; $P = .18$) (Figure 3).

When patients with GSE findings were stratified by presence or absence of gangrene, patients with gangrenous changes had an 85% increase in odds of any SSI (OR, 1.85; 95% CI, 1.33-2.58; $P < .001$) and 2.1-fold increased odds of OSI (OR, 2.12; 95%

Figure 4. Association of Gangrenous, Suppurative, and Exudative (GSE) Findings With Resource Utilization Outcomes in Children With Nonperforated Appendicitis



CI, 1.24-3.62; $P = .006$) when compared with patients without GSE findings. Patients with suppuration or exudate without gangrene had 97% increase in odds of any SSI (OR, 1.97; 95% CI, 1.18-3.30; $P = .01$) and 2.2-fold increased odds of OSI (OR, 2.24; 95% CI, 1.11-4.54; $P = .03$) (Figure 3). Neither gangrenous changes nor suppurative/exudative changes alone were independently associated with increased incisional SSI.

Association of GSE Findings With Resource Utilization

The overall rate of postoperative abdominal imaging was 4.0%, and patients with GSE findings had higher rates compared with those without GSE findings (5.8% vs 3.7%; $P = .005$). On multivariable analysis, GSE findings were associated with a 70% increase in the odds of postoperative abdominal imaging compared with those without GSE findings (OR, 1.70; 95% CI, 1.23-2.36; $P = .002$) (Figure 4). When stratified by type of GSE findings, gangrenous changes were associated with 2.2-fold increased odds of postoperative abdominal imaging compared with those without GSE findings (OR, 2.23; 95% CI, 1.55-3.19; $P < .001$) (Figure 4). The presence of suppurative or exudative changes alone was not associated with increased postoperative imaging on stratified analysis (OR, 1.24; 95% CI, 0.79-1.95; $P = .36$) (Figure 4).

The mean (SD) postoperative LOS was 1.0 (1.8) days, and patients with GSE findings had significantly longer mean postoperative LOS compared with those without GSE findings (1.6 [2.1] days vs 0.9 [1.7] days; $P < .001$). On multivariable analysis, GSE findings were associated with a 43% longer mean postoperative LOS compared with those without GSE findings (RR, 1.43; 95% CI, 1.32-1.54; $P < .001$). When stratified by type of GSE findings, gangrenous changes and suppurative or exudative changes without gangrene were independently associated with a 57% and 29% increase in mean postoperative LOS, respectively, compared with those with-

out any GSE changes (RR, 1.57; 95% CI, 1.39-1.78; $P < .001$, and RR, 1.29; 95% CI, 1.14-1.45; $P < .001$) (Figure 4).

The overall revisit rate was 6.9%, which was similar between patients with and without GSE findings (7.0% vs 6.8%; $P = .83$). On multivariable analyses, there remained no association between GSE changes and revisits, including after stratification by the presence or absence of gangrenous changes (Figure 4).

Discussion

In this multicenter analysis of 6133 children with nonperforated appendicitis, the presence of gangrenous, suppurative, or exudative changes was associated with increased risk of OSI, postoperative abdominal imaging, and prolonged postoperative LOS. Furthermore, it is noteworthy that findings of gangrenous changes and suppuration/fibrinous exudate without gangrene were both independently associated with increased OSI risk and resource utilization. These findings would suggest that bacterial translocation and increased risk for adverse events can occur even in the absence of visible gangrene or frank necrosis.

Previous studies have provided conflicting data as to the association of GSE findings with outcomes and the utility of postoperative antibiotics in patients with nonperforated appendicitis. In a single-center, prospective analysis involving 69 children with gangrenous appendicitis, SSI rates remained unchanged (2.9%) after postoperative antibiotics were removed from the clinical pathway.¹³ However, postoperative LOS was longer in patients with gangrenous appendicitis compared with those without gangrenous findings (1.4 vs 1.0 days).¹³ In another single-center, prospective study involving 58 children with gangrenous appendicitis, a decrease in mean

postoperative LOS (1.9 vs 3.0 days) without an increase in SSI rates was observed after postoperative antibiotics were limited to 24 hours.¹² In a multicenter, prospective analysis of 3597 adult patients with appendicitis, cases of nonperforated appendicitis with gangrenous changes were associated with an increased rate of OSI compared with cases when these findings were absent (6% vs 1%).¹⁴ In another prospective, multicenter analysis including 1863 adults, presence of gangrenous changes was not associated with increased SSI risk.¹⁵ The ability to compare results across studies has been limited by lack of standardized, validated definitions for both GSE findings and SSI events. Generalizability of existing data in the pediatric population has been further limited by single-center study designs and relatively small sample sizes.

To our knowledge, the present study represents the largest analysis to date examining the associations of GSE findings in appendicitis in adults or children and is the first multicenter study to specifically explore outcomes in the pediatric population. Outcome data used in this analysis were obtained from NSQIP-Pediatric data, which is abstracted through a standardized, rigorous medical record review process by dedicated American College of Surgeons trained personnel.^{20,21} This study also differs from previous analyses in not only evaluating the association of gangrenous findings with outcomes, but also establishing the clinical relevance of suppurative and exudative appendicitis in the absence of gangrene and necrosis. To our knowledge, this study also reports the first multicenter effort to develop and assess the interrater reliability of a standardized definition and approach for identifying GSE findings, ensuring that the criteria used in this analysis are reliable, generalizable, and clinically meaningful.

The results of this study demonstrate that GSE findings are associated with increased risk of infectious complications and resource utilization in children with nonperforated appendicitis. Longer postoperative LOS observed in patients with GSE findings may be driven by several factors, including a higher risk of infectious complications, longer time to full convalescence, assignment to postoperative clinical pathways mandating inpatient observation or additional intravenous antibiotics based on intraoperative findings without other clinical indications, or a combination of these. Future work is needed to establish best practices in this cohort of children with nonperforated appendicitis to optimize resource utilization, antibiotic stewardship, and SSI prevention. Such investigation will need to establish the benefit, if any, of postoperative antibiotics and, if beneficial, whether these should be administered orally or intravenously and for what duration. These considerations could have important implications for refining fast-track, same-day discharge protocols for children with nonperforated disease.

The magnitude of variation in rates of GSE findings among hospitals was another noteworthy finding and may have important implications for comparative performance reporting. Without adjustment for GSE findings, hospitals with a relatively high proportion of cases with GSE findings may appear to have worse outcomes and higher resource utilization compared with peer hospitals with lower rates of GSE findings. Refinement of the existing appendicitis severity classification sys-

tem in NSQIP-Pediatric to include GSE findings should be considered to provide more robust and accurate comparative performance assessment between hospitals. Given that rates of GSE findings varied more than 7-fold among hospitals, such adjustment is likely to influence both relative performance ranking as well outlier status among peer hospitals. Further, accurate reporting of GSE findings may have important implications for the validity of comparative effectiveness research studies involving children with nonperforated disease.

Limitations

This study has several important limitations. NSQIP-Pediatric data are retrospectively collected and thus subject to errors due to misclassification or clinical documentation. Data regarding postoperative antibiotic use and duration were not available, and these factors may be associated with the outcomes observed in this study. However, postoperative antibiotics would more likely be used in cases where GSE findings were encountered. This would bias the results of this study toward the null hypothesis that GSE findings are not associated with worse outcomes. A similar effect would occur because of errors in misclassification of GSE findings based on accuracy of the dictated operative report. An error of omission (eg, not dictating GSE findings when present) would likely be more common than reporting GSE findings in an operative note when they were absent, which would also bias the results toward the null hypothesis. Based on these considerations, it is likely that the results of this analysis may have underestimated the true magnitude of associations between GSE findings and surgical site infections and resource utilization. Retrospective review of operative reports to determine presence of GSE findings may be subject to additional errors in misclassification because of the subjective nature of describing intraoperative findings. However, it is noteworthy that excellent interrater agreement was found for assessing the presence or absence of GSE findings across surgeon reviewers. Furthermore, hospitals participating in the EPSN research consortium are largely academic, freestanding children's hospitals, and therefore these results may not be generalizable to other clinical settings.

Conclusions

Despite the limitations, we can conclude that risk of infectious complications and resource utilization are both increased in the presence of gangrenous, suppurative, or exudative changes in children with nonperforated appendicitis. Future investigation is needed to define optimal management in this subset of children with appendicitis, including whether or not postoperative antibiotics and routine inpatient observation are warranted and, if so, for what duration. Development of evidence-based best practices could have important implications from a public health perspective given the large volume of children with nonperforated appendicitis and the degree of equipoise surrounding management of GSE findings. While this analysis only focused on outcomes associated with the pediatric population, the results of this study may also have implications for the management of adults with nonperforated appendicitis.

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Invited Commentary

Gangrenous, Suppurative, and Exudative Nonperforated Appendicitis—A Distinct Pathology?

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The antibiotics regimen for patients with appendicitis is typically dictated by evidence of appendiceal perforation.^{1,2} Although uncomplicated (nonperforated) appendicitis is typically managed with a single dose of intravenous antibiotics preoperatively, complicated appendicitis generally requires a prolonged course of antibiotics in various combinations of intravenous and a strong push to transition to oral doses owing to the higher risk of adverse outcomes, such as organ-space infection.² There is a subset of patients, however, representing approximately 20% of cases, with nonperforated appendicitis but evidence of gangrene, suppuration, or fibrinous exudate (GSE) at the time of appendectomy.^{3,4} Conflicting data on how best to manage these patients have led to variability in postoperative antibiotic use, management, and outcomes.³⁻⁶

In a retrospective, multicenter, cohort study using the pediatric National Surgical Quality Improvement Program database, Cramm et al⁷ evaluated whether GSE findings increase the risk of infectious complications and resource utilization in the management of children with nonperforated appendicitis. This is an important question with clinical significance given the high incidence of appendicitis in the pediatric population and the lack of guidelines dictating the management of children with GSE findings at appendectomy. Their results demonstrate that GSE findings are an independent risk factor of postoperative infectious complications in nonperforated appendicitis. Furthermore, their data suggest that GSE findings may warrant different management than the single dose of an-

tibiotics used preoperatively for nonperforated appendicitis without GSE findings.

We commend the authors on their study design,⁷ specifically the use of multiple centers, standardized definitions of GSE findings, assessment of interrater reliability of GSE definition criteria, and subgroup analysis based on gangrene vs suppuration and exudate. However, the use of intraoperative photographs of inflamed appendixes, rather than operative notes, may have allowed for a less biased assessment of GSE findings. Furthermore, the level of training or experience of the writers of the operative reports (junior resident vs senior resident vs attending surgeon) is unclear, and as the authors acknowledge, many operative notes are based on templates with minor case-based adjustments. Strong interrater reliability of GSE criteria based on intraoperative laparoscopic photographs may have diminished bias introduced by the subjective nature of describing intraoperative findings. In addition, while statistically significant, the difference in mean postoperative length of stay of 0.7 days between groups may not be clinically significant and is likely driven by surgeon bias and time of operation as opposed to data or protocol-driven management.

Overall, the authors are commended for their robust study design⁷ and data demonstrating the importance of GSE findings in the management of children with nonperforated appendicitis. Further work is needed to determine whether GSE findings of appendicitis should require a prolonged therapeutic administration of antibiotics regimen or otherwise alter clinical management in children with uncomplicated appendicitis and GSE findings.

ARTICLE INFORMATION

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