Comparative effectiveness of amoxicillin versus amoxicillin-clavulanate among adults with acute sinusitis in emergency department and urgent care settings

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Abstract

Objective: To compare the effectiveness of amoxicillin-clavulanate versus amoxicillin for adults diagnosed with acute sinusitis (AS). A secondary objective compared antibiotic effectiveness in patients meeting risk criteria for treatment failure.

Methods: A retrospective cohort study of adults diagnosed with AS prescribed amoxicillin ± clavulanate within Veterans Affairs emergency departments from 2012–2019 was conducted. The primary outcome was sinusitis-related return visits for amoxicillin versus amoxicillin-clavulanate. Secondary outcomes included 30-day infectious complications, gastrointestinal-related adverse events (AEs), and hospitalizations. Propensity-score matching and logistic regression models adjusted for potential confounders.

Results: A total of 89,627 AS patient visits were identified: 18,576 prescribed amoxicillin and 71,051 amoxicillin-clavulanate. Most patients were male (75,604; 84.4%) and afebrile (80,624; 91.7%). The propensity score-matched cohort comprised 17,929 amoxicillin and 42,294 amoxicillin-clavulanate patient visits. There was no difference in sinusitis-related return visits between amoxicillin (4.9%) and amoxicillin-clavulanate (5.1%) (adjusted odds ratio [OR], 0.96; 95% confidence interval [CI], 0.88, 1.04; P = 0.317). Infectious complications (amoxicillin [0.3%] vs amoxicillin-clavulanate [0.4%]); (adjusted OR, 0.78; 95% CI, 0.57, 1.07; P = 0.124) and hospitalization (amoxicillin [2.0%] vs amoxicillin-clavulanate [2.4%]); (adjusted OR, 0.92; 95% CI, 0.81, 1.04;
Gastrointestinal-related AEs were lower with amoxicillin (0.5%) relative to amoxicillin-clavulanate (0.7%); (adjusted OR, 0.67; 95% CI, 0.53, 0.86; \( P = 0.002 \)). Comorbidity was the only guideline-recommended risk factor that was a significant predictor of infectious complications with respect to treatment (amoxicillin vs amoxicillin-clavulanate, OR, 0.63; 95% CI, 0.40 to 0.94; \( P = 0.022 \)).

**Conclusion:** Amoxicillin demonstrated similar efficacy to amoxicillin-clavulanate for AS with fewer gastrointestinal-related AEs. Amoxicillin is a viable option in adults with AS meeting criteria for antibiotic therapy.

**KEYWORDS** adverse drug event, amoxicillin-clavulanate, antimicrobial stewardship, clinical outcomes, outpatient, sinusitis

1 | INTRODUCTION

1.1 | Background

Acute rhinosinusitis affects 1 in 8 adults in the United States, culminating in almost 30 million annual cases. Most cases are of viral etiology; but, in a subset of rhinosinusitis cases where specific criteria are met, a probable bacterial infection warrants antibiotic use.\(^1,2\) Infectious Diseases Society of America (IDSA) guidelines recommend 3 criteria where antibiotics are indicated: (1) persistent symptoms and not improving (\( \geq 10 \) days), (2) worsening symptoms (eg, new onset fever, nasal discharge/cough), or (3) severe symptoms (eg, purulent nasal discharge or pain lasting \( \geq 3 \) days or high fever \( \geq 102^\circ F \)).\(^3\) The American College of Emergency Physicians also recommends limiting antibiotic treatment to patients meeting similar criteria.\(^4\)

Antibiotic recommendations for sinusitis are not uniform across professional organizations which may contribute to variability in prescribing practices. IDSA guidelines recommend amoxicillin-clavulanate as preferred over amoxicillin for empiric therapy in adults (weak recommendation, low evidence) meeting treatment criteria for acute bacterial sinusitis (eg, acute sinusitis).\(^3\) This recommendation is based on concerns that a high proportion of *Haemophilus* isolates can produce \( \beta \)-lactamase that hydrolyze amoxicillin but remain susceptible to amoxicillin-clavulanate.\(^5\)

American Academy of Otolaryngology (AAO) guidelines recommend amoxicillin with or without clavulanate for patients meeting treatment criteria.\(^6\) Authors acknowledge that comparative studies were insufficiently powered to detect differences in outcomes given the relatively minor benefit of antibiotics for acute sinusitis. These guidelines recommend antibiotic selection be based on the presence of established risk factors for resistant organisms in situations in which bacterial resistance is likely (eg, antibiotic use in the past month), the presence of moderate-to-severe infection (eg, frontal or sphenoidal sinusitis, temperature \( > 102^\circ F \)), comorbidities (eg, immunosuppression, renal disease) or geriatric patients (age > 65 years old). These risk factors were established based on studies of antibiotic resistance in pathogenic isolates recovered predominantly from children; more evidence is warranted to assess their association with clinical outcomes irrespective of treatment selection in adults.

1.2 | Importance

Amoxicillin-clavulanate is known to cause gastrointestinal-related adverse antibiotic events and is the most frequently prescribed antibiotic leading to hospitalization for drug-induced liver disease.\(^7\) It is unknown if the potential benefits of the increased spectrum of activity for amoxicillin-clavulanate for acute sinusitis treatment outweigh the increased risk of toxicity or the promotion of antibiotic resistance as compared to amoxicillin.

1.3 | Objective

The primary goal was to determine if prescribing amoxicillin for acute sinusitis is associated with a difference in sinusitis-related return visits, infectious complications, gastrointestinal-related adverse antibiotic events, or hospitalizations compared to amoxicillin-clavulanate. Additional goals included assessment of the relationship between AAO guideline-based risk factors and treatment failure for amoxicillin and amoxicillin-clavulanate, and assessment of outcomes associated with antibiotic therapy compared to no antibiotic therapy.

2 | METHODS

2.1 | Study design and setting

A nationwide retrospective cohort of adults treated for acute sinusitis within Veterans Healthcare Administration (VHA) emergency department and urgent care settings between January 2012 (IDSA guideline publication year) and September 2019 was created. Demographic, diagnostic, treatment, and outcomes data were extracted from the VHA Corporate Data Warehouse (CDW).
### Selection of participants

Demographic data included sex, patient age, index visit temperature, and select comorbidities (ie, chronic obstructive pulmonary disease, hemodialysis, immunosuppression, neoplasm). Comorbidities were identified by diagnostic codes or medications filled specifically for those conditions. Acute sinusitis was identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or equivalent International Classification of Diseases, Tenth Revision (ICD-10) codes (eTable S7).

Visits with previous acute respiratory tract infection diagnoses (sinusitis, pharyngitis, bronchitis, or other upper viral illnesses) within the prior 30 days, and visits with diagnostic codes indicating chronic sinusitis or concurrent infection (eg, pneumonia, cellulitis) requiring antibiotic treatment were excluded (eTable S7). A matched propensity score method was used to adjust for potential confounders of antibiotic therapy (eTables 2–6). Patients who were prescribed amoxicillin-clavulanate were matched with patients prescribed amoxicillin alone. Propensity scores were estimated from a logistic model that included time, facility, and covariates associated at the \( P < 0.20 \) level with the return visit outcome (eTable S2). Matching was performed with Matchit in RStudio (R version 4.0.2) using maximum caliper width 0.2 standard deviations of the logit of propensity scores. The odds ratio of sinusitis-related return visits for amoxicillin relative to amoxicillin-clavulanate was estimated using logistic regression.

### Exposures

Antibiotic prescriptions were attributed to the visit if filled within 2 days before and 3 days after the index visit date.

### Outcomes

A return visit for acute sinusitis was defined as a new outpatient visit with a diagnostic code for acute sinusitis within 30 days of the index visit. Potential infectious complications (ie, *Clostridioides difficile* infections, pneumonia, meningitis, mastoiditis, or facial cellulitis) were identified by a new outpatient or inpatient diagnostic code for these conditions within 30 days following the index visit (eTable S7). Return visits for gastrointestinal-related adverse antibiotic events were identified by outpatient visits or inpatient admissions with diagnostic codes consistent with potential gastrointestinal-related adverse antibiotic events (ie, diarrhea, colitis, hepatitis, nausea) for visits that occurred within 14 days after the index acute sinusitis visit if the patient did not have a similar diagnostic code within 6 months preceding the visit (eTable S7). Hospitalizations were defined by an admission date that occurred between 1 and 30 days following the index visit.

### Analysis

A matched propensity score method was used to adjust for potential confounders of antibiotic therapy (eTables 2–6). Patients who were prescribed amoxicillin-clavulanate were matched with patients prescribed amoxicillin alone. Propensity scores were estimated from a logistic model that included time, facility, and covariates associated at the \( P < 0.20 \) level with the return visit outcome (eTable S2). Matching was performed with Matchit in RStudio (R version 4.0.2) using maximum caliper width 0.2 standard deviations of the logit of propensity scores. The odds ratio of sinusitis-related return visits for amoxicillin relative to amoxicillin-clavulanate was estimated using logistic regression.

### The Bottom Line

Amoxicillin demonstrated similar efficacy to amoxicillin-clavulanate for acute sinusitis with no significant difference in sinusitis-related revisit rates (adjusted odds ratio [OR], 0.96; 95% confidence interval [CI], 0.88–1.04; \( P=0.317 \)) and with reduced gastrointestinal-related adverse events (adjusted OR, 0.67; 95% CI, 0.53–0.86; \( P=0.002 \)). Amoxicillin is a viable treatment option in adults with acute sinusitis that require antibiotics. Careful identification of patients for whom to prescribe and withhold antibiotics should be made using guideline-recommended criteria to avoid infectious complications.

#### AAO guideline-based risk factors for resistant organisms that were available within the CDW were included as covariates in the model including antibiotic use in the past 30 days, frontal and sphenoidal sinusitis diagnoses, history of recurrent sinusitis within the past 30 days, comorbidities, patient age, and an indicator variable for temperature \( ≥102°F \) consistent with the potential for severe disease based on the presence of a “high fever” according to IDSA guidelines. Other variables of interest including visit date, facility, healthcare practitioner (physician and non-physician), clinical setting (ED vs urgent care), and patient sex were included as covariates in the model. Generalized estimating equation logistic regression models were used to account for infectious complications, gastrointestinal-related adverse drug events, and hospitalization endpoints for amoxicillin relative to amoxicillin-clavulanate. An identical approach was used to compare no antibiotic treatment to amoxicillin and to amoxicillin-clavulanate.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used as a guideline for assessing methodological and reporting quality. This research complied with all federal guidelines and Department of Veterans Affairs policies relative to human subject research (ie, approved by the institutional review board).

### RESULTS

#### Characteristics of study subjects

Of the 89,627 patient visits for acute sinusitis, there were 18,576 and 71,051 patient visits identified in the amoxicillin and amoxicillin-clavulanate groups, respectively (Figure 1). Most patients were male (75,604; 84.4%), middle aged (median age 56 years), and did not have a fever (\(<99.0°F; n=78,972; 89.8\%). Compared to those prescribed amoxicillin-clavulanate, patients prescribed amoxicillin were less likely...
Study flow diagram. Multiple initial antibiotics prescribed within 24 hours were defined as ≥ 2 antibiotics ordered within ≤ 24-hour timeframe of index visit date and time. Missingness includes one patient who didn’t have a physician, mid-level, or other healthcare practitioner type specified and patients that did not have a systolic blood pressure documented. Propensity-matched case counts represent primary endpoint. Abbreviations: ED, emergency department; UC, urgent care.
to have comorbidities, less likely to have a high fever, and more likely to be treated by a non-physician healthcare practitioner (Table 1). Propensity matching was effective in reducing group differences for all covariates except for facility location and healthcare practitioner type (eTable S3a–d).

### 3.2 Main results

Sinusitis-related return visits occurred in 3,550 (5.1%) of amoxicillin-clavulanate and 892 (4.9%) of amoxicillin patient-visits (P = 0.305). After adjustment for covariates, there was no difference in acute sinusitis-related return visits for amoxicillin relative to amoxicillin-clavulanate treatment (adjusted OR, 0.96; 95% CI, 0.88–1.04; P = 0.317) (Table 2).

There were 309 (0.4%) infectious complications for amoxicillin-clavulanate and 58 (0.3%) for amoxicillin (adjusted OR, 0.78; 95% CI, 0.57–1.07; P = 0.124). The most common infectious complications were pneumonia (n = 320), *Clostridioides difficile* infections (n = 22), mastoiditis (n = 10), facial cellulitis (n = 10), and meningitis (n = 6). No significant difference in the unadjusted rates for specific infectious complications were observed except for an increased risk of *Clostridioides difficile* infections associated with amoxicillin-clavulanate (n = 22; 0.03%) versus amoxicillin (n = 0; 0.00%) (Table 2).

Documented gastrointestinal-related adverse antibiotic events occurred in 481 (0.7%) of amoxicillin-clavulanate and 84 (0.5%) of amoxicillin patient visits. After adjustment for covariates, treatment with amoxicillin relative to amoxicillin-clavulanate was associated with fewer gastrointestinal-related adverse antibiotic events (adjusted OR, 0.67; 95% CI, 0.53–0.86; P = 0.002) (Table 2). Return visits and/or admissions for diarrhea and colitis more common (0.25% vs 0.46%; adjusted OR, 0.67; 95% CI, 0.53–0.86; P = 0.002) (Table 2). Return visits and/or admissions for diarrhea and colitis more common (0.25% vs 0.46%; adjusted OR, 0.67; 95% CI, 0.53–0.86; P = 0.002) (Table 2).

There was no difference in all-cause hospitalizations between treatment with amoxicillin (2.0%) relative to amoxicillin-clavulanate (2.4%) (adjusted OR, 0.92; 95% CI, 0.81–1.04; P = 0.173). The most common admitting diagnoses were angina (n = 177), pneumonia (n = 83), and chronic obstructive pulmonary disease exacerbation (n = 82).

Infections complications and hospitalizations were more common in males [infectious complications [males 0.44% vs females 0.27%; P = 0.005; hospitalizations [males 2.43% vs females 1.58%; P < 0.005]]. Gastrointestinal-related adverse antibiotic events were more common in females (males 0.60% vs females 0.89%; P < 0.005). There was no statistical difference between sex and sinusitis-related revisits.

As we were not able to determine which patients met IDSA criteria for treatment of acute bacterial sinusitis through ICD-based coding, we conducted an additional subgroup analysis for patients with a high fever, which served as a proxy for “severe” presentation. There was no difference in revisit rates (amoxicillin [n = 2 of 39]) 5.1% versus amoxicillin-clavulanate [n = 15 of 211] 7.1%; P = 0.483) with respect to treatment in patients with high fever. Treatment with amoxicillin relative to amoxicillin-clavulanate was associated with fewer infectious complications (amoxicillin 0.0% vs amoxicillin-clavulanate 0.67%) (Table 2). Return visits and/or admissions for diarrhea and colitis more common (0.25% vs 0.46%; adjusted OR, 0.67; 95% CI, 0.53–0.86; P = 0.002) (Table 2). Return visits and/or admissions for diarrhea and colitis more common (0.25% vs 0.46%; adjusted OR, 0.67; 95% CI, 0.53–0.86; P = 0.002) (Table 2).

**TABLE 1** Baseline characteristics for patients diagnosed with acute bacterial sinusitis treated with amoxicillin-clavulanate or amoxicillin

| Demographicsa | Unmatched | Matched |  |
|---------------|-----------|---------|---|
|               | Amoxicillin (n = 18,576) | Amoxicillin-clavulanate (n = 71,051) | p<sup>b</sup> | Amoxicillin (n = 17,929) | Amoxicillin-clavulanate (n = 42,294) | p<sup>b</sup> |
| Male gender, No. (%) | 15,621 (84.1) | 59,983 (84.4) | 0.275 | 15,082 (84.1) | 35,749 (84.5) | 0.216 |
| Patient age, years [mean (SD)] | 55.6 (15.1) | 55.6 (14.4) | 0.916 | 55.6 (15.1) | 55.6 (14.5) | 0.864 |
| Healthcare practitioner type, No. (%) | | | | | | |
| Physician | 11,118 (59.9) | 44,877 (63.2) | <0.001 | 10,721 (59.8) | 26,611 (62.9) | <0.001 |
| Advanced practice practitioner (nurse practitioner, physician assistant) | 6,522 (35.1) | 22,621 (31.8) | <0.001 | 6,294 (35.1) | 13,562 (32.1) | <0.001 |
| Other | 936 (5.0) | 3,553 (5.0) | 0.835 | 914 (5.1) | 2121 (5.0) | 0.669 |
| Comorbidities<sup>c</sup>, No. (%) | | | | | | |
| No comorbidities | 11,350 (61.1) | 42,581 (59.9) | 0.004 | 10,940 (61.0) | 25,599 (60.5) | 0.262 |
| 1 comorbidity | 6,136 (33.0) | 24,568 (34.6) | <0.001 | 5,938 (33.1) | 14,287 (33.8) | 0.117 |
| ≥ 2 comorbidities | 1,090 (5.9) | 3,902 (5.5) | 0.048 | 1,051 (5.9) | 2,408 (5.7) | 0.421 |
| Temperature categories, No. (%)<sup>d</sup> | | | | | | |
| < 102° F | 18,135 (99.8) | 69,359 (99.7) | 0.041 | 17,896 (99.8) | 42,178 (99.7) | 0.051 |
| ≥102° F | 33 (0.2) | 188 (0.3) | | 33 (0.2) | 116 (0.3) | |

<sup>a</sup>Percentages rounded and may not reflect a total of 100%.

<sup>b</sup>Continuous variables are compared using a 2-sample t test; categorical variables, with a chi-square or Fisher’s exact test.

<sup>c</sup>Comorbidities evaluated include bone marrow transplant, chronic obstructive pulmonary disease, hemodialysis, immunosuppressed, neoplasms, and solid organ transplant.

<sup>d</sup>Data on temperature were missing for 2.1% of the amoxicillin-clavulanate patient-visits and 2.2% of the amoxicillin patient-visits.
2.4%; \( P < 0.005 \) and hospitalizations (amoxicillin 2.5% vs amoxicillin-clavulanate 7.1%; \( P = 0.036 \)).

AAO criteria were analyzed based on their predictive value for modeled clinical endpoints consistent with treatment failure due to resistant organisms. Patient visits were stratified by the presence of AAO criteria significantly associated with each endpoint, and ORs were calculated for amoxicillin relative to amoxicillin-clavulanate. The presence of comorbidity was the only subgroup analysis that proved to be a significant predictor of infectious complications with respect to treatment (amoxicillin vs. amoxicillin-clavulanate, OR, 0.63; 95% CI, 0.40–0.94; \( P = 0.022 \)); when *Clostridioides difficile* infections were removed from the composite infectious complications outcome, infectious complications were still different between amoxicillin versus amoxicillin-clavulanate (OR, 0.66; 95% CI, 0.43–1.00; \( P = 0.049 \)) (eTable S1).

Finally, comparison of efficacy outcomes between antibiotic therapy and no prescription of antibiotics were performed. After propensity matching, there were 14,070 and 18,521 acute sinusitis patient-visits in the amoxicillin versus no antibiotic groups, respectively; there were 21,981 and 20,904 acute sinusitis patient-visits in the matched amoxicillin-clavulanate versus no antibiotic groups, respectively. Comparison of amoxicillin and amoxicillin-clavulanate to no prescription of antibiotics for acute sinusitis revealed no difference in sinusitis-related revisits; however, there were differences in infectious complications and hospitalizations. Treatment with amoxicillin (0.3%) versus no antibiotics (0.7%) was associated with less infectious complications (adjusted OR, 0.51; 95% CI, 0.15–0.86; \( P < 0.005 \)) and fewer hospitalizations (amoxicillin 2.1%, no antibiotics 3.6%, adjusted OR, 0.54; 95% CI, 0.39–0.69; \( P < 0.005 \)). Treatment with amoxicillin-clavulanate (0.4%) versus no antibiotics (0.7%) was also associated with fewer infectious complications (adjusted OR, 0.62; 95% CI, 0.38–0.87; \( P < 0.005 \)) and fewer hospitalizations (amoxicillin-clavulanate 2.5%, no antibiotics 3.8%, adjusted OR, 0.65; 95% CI, 0.53–0.76; \( P < 0.005 \)).

### Limitations

Limitations include dependence upon diagnostic codes to identify acute sinusitis and select study endpoints as well as the retrospective design. Although professional guidelines recommend different diagnosis and treatment approaches for acute sinusitis and acute bacterial sinusitis, ICD-based coding does not differentiate between the 2 conditions. Thus, the cohort consistent of patients with both conditions. In a prior chart review of 715 cases of acute sinusitis identified using the same administrative codes, 79% of patient visits with a diagnostic code for acute sinusitis had at least 1 sinusitis symptom documented although only 38% had documentation of IDSA criteria for prescribing antibiotics. To account for clinicians preferentially treating select patients with amoxicillin-clavulanate and to increase causal inference of the retrospective design, we propensity-matched treatment groups. Guideline-suggested criterion for preferentially prescribing amoxicillin-clavulanate over amoxicillin (eg, temperature, frontal sinusitis, comorbidity, age) were used to estimate treatment effects; however, it is possible that unmeasured confounding impacted the results such as healthcare practitioner type—which despite propensity-matching, was independently associated with select outcomes. In addition, the ICD-based measurement of gastrointestinal-related adverse events had limited sensitivity and specificity to identify true antibiotic adverse events. Conservatively, application of the findings should be limited to episodes of uncomplicated acute sinusitis in primarily elderly adult males without recent antibiotic exposures.

### Discussion

In this large retrospective cohort study of adults with acute sinusitis, there were no differences in return visits or infectious complications...
between amoxicillin and amoxicillin-clavulanate treatment. However, Clostridiodes difficile and gastrointestinal adverse events were significantly higher in patients treated with amoxicillin-clavulanate as compared with amoxicillin. Further, we observed a reduction in infectious complications and hospitalizations in patients that received antibiotics compared with no antibiotics. Explanations for the lack of observed difference in treatment outcomes between amoxicillin and amoxicillin-clavulanate highlight the relatively low prevalence of infectious complications overall and the diminished importance of pathogens other than Streptococcus pneumoniae. As sinus aspiration for uncomplicated acute sinusitis is uncommon, we were not able to determine microbial etiology within the cohort. Although the diagnosis of gastrointestinal-related adverse antibiotic events was low, only conditions serious enough to warrant revisit or admission to the hospital were captured. Some clinical trials and postmarketing studies suggest that amoxicillin-clavulanate gastrointestinal toxicity incidence is twice that of amoxicillin (13% vs 7%). Clavulanate also appears to reduce beneficial microbiota relative to amoxicillin alone, which may contribute to the observed increase in Clostridiodes difficile infections.

This study was able to assess the AAO guideline-based risk factors for resistant organisms with respect to clinical outcomes of sinusitis-related return visits, infectious complications, and all-cause hospitalizations—endpoints that would be expected to be affected by insufficient microbial coverage. Although these factors may be predictive of antibiotic resistance in some studies and useful for identifying patients that may be at risk for worsening clinical outcomes in general, this study suggests they did not influence outcomes of empiric treatment for acute sinusitis between amoxicillin versus amoxicillin-clavulanate.

Plausible explanations for the finding that patients prescribed antibiotics had a lower infectious complication and hospitalization rate than those not prescribed antibiotics include poor selection of patients for withholding antibiotics or that antibiotics may prevent the development of acute bacterial sinusitis in a subset of patients with acute viral sinusitis. Multiple randomized-control trials have demonstrated a slight benefit of antibiotic treatment over placebo for acute sinusitis. Our retrospective cohort was substantially larger and had generally older male patients than prospective studies or meta-analyses, and the absolute difference in all-cause hospitalization was small. The observation in our study is consistent with the findings of the aforementioned VHA chart-level review of acute sinusitis. In that study patients with acute sinusitis who did not receive antibiotics were more likely to have a return encounter with the healthcare system; particularly for patients who met IDSA criteria for treatment that did not receive antibiotics. Upper respiratory tract viral infection is a well-established risk factor for pneumonia, which was the most common infectious complication observed in our study. Most studies investigating the role of antibiotic prophylaxis for upper respiratory tract infections are >50 years old, had small sample size, and were conducted in pediatric or young adult populations. Generally the studies did not demonstrate a reduction in complications. However, a large retrospective analysis of upper respiratory tract infections conducted in the United Kingdom found a similar risk of developing pneumonia within 30 days for patients not treated with antibiotics, which was accentuated in patients >65 years of age. The mean age in our cohort was older than the age of participants in clinical trials.

Placing the study findings into clinical context, for every 500 patients treated with amoxicillin instead of amoxicillin-clavulanate 1 ED visit for a gastrointestinal-related adverse event could be prevented without affecting efficacy outcomes. The number needed to treat to prevent 1 infectious complication with antibiotics was 250 for amoxicillin and 333 with amoxicillin-clavulanate relative to withholding antibiotics. However, it is important to recognize that the study included all patients with a diagnosis of acute sinusitis and was not designed to identify which patients are more likely to experience complications. Further, the study does not account for potential beneficial effects of reduced antibiotic use on antibiotic resistance. Study strengths include the large nationwide cohort of acute sinusitis patient visits and the integrated electronic health record, which allowed identification of outpatient acute sinusitis diagnosis and treatment as well as both outpatient and inpatient complications.

Most prospective comparative studies of specific antibiotics for acute sinusitis were conducted as regulatory studies with insufficient sample sizes to detect relatively uncommon endpoints. We are unaware of other acute sinusitis retrospective studies of similar size and scope as our study, and we believe it is unlikely that large prospective trials will be conducted.

In conclusion, in this large cohort, the potential clinical benefits of amoxicillin-clavulanate did not outweigh the increased risk of toxicity compared to amoxicillin for acute sinusitis treatment of adults in the emergency care setting. The observed increase in 30-day return visits and hospitalizations for patients not treated with antibiotics requires further study.

AUTHOR CONTRIBUTIONS

SAR formatted data from the cohort for analysis, created the univariate models, propensity-matched models, and multivariate logistic regression models. She was the lead author of the text. KMK created the manuscript concept and hypotheses. He was the primary editor and secondary author of the text. RER was the statistician who proposed the GLM and GEE modeling approach. SAR implemented the modeling approaches and interpreted the results. MN extracted the data for the initial cohort including the covariates and respective definitions for each patient-visit. BP helped to develop the adverse event coding schema and provided edits to the text. ALH and MS provided edits to the text with expert advice based on their clinical and research experience and work on numerous acute upper respiratory infection projects.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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