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# Antibiotic-associated diarrhoea in emergency department observation unit patients

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## SUMMARY

*Clostridium difficile* diarrhoea is an urgent threat to patients, but little is known about the role of antibiotic administration that starts in emergency department observation units (EDOUs). We studied risk factors for antibiotic-associated diarrhoea (AAD) and *C. difficile* infection (CDI) in EDOU patients. This prospective cohort study enrolled adult patients discharged after EDOU antibiotic treatment between January 2013 and 2014. We obtained medical histories, EDOU treatment and occurrence of AAD and CDI over 28 days after discharge. We enrolled and followed 275 patients treated with antibiotics in the EDOU. We found that 52 (18·6%) developed AAD and four (1·5%) had CDI. Patients treated with vancomycin [relative risk (RR) 0·52, 95% confidence interval (CI) 0·3–0·9] were less likely to develop AAD. History of developing diarrhoea with antibiotics (RR 3·11, 95% CI 1·92–5·03) and currently failing antibiotics (RR 1·90, 95% CI 1·14–3·16) were also predictors of AAD. Patients with CDI were likely to be treated with clindamycin. In conclusion, AAD occurred in almost 20% of EDOU patients with risk factors including a previous history of diarrhoea with antibiotics and prior antibiotic therapy, while the risk of AAD was lower in patients receiving treatment regimens utilizing intravenous vancomycin.

**Key words**: Antibiotics, *Clostridium difficile*, diarrhoea, gastrointestinal infections, infectious disease.

## INTRODUCTION

Antibiotic-associated diarrhoea (AAD) is a common complication of antibiotic administration. The frequency of AAD varies among antibacterial agents and is influenced by patient's age and medical comorbidities [1]. Non-white Hispanics have also been shown to have higher rates of AAD [2]. Most studies have evaluated risk factors for AAD in 10–20% of inpatients that develop the disease [3]. The only emergency department (ED)-based study found that 18% of ED patients developed AAD – 12·3% treated with oral antibiotics alone compared to 25·7% of patients treated with intravenous (IV) antibiotics [2]. Attention continues to focus on AAD being caused by the toxin producing bacteria *Clostridium difficile. C. difficile* infection (CDI) occurs in 10–20% of AAD cases [4] and, due to its recent marked increases in both prevalence and severity, has become the leading cause of gastroenterological hospitalizations and deaths accounting for over half a million infections and 29 000 deaths annually [5, 6]. Little is known about the role of antibiotics administered in the ED on the development of CDI.

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One-third of US hospitals use emergency department observation units (EDOUs) to treat >2·3 million patients presenting to the ED, with the number of patients treated increasing each year [7]. Most EDOUs use specific protocols to treat patients that are referred from the ED for a time period typically <24 h [8]. Protocol-driven EDOUs have provided favourable patient outcomes [9], which has allowed the number of disease conditions treated in EDOUs to steadily rise. Although EDOUs are routinely utilized for the treatment of bacterial infections such as skin and soft tissue infections (SSTIs), urinary tract infections, and respiratory tract infections, there is little information on patient outcomes [10, 11], particularly occurrence of AAD and CDI.

Over the past decade, failure to treat bacterial infections with outpatient antibiotics has increased by 12%, with more than one in ten first-line antibiotic monotherapies failing [12]. EDOUs are increasingly being used for primary treatment of bacterial infections and after outpatient treatment failure. Little is known about the consequences of the wide range of antibiotics used in EDOUs, particularly AAD and CDI [2]. The objectives of this study were to describe the prevalence of various antibiotics used in EDOUs and the occurrence of any diarrhoeal symptoms, AAD, and CDI over a 1-year period.

## METHODS

### Study design

The University of Massachusetts Medical Center is a 781-bed academic tertiary-care facility that sees >130 000 emergency visits/year and has a nine-bed 24-h EDOU. This is a prospective cohort of adult EDOU patients who were treated for an acute bacterial infection over a 12-month period from January 2013 to December 2013. The hospital's institutional review board (IRB) approved the study (IRB docket no. H00001871).

### Study setting and population

Patients were eligible for participation if they were discharged home after any duration of stay in the EDOU, and either received antibiotics in the EDOU or upon discharge. Potential subjects were identified using EDOU census logs at the end of each month, and contacted by telephone 28 days after their discharge date and asked if they were willing to participate in a telephone survey. This contact window was selected to span the time during when AAD and CDI symptoms typically occur after taking antibiotics, while trying to minimize recall bias [13]. Patients were eligible if they were English-speaking, aged $\geqslant$18 years, and had a working phone number. Patients were excluded upon initial phone screening if they had diarrhoea on ED presentation or within the preceding 4 weeks, were unable to cooperate with the questionnaire or recall events surrounding their care, or declined to be interviewed.

### Study protocol

After the patient agreed to participate, a standardized survey was administered by telephone and included questions pertaining to the patient's antibiotic compliance, occurrence of symptoms of AAD or CDI, subsequent healthcare visits/hospitalizations, and any other complication from initial EDOU treatment. Medical histories and allergies were obtained and confirmed through chart review. The Charlson comorbidity index (CCI) was calculated and used to rank patients' medical comorbidities [14, 15]. Information pertaining to initial ED presentation, EDOU hospital course, and antibiotic treatments used were obtained from the medical records. Symptoms of diarrhoea were self-reported and defined as any loose stools during the observation period. AAD was defined as $\geqslant$3 loose stools per day for $\geqslant$2 consecutive days [3, 16]. Mild diarrhoeal illness was defined as diarrhoeal symptoms not fulfilling the criteria for AAD. CDI was defined as AAD that led to a diagnosis of *C. difficile* infection and/or new treatment prescribed for CDI. *C. difficile* infection was confirmed if there was a report of a stool test positive for *C. difficile* toxins (two of the four CDI patients). Stool samples were tested for the presence and concentration of *C. difficile* toxin A using a 5D8-2C7 mAb pair-based ELISA assay. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Massachusetts Medical School [17].

### Measurements

The primary study outcomes were the development of any diarrhoeal symptoms, AAD and CDI. Failure of EDOU therapy was defined as incomplete resolution of infectious symptoms that resulted in an additional healthcare visit in which antibiotic therapy was altered either via hospitalization or ambulatory visit.

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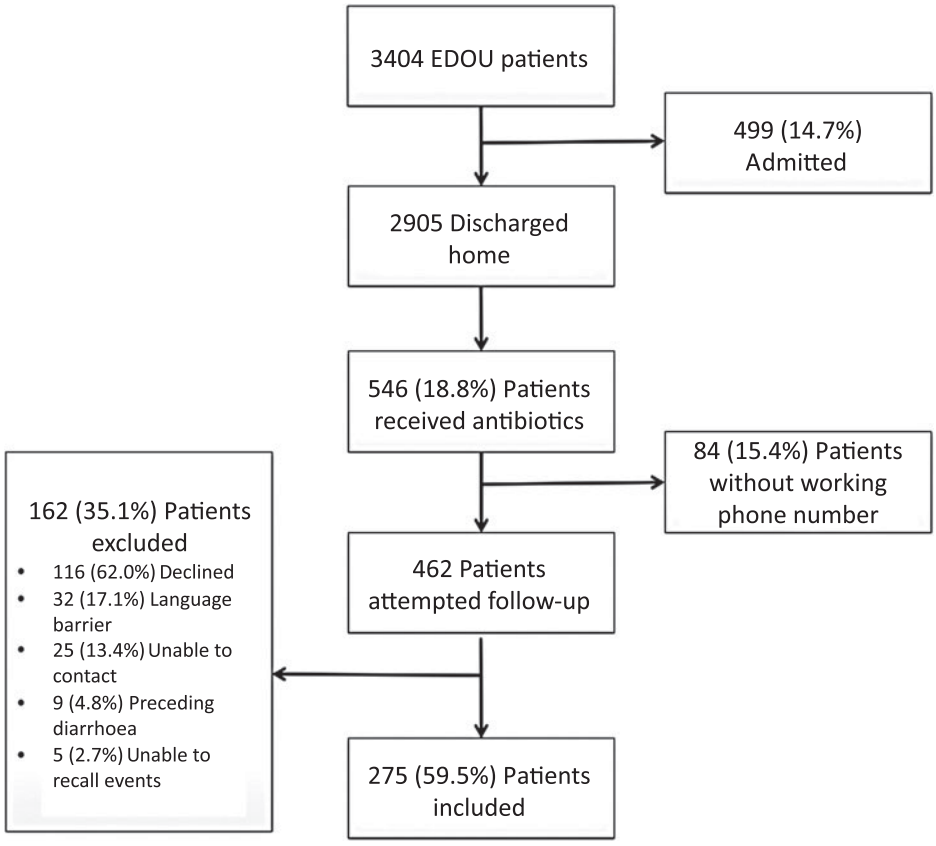


**Fig. 1.** Flow chart of the study. EDOU, Emergency department observation unit.

### Data analysis

We used $\chi^2$ tests to compare rates of AAD in categories of single variables and regression analysis to assess variables' effects, adjusted for the contributions of other variables. The software used for the analysis was Prism Release 6 (GraphPad Software Inc., USA). Regression was performed using the statistical software R (R Studio, USA). We built generalized linear models to perform Poisson regression with robust error variance estimation (PRwREV) for data with binary outcomes [18]. We preferred this approach as it enabled direct estimation of relative risk for a common outcome, in contrast to logistic regression [19]. Due to the large number of covariates, for computational feasibility we focused only on additive effects (i.e. we neglected higher-order interactions). Starting variables for multivariate model building were selected first from an *a-priori* hypothesis and then added to univariate data analysis. Automated model selection analysis was performed using the *glmulti* function from the R package [20]. The optimal model was the one with minimum Akaike's Information Criterion (AIC) [21]. We performed power analysis using simulations [22]. Given the predicted incidence rate of the major statistically significant covariates we generated 10 000 random sets of Poisson-distributed binary data. The power of the study to detect different multivariate predictors was determined by simulation, using 10 000 random sets of Poisson-distributed binary data. The incidence of AAD was assumed to be 23·5%. Based on a sample size of 251 there was 80% power to detect predictors with a relative risk of <0·61 or >1·39 and 90% power to detect relative risk of <0·53 or >1·47 (two-sided $\alpha$ 0·05). The study did not have sufficient power to reliably detect predictors with relative risks closer to 1 than those specified.

## RESULTS

### Characteristics of the study subjects

During the 1-year study period, there were 2905 patients treated in the EDOU and discharged home (Fig. 1). Of these, 18·8% were treated with antibiotics for an infection leaving 546 eligible patients. We were unable to contact 84 subjects due to a lack of contact information. Of the remaining 462 patients, 116

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Table 1. *Characteristics of study patients*

| | No symptoms | | Diarrhoea patients | | | |
|---|---|---|---|---|---|---|
| Demographics | *n* | (%) | *n* | (%) | RR | 95% CI |
| Age† | 46·7 | (17·5) | 46·1 | (16·9) | 1·00 | (0·99–1·01) |
| Female | 99 | (49·5) | 44 | (58·7) | 1·31 | (0·88–1·94) |
| White | 160 | (80·0) | 57 | (76·0) | 0·85 | (0·54–1·31) |
| Hispanic | 19 | (9·5) | 14 | (18·7) | 1·68* | (1·07–2·65) |
| African American | 10 | (5·0) | 1 | (1·3) | 0·32 | (0·05–2·12) |
| Asian | 3 | (1·5) | 1 | (1·3) | 0·82 | (0·17–5·06) |
| Medical history | | | | | | |
| CCI 0 | 125 | (62·5) | 49 | (65·3) | 1·09 | (0·73–1·64) |
| CCI 1 | 37 | (18·5) | 14 | (18·7) | 1·01 | (0·61–1·65) |
| CCI 2 | 25 | (12·5) | 7 | (9·3) | 0·73 | (0·39–1·56) |
| CCI $\geqslant 3$ | 13 | (6·5) | 5 | (6·7) | 1·02 | (0·47–2·21) |
| Hx. diarrhoea | 33 | (16·5) | 33 | (44·0) | 2·49* | (1·73–3·58) |
| Current Abx. | 30 | (15·0) | 22 | (29·3) | 1·78* | (1·20–2·64) |
| Condition treated | | | | | | |
| Cellulitis | 127 | (63·5) | 41 | (54·7) | 0·77 | (0·52–1·13) |
| Abscess | 19 | (9·5) | 10 | (13·3) | 1·31 | (0·76–2·25) |
| ENT | 20 | (10·0) | 9 | (12·0) | 1·16 | (0·65–2·07) |
| UTI | 13 | (6·5) | 6 | (8·0) | 1·17 | (0·59–2·34) |
| Pneumonia | 10 | (5·0) | 4 | (5·3) | 1·05 | (0·45–2·46) |
| Dental | 8 | (4·0) | 3 | (4·0) | 1·00 | (0·37–2·68) |
| Prophylaxis | 3 | (1·5) | 2 | (2·7) | 1·48 | (0·50–4·41) |
| Hours in ED† | 20·1 | (12·1) | 18·8 | (12·6) | 0·99 | (0·98–1·01) |
| Treatments | | | | | | |
| 1st-gen. cephalosporins | 73 | (36·5) | 73 | (37·3) | 1·03 | (0·69–1·53) |
| 3rd-gen. cephalosporins | 26 | (13·0) | 13 | (17·3) | 1·27 | (0·78–2·08) |
| Vancomycin | 66 | (33·0) | 13 | (17·3) | 0·52* | (0·30–0·89) |
| Clindamycin | 58 | (29·0) | 25 | (33·3) | 1·16 | (0·77–1·74) |
| Macrolide | 12 | (6·0) | 5 | (6·7) | 1·08 | (0·51–2·33) |
| Penicillin | 9 | (4·5) | 4 | (5·3) | 1·14 | (0·49–2·63) |
| Penicillin/I | 19 | (9·5) | 15 | (20·0) | 1·77* | (1·14–2·74) |
| Quinolone | 14 | (7·0) | 9 | (12·0) | 1·49 | (0·86–2·59) |
| Sulfonamide | 59 | (29·5) | 19 | (25·3) | 0·86 | (0·55–1·34) |
| Doxycycline | 21 | (10·5) | 3 | (4·0) | 0·44 | (0·15–1·28) |
| Nitrofuantoin | 0 | (0) | 2 | (2·7) | 3·74* | (3·07–4·55) |
| Metronidazole | 4 | (2·0) | 4 | (5·3) | 1·88 | (0·91–3·87) |
| Number of classes† | 1·8 | (0·9) | 1·9 | (0·9) | 1·06 | (0·82–1·36) |
| Abx given intravenously | 147 | (73·5) | 55 | (73·3) | 0·99 | (0·64–1·54) |
| Probiotic | 15 | (7·5) | 4 | (5·3) | 0·76 | (0·31–1·85) |

RR, Relative risk; CI, confidence interval; Hx, history; Abx, antibiotics; CCI, Charlson comorbidity index; ENT, ear, nose and throat infection; UTI, urinary tract infection; ED, emergency department; Penicillin/I, penicillin inhibitor combination.
† Data represented as means (standard deviation).
* $P < 0{\cdot}05$

declined to be part of the study, 32 could not communicate in English, 25 fell out of the 4-week window for contact, five were unable to recall events surrounding their EDOU stay and nine had diarrhoea within 4 weeks prior to their EDOU admission. The final study consisted of 275 patients. The study population was primarily white non-Hispanic with a mean age of 47 years and a similar distribution of men and women (Table 1). The majority of patients had no medical comorbidities (CCI = 0) with 24% having previously experienced diarrhoea on antibiotics and 18·9% of patients currently taking antibiotics prior to the ED visit (i.e. failing outpatient therapy). There were seven categories of infection type treated within the EDOU. The majority of patients were treated for SSTIs (combination of abscess and cellulitis) followed

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by ear, nose and throat infections, urinary tract infections, bacterial pneumonia, dental infections, and finally antibiotic therapy for prophylaxis. The most common antibiotics prescribed were first-generation cephalosporins followed by clindamycin, vancomycin and sulfonamides (i.e. trimethoprim/sulfamethoxazole). Patients on average were treated with more than one class of antibiotic and few patients (6·9%) were prescribed a probiotic as part of their care.

### Main results

Upon follow-up the majority of patients (89·5%) completed the full course of antibiotics prescribed to them. Other outcomes included a small percentage of subjects that either failed therapy and required hospitalization (6·5%) or had their antibiotics stopped by another provider due to a change in diagnosis of bacterial infection (5·1%). More than one in four (27·3%) patients experienced diarrhoea during the course of follow-up with 18·6% [95% confidence interval (CI) 13·2–23·2] of patients fulfilling the definition of AAD. Significant differences in patient demographics and treatment regimens were noted between patients that developed diarrhoea and those that did not (Table 1). Hispanics were 68% more likely to develop diarrhoea on antibiotics than the other racial groups studied [relative risk (RR) 1·68, 95% CI 1·07–2·65]. Additionally patients with a previous history of diarrhoea on antibiotics, and patients presenting to the ED failing antibiotic therapy were more likely to develop diarrhoea than respective comparison groups as a result of their EDOU treatment. Examination of the eight classes of antibiotics given in the EDOU and at discharge, showed that patients that received penicillin inhibitor (penicillin/I) combination antibiotics (i.e. ampicillin/sulbactam) were significantly more likely to develop diarrhoea while patients treated with vancomycin were 48% less likely to develop diarrhoea (RR 0·52, 95% CI 0·30–0·89).

### Effect of multiple antibiotics

After completion of therapy 44·4% of patients were treated with only one class of antibiotic, 34·5% received two classes and 21·1% received $\geqslant 3$ classes of antibiotics. We did not observe any differences in the rates of AAD depending on the number of classes used as a whole; however, among specific antibiotic classes there was a significant increase in the rate of AAD when used in combination therapy. Among patients treated with clindamycin, use of clindamycin alone was associated with a markedly reduced risk for developing AAD (14·6%) compared to patients in whom clindamycin was combined with another class of antibiotics (31·4%, $P = 0{\cdot}07$). Patients receiving clindamycin combination therapy had twice the risk of developing AAD compared to those treated with clindamycin alone (RR 2·16, 95% CI 0·93–5·00). A similar non-significant trend was seen in the penicillin/I combination antibiotic-treated patients (26·7% *vs.* 42·1%, $P = 0{\cdot}35$).

### Poisson regression model

To determine the set of covariates significantly affecting the risk of AAD (not any diarrhoea symptoms) we performed PRwREV for data with binary outcome. To determine the model (e.g. set of covariates) best explaining AAD outcome in this population we first built a generalized linear model were AAD was regressed against all the covariates simultaneously. We then used automated-model selection to determine the combination of demographics, medical history and treatment covariates that best fit the AAD profile. The optimal model is:

$$\begin{aligned}\text{AAD} \sim 1 &+ \text{Gender} + \text{Age} + \text{HxDiarrhoea} \\ &+ \text{CurrentAbx} + \text{Vancomycin} + \text{Clindamycin or} \\ &\text{Penicillin or third} - \text{generation Cephalosphorin.}\end{aligned}$$

Based on the results of this model (Table 2), patients with a history of diarrhoea from previous antibiotic use were three times more likely to develop AAD while patients failing antibiotic therapy (i.e. taking a previously prescribed antibiotic at the time of the ED visit) were 90% more likely to develop AAD after EDOU discharge. By contrasr, patients treated in the EDOU with vancomycin were 48% less likely to develop AAD. Patients treated with two of the following three antibiotics: clindamycin, penicillin/I and third-generation cephalosporins were 78% more likely to go on to develop AAD.

### *C. difficile* cases

In this study four patients went on to develop CDI (Table 3). These patients were young with no medical comorbidities except one subject with a CCI of 1. Three of the four patients had previously received clindamycin.

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Table 2. *Poisson regression model factors affecting the risk of antibiotic-associated diarrhoea*

| | Regression coefficient | | Relative risk | | |
|---|---|---|---|---|---|
| | Average | 95% CI | Average | 95% CI | *P* value |
| Hx. diarrhoea | 1·134 | (0·651 to 1·617) | 3·109 | (1·918 to 5·039) | $<1 \times 10^{-6}$ |
| Current Abx. | 0·641 | (0·132 to 1·150) | 1·898 | (1·141 to 3·157) | 0·0136 |
| Vancomycin | −0·661 | (−1·319 to –0·002) | 0·517 | (0·267 to 0·999) | 0·0495 |
| Clindamycin/penicillin/I/ 3rd-gen. cephalosporins* | 0·577 | (−0·090 to 1·244) | 1·781 | (0·914 to 3·471) | 0·0897 |

CI, Confidence interval; Hx, History; Abx, antibiotics; Penicillin/I, penicillin inhibitor combination.
* Treatment with any two of the above three antibiotics.

Table 3. *Characteristics of patients that developed Clostridium difficile infection*

| ID | Age | Sex | Race | Hx. diarrhoea | Current Abx. | CCI | Diagnosis | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| 1 | 31 | F | White | No | Yes | 0 | Abscess | 1st gen., clindamycin |
| 2 | 20 | F | Black | No | Yes | 0 | ENT | Clindamycin, macrolide |
| 3 | 54 | F | White | No | No | 0 | Cellulitis | Clindamycin |
| 4 | 41 | M | Hispanic | Yes | Yes | 1 | ENT | 3rd gen. cephalosporins, penicillin/I, macrolide |

Hx, History; Abx, antibiotics; CCI, Charlson comorbidity index; F, female; M, male; Penicillin/I, penicillin inhibitor combination; ENT, Ear, nose and throat infection.

## DISCUSSION

This is the first study to report AAD rates and risk factors for AAD in patients discharged home after a stay in an EDOU. A wide range of antibiotics were used in the EDOU and on discharge from the EDOU. One in four patients treated within the EDOU developed diarrhoea with the majority of these meeting the definition of AAD and 8% going on to develop CDI. Patients treated with regimens utilizing IV vancomycin were less likely to develop AAD, while patients who had a history of diarrhoea with antibiotics or who had failed outpatient antibiotic therapy were more likely to develop AAD. Combining the use of $\geqslant 2$ antibiotics within the group of antibiotic classes well known for causing AAD (clindamycin, penicillin/I or third-generation cephalosporins) [2] also led to a greatly increased risk of developing AAD.

AAD is a well-known complication of antibiotic therapy [23]. We found similar rates of AAD after a stay in the EDOU as we have previously reported from a multicentre ED cohort study comparing patients treated with IV, but not oral-alone antibiotic regimens [2]. The rate of AAD also falls within the range of other AAD studies involving ambulatory settings [24]. Furthermore, we observed similar antibiotic classes being most frequently associated with AAD, namely clindamycin, third-generation cephalosporins, and penicillin/I antibiotics. When patients received combinations of $\geqslant 2$ of these classes they were 78% more likely to develop AAD compared to all other treatment regimens after controlling for confounders. Clindamycin was associated with the majority of CDI cases. Interestingly, we found that patients receiving initial ED antibiotic therapy using IV vancomycin were 48% less likely to develop diarrhoea compared to patients who were not treated with vancomycin. Pharmacologically, this finding makes sense since intravenously delivered vancomycin has poor penetration through the intestinal wall [25]. Vancomycin may be a better first-line IV therapy especially for SSTIs if, through its use, patients have a reduced risk for AAD and CDI.

Other significant factors associated with the development of AAD were if the patient had a history of diarrhoea on antibiotics or if they presented to the ED currently taking antibiotics failing outpatient therapy. The effect of antibiotics on the gut microbiome are profound with a rapid loss of diversity that often does not return fully to its initial state [26]. A history of AAD

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may lead to an increased risk of further developing AAD and CDI due to persistent changes in the gut microbiome [27]. Additionally, if significant changes in the microbiome commence 24 h after initiating antibiotics [28], introducing an antibiotic change, especially into a broad spectrum antibiotic class, may be too much for the native gut flora to handle thus leading to AAD. The higher rate of AAD in Hispanic patients in this study confirms our previous finding reported from within the general ED population [2]. Further investigation into how the Hispanic gut flora responds to an antibiotic challenge may provide insight into this clinical observation.

A limitation of this study is that it reports data from a single site. This study is also limited in the number of patients enrolled and cases recorded. Following up this investigation with a multi-centre cohort study would strengthen the findings; however, we are reporting on similar trends already reported from our previous larger multi-centre ED investigation. Of the potential patient population we were only able to enrol 60% of patients approached which represents a potential source of bias; however, these enrolment success numbers are consistent with other observational studies.

In conclusion, based on our findings, we recommend that there is an urgent need to develop antibiotic guidelines to reduce the healthcare burden of AAD during and after admission to EDOUs and to consider adjuvant treatment, such as probiotics, for those at highest risk of developing AAD. Given that EDOUs treat >2·3 million patients annually in the United States alone [7], antibiotic guidelines and preventative treatments could affect 34 000 cases of CDI annually. Vancomycin as an initial antibiotic treatment may be considered when administering IV therapy for a SSTI where MRSA coverage is warranted; however, its relation to lower risks for AAD needs further study.

## DECLARATION OF INTEREST

None.

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