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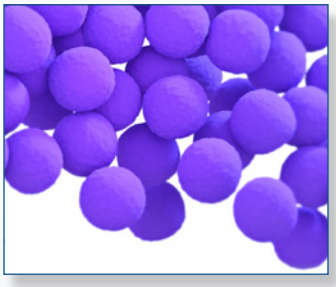
John R. Lonks, MD



Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

This and the cover image of *Clostridioides difficile* appear in the CDC's Antibiotic Resistance Threats in the United States 2019 Report, which includes the latest national death and infection estimates that underscore the continued threat of antibiotic resistance in the U.S.

According to the report, more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result. In addition, 223,900 cases of *Clostridioides difficile* occurred in 2017 and at least 12,800 people died.

The full report is available online at www.cdc.gov/DrugResistance/Biggest-Threats.html

[CDC IMAGES: ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2019. ATLANTA, GA: US DEPARTMENT OF HEALTH AND HUMAN SERVICES, CDC; 2019.]

Examining the Components of Effective Infection Control and Prevention

JOHN R. LONKS, MD
GUEST EDITOR

The depth and breadth of Infection Control includes many different microorganisms as well as sites of infection. The number one microorganism causing hospital infections is *Clostridioides difficile* (formerly *Clostridium difficile*).[1] *C. difficile* poses many challenges for its reduction both here in the United States and abroad.[2] In this issue, Steeves et al showed that it took multiple interventions to reduce the rate of hospital acquired *C. difficile*. Kelly et al performed a retrospective chart review of antibiotics received by patients with nosocomial *C. difficile* and showed that there was no overuse of high-risk antibiotics or unnecessary use of antibiotics. Lonks et al showed that at least 5.5% of hospitalized patients were colonized with *C. difficile*. These colonized patients if inappropriately tested for *C. difficile* would be misclassified as infected. Patients with unrecognized *C. difficile* colonization may act as a reservoir in the hospital. Additionally, one patient was misclassified as having nosocomial *C. difficile* since the stool specimen was sent to the clinical laboratory on hospital day 4; however, culture data showed that they were colonized at the time of admission.

The empiric choice of antibiotics for surgical prophylaxis is challenging. One strategy is to base antibiotic surgical prophylaxis on the hospital's antibiogram. Crawford et al compared the rate of methicillin resistance among *Staphylococcus aureus* isolated from nares cultures of patients undergoing elective lower extremity joint replacement to the hospital's antibiogram. The antibiogram markedly overestimated the proportion of *Staphylococcus aureus* that is methicillin resistant.

Urinary tract infections are common. Asymptomatic bacteriuria and colonization of urinary catheters lead to positive laboratory culture result. However, these conditions do not require treatment with antibiotics. Positive culture results may lead to a patient being falsely classified as having a catheter associated urinary tract infection. Moreover, unnecessary antibiotic therapy can lead to adverse side effects, drug-drug interactions, *C. difficile* infection and antibiotic resistance. Macias-Gil et al provide a clinically oriented, in-depth review of this topic.

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Author

John R. Lonks, MD, Associate Professor of Medicine and Associate Professor of Medical Science, The Warren Alpert Medical School of Brown University, Providence, Rhode Island; Director, Inpatient Infectious Diseases Consult Service Hospital Epidemiologist/Infection Control, The Miriam Hospital, 164 Summit Avenue, Providence, Rhode Island.

MRSA Prevalence in Preoperative *S. aureus* Nasal Culture Isolates is Significantly Different From a Traditional Hospital-wide Antibiogram

ANDREW R. CRAWFORD, MD; NANCY VALLANDE, MS; JOHN R. LONKS, MD

ABSTRACT

Hospital antibiograms, because they are typically derived from samples obtained from hospitalized patients, may overestimate the prevalence of methicillin resistance in *S. aureus* in individuals presenting to the hospital for surgery. Because hospital antibiograms are commonly used to justify empiric perioperative prophylactic antibiotic selection prior to surgery, this may lead to unnecessary treatment with broad-spectrum antibiotics such as vancomycin. In a single-institution study, we observed that in our hospital antibiogram the proportion of *S. aureus* that are methicillin-resistant (MRSA) was significantly higher (45%) than isolates in preoperative nasal cultures obtained at the same hospital in outpatients prior to their lower extremity joint replacement surgery (13%): mean difference 0.32, [95% CI 0.25, 0.39], p <0.0001. These data suggest that hospital antibiograms may overstate the true prevalence of MRSA in those at risk for MRSA surgical site infections who present from the outpatient setting.

KEYWORDS: antibiogram, antibiotic prophylaxis, arthroplasty, surgery, microbial colonization

INTRODUCTION

Surgical site infections (SSI) are potentially catastrophic complications of lower extremity joint replacements. They contribute to increased postoperative morbidity and mortality, and produce a substantial financial burden on the healthcare system. According to National Healthcare Safety Network data, *Staphylococcus aureus* (*S. aureus)* was responsible for 30% of SSIs, and 47% of SSIs following orthopedic procedures. Methicillin-resistant *S. aureus* (MRSA) were found in 44% of SSIs in which *S. aureus* was the causative bacteria.[1]

Providers select an agent active against *S. aureus* when prescribing an antibiotic perioperatively and must strongly consider the risk of MRSA SSI. To assist with this decision, they often rely on institution-specific data regarding the incidence of SSI involving methicillin-resistant gram-positive bacteria. Alternatively, they may rely on a hospital-wide antibiogram, which provides data on institution-specific bacterial resistance patterns. Antibiograms include the antibiotic susceptibilities of bacteria cultured from samples collected by that institution's laboratories each year.[2] Samples which make up these antibiograms are often collected primarily from inpatients, which could over-represent the prevalence of local antibacterial resistance. We hypothesized that the hospital-wide antibiogram at The Miriam Hospital, a 247-bed teaching hospital, may overstate the true proportion of *S. aureus* which is methicillin-resistant in a population at risk for MRSA SSI. We propose that an antibiogram composed specifically from *S. aureus* nasal cultures from patients undergoing lower extremity joint replacement would more accurately reflect the prevalence of the burden of colonization with methicillin-resistant *S. aureus* in this population.

METHODS

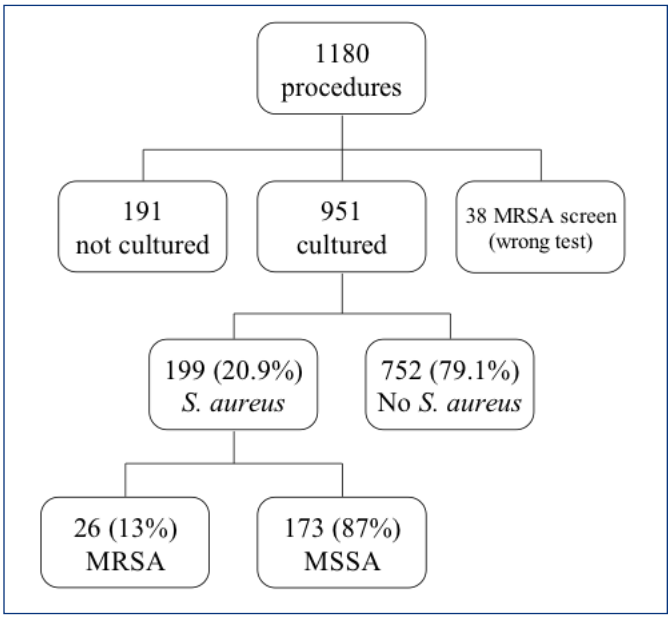
All hip or knee replacements at The Miriam Hospital in 2012 were identified using the TheraDoc™ clinical surveillance software. The following demographic data was then obtained from the hospital EMR for each corresponding patient: age, gender. Preoperative *S. aureus* testing date was collecting along with testing method and result. Only results from culture-based nasal *S. aureus* (methicillin-susceptible and methicillin-resistant) testing were included in the study. Some patients underwent more than one joint replacement during the year. For these patients, intervals between subsequent surgeries were considered re-colonization opportunities. The hospital-wide antibiogram, accessed from the Microbiology Laboratory, was developed using a patient-based algorithm; it includes the first isolate per patient during 2012. The hospital-wide antibiogram does not include results from MRSA screening. Stata/SE™ version 12 software was used for statistical analysis.

This study was part of a quality improvement project and did not meet the definition of research. Hence, it was exempt from the need of approval of an institutional review board.

RESULTS

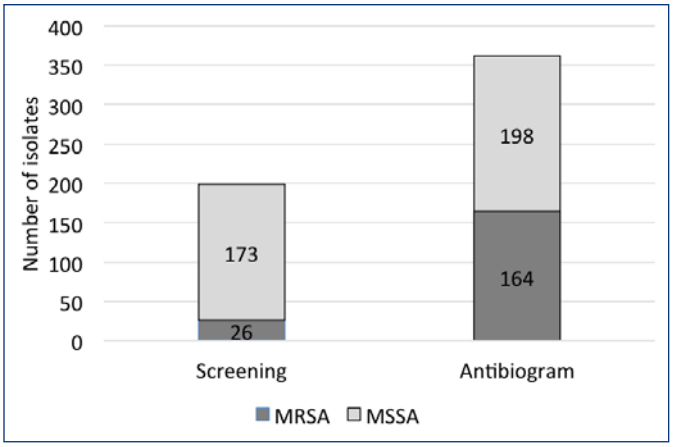
There were 1180 procedures among 1129 patients: 749 knee replacements and 431 hip replacements. 64% of patients in these procedures were women, 36% men. Mean and median ages were 67 and 66, respectively. For 81% (951) of these procedures, patients underwent nasal *S. aureus* culturing

Figure 1. Preoperative *S. aureus* nasal culture results among 1180 total joint replacement surgeries during 2012.



prior to surgery. Results from 38 tests using MRSA screens (of which 2 were positive), which did not detect MSSA, were not included in the data analysis. For 191 procedures, there was no preoperative *S. aureus* testing performed. The mean interval between culturing and surgery was 24.7 days, with a median of 26 days. 199 (21%) of nasal cultures were positive for *S. aureus*. Of those, 26 (13%) were MRSA, the remainder being MSSA. The results of the cultures are summarized in **Figure 1**. The hospital-wide antibiogram contained 362 *S. aureus* isolates; 164 (45%) of these were MRSA, the remainder being MSSA. The proportion of *S. aureus* isolates

Figure 2: Proportion of methicillin-resistance in *S. aureus* isolated in lower extremity joint replacement preoperative screening nasal culture (n=199), compared to isolates in hospital-wide antibiogram (n=362).



MSSA = methicillin-sensitive *S. aureus*. MRSA = Methicillin-resistant *S. aureus*. Proportions were compared using two-sample test of proportions, difference was 0.32, [95% CI 0.25, 0.39], p <0.0001.

that were found to be MRSA during preoperative culturing was compared to the same proportion in the 2012 Miriam Hospital antibiogram using the two-sample test of proportions (**Figure 2**). The difference was 0.32, [95% CI 0.25, 0.39], p <0.0001.

DISCUSSION

Several different organizations recommend a first-generation cephalosporin such as cefazolin or vancomycin as first-line for perioperative prophylaxis during orthopedic surgery.[3] In these guidelines, vancomycin is not recommended for routine use, but rather for individuals with beta-lactam allergies or risk factors for MRSA. Vancomycin use is also justified in instances of high institutional prevalence of colonization or infection with methicillin-resistant gram-positive bacteria, although no threshold for this has been defined.

Antibiograms are important tools for the empiric treatment of suspected bacterial infections in the hospital setting before specific culture and sensitivity results are available, and for prophylaxis perioperatively to reduce the risk of postoperative SSI. However, these are typically composed of samples isolated mainly from inpatients. The hospital provides a niche for bacteria to become exposed to multiple antibiotics as they travel between patients and the hospital environment; this selective pressure drives resistance. Thus, samples from the inpatient population are not an accurate representation of the bacterial skin flora that put patients at risk of SSIs when they present for surgery from the community. Furthermore, it is more common for bacteria colonies from the patient's own skin, rather than exogenous spread from the hospital environment or providers, to be the inciting organisms for a SSI.[4] Hospital-wide antibiograms may therefore lead to the overuse or misuse of perioperative antibiotics.

Several novel approaches have been proposed to enhance the utility of hospital-wide antibiograms. These include a "weighted-incidence" antibiogram, which integrates the relative frequency of organisms causing a particular infection with their resistance patterns.[5] Studies creating hospital unit-specific antibiograms have demonstrated that the percentage of *S. aureus* isolates susceptible to methicillin may be significantly higher in the medical ICU when compared to a hospital-wide antibiogram.[6,7] One study demonstrated that antibiotic sensitivities can differ significantly when comparing antibiograms developed from bacteria isolated >48 hours after admission (hospital-acquired) and those isolated <48 hours before admission (community acquired).[8]

Our study demonstrates that using susceptibility results of preoperative nasal cultures for *S. aureus* will allow for the more rational selection of empiric antibiotic prophylaxis during lower extremity joint replacement, as compared to using a hospital-wide antibiogram which displays a significantly higher proportion of *S. aureus* which are resistant

to methicillin. Among the 951 patients who underwent nasal culturing for *S. aureus*, only 2.7% had MRSA. This strongly suggests that reliance on a hospital-wide antibiogram, which typically display a significantly higher prevalence of methicillin-resistance in *S. aureus* isolates, will lead to unnecessary use of vancomycin.

Our study has limitations. Our data was obtained from preoperative cultures at one institution, so these may not be generalizable to other institutions or to populations with greater risk factors for MRSA colonization. Swabbing in other locations known to contain *S. aureus* such as the perineum or axillae could potentially improve the sensitivity of the preoperative culturing and provide a larger sample of *S. aureus* isolates, although it is unlikely that this would affect the comparison. Further work to obtain preoperative nasal culturing for *S. aureus* from patients preparing for a wider variety of surgeries would give us a more robust sample size and more demographically diverse patient makeup, thus increasing the utility of our preoperative nasal culture antibiogram. Future studies could also be employed to determine the clinical effectiveness of a preoperative culture antibiogram in preventing *S. aureus* SSI as compared to the traditional hospital-wide antibiogram.

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Authors

Andrew R. Crawford, MD; Department of Health Services, Policy and Practices, Brown University, Providence, RI; Dartmouth-Hitchcock Medical Center, Department of Medicine, Endocrinology Section, Lebanon, NH.

Nancy Vallande, MS; Department of Infection Control, The Miriam Hospital, Providence, RI.

John R. Lonks, MD; Department of Infection Control, The Miriam Hospital; Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

Correspondence

John R. Lonks, MD
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906
401-793-4620
Fax 401-793-4534.
JLonks@lifespan.org

Safety and Nosocomial *Clostridioides difficile* Infections

SUSAN STEEVES, MSN, RN; NANCY VALLANDE, MS; JOHN R. LONKS, MD

ABSTRACT

The rate of nosocomial *C. difficile* in the state of Rhode Island is among the highest in the country. Multiple factors impact the occurrence of nosocomial *C. difficile*. Improvement in a single factor may not lead to a decrease in the rate. We report the results of a multidisciplinary team that implemented multiple interventions, which led to a 42% reduction of nosocomial *C. difficile* at The Miriam Hospital.

KEYWORDS: *Clostridioides difficile*, multidisciplinary, safety, nosocomial

INTRODUCTION

*Clostridioides (*formerly *Clostridium) difficile* is the most common organism causing nosocomial infections.[1] In the United States, *C. difficile* is estimated to cause about 450,000 infections and approximately 29,000 deaths.[2] Previous studies have demonstrated that up to 15% of adults are colonized with toxigenic *C. difficile,* and almost 50% of elderly adults in long-term care facilities or nursing homes may be colonized with the bacteria .[3,4] Infections due to *C. difficile* can cause devastating complications such as acute renal failure, colectomy and death as well as leading to increased length of stay, excess morbidity and rising healthcare costs. The rate of nosocomial *C. difficile* in Rhode Island (RI) is among the highest in the country. In the period April 1, 2018 to March 31, 2019, Rhode Island ranked 49 out of 50.[5]

BACKGROUND

The Miriam Hospital is a 247-bed teaching hospital in Providence, RI. Despite reduction efforts during 2014–2015, the rate of nosocomial *C. difficile* remained above the national benchmark. During the second quarter of 2016, a multidisciplinary team was created that included Infection Control, Housekeeping, Nursing, Administration, Quality, Safety and Patient Care Equipment staff. Implementation of the recommendations of this group, based on literature review of best practices started during the third quarter of 2016. Consensus best practices include antimicrobial stewardship, surveillance, case isolation, use of personal protective equipment, effective cleaning within the hospital environment, and education.[2,6] The team took a multi-pronged approach to implementing in-hospital interventions.

METHODS/INTERVENTIONS

Ordering (correct ordering)

Appropriate and inappropriate stool testing was addressed. Education was provided to nurses and providers to send only loose stool specimens for *C. difficile* testing. An electronic order panel was created for ordering *C. difficile* testing and consisted of two questions, 1) has the patient had 3 or more loose stools (appropriate testing) within 24 hours and 2) has the patient had recent laxative use (inappropriate testing). It was discovered upon review of documentation in the electronic medical record that not all stools were recorded. Nurses documented whether a patient had a bowel movement, but nursing assistants did not. The electronic medical record was modified so that nursing assistants could document frequency and consistency of bowel movements. As part of the *C. difficile* electronic order panel, the number of bowel movements was displayed to the provider as an aid for appropriate testing. Hence, inappropriate testing could occur if a stool was collected from a patient who was given a laxative, developed loose stools and was colonized with *C. difficile* thus producing a false positive lab result.

Initiation of precautions

In order to initiate early precautions and reduce inappropriate testing, nurses were educated and feedback provided on a nurse driven protocol so that a stool for *C. difficile* could be obtained by a nurse and sent to the lab, provided the patients had 3 or more loose bowel movements in 24 hours and had not recently received a laxative. This would lead to earlier detection of *C. difficile* infection. Patients were placed on contact precautions while the *C. difficile* test was pending, leading to a potential reduction in transmission prior to a lab test to confirm the diagnosis.

Duration of contact precautions

Patients with *C. difficile* infection are maintained on Contact Precautions for the duration of their hospitalization. If the diarrhea resolves, the patient's room and the equipment in the room can still be contaminated with *C. difficile*.

Because the spores can persist in the environment for extended periods – months or years on inanimate surfaces – patients are not taken off contact precautions.[7]

Hand hygiene and Personal Protective Equipment (PPE)

Transmission via healthcare workers can be decreased using personal protective equipment (PPE), e.g. gowns and gloves, when taking care of patients who have *C. difficile* infection. Therefore, poor compliance with using gowns and gloves is one latent factor in the development of nosocomial *C. difficile*. Despite compliance, during the process of removing gowns and gloves, there may be inadvertent contamination of a healthcare worker's hands or clothing. All nurses received competency training on hand hygiene and use of PPE during 2017. The training included hands-on demonstration of competency.

Environment (room)

Reducing environmental contamination includes cleaning of patients' rooms daily and upon discharge from the hospital. Patient rooms should be thoroughly cleaned prior to receiving the next patient. Optimum cleaning of the room includes sufficient dedicated time, equipment and appropriate cleaning agents. Environmental cleaning practices including the use of cleaning agents (hydrogen peroxide and sodium troclosene) and disposable mop heads and cloths were implemented. A stainless-steel cleaning cart was purchased to hold the cleaning agents and supplies used for rooms that housed patients with *C. difficile* and other micro-organisms that required special cleaning. Discharge cleaning was performed with two housekeeping staff. Ultraviolet light surface decontamination has been successfully used in infection control and was used in rooms after a patient is discharged and the room cleaned.[8] As part of the *C. difficile* improvement process, the use of ultraviolet light surface decontamination was prioritized to those rooms that had housed a patient with *C. difficile*.

Environment (equipment)

C. difficile can contaminate shared equipment that is used in patients' rooms. Thorough cleaning of the equipment is needed to prevent transmission to other patients. Patient-care equipment was cleaned with bleach wipes after each use.

Cleaning: "Scrub Club"

Contaminated equipment and surfaces are potential environmental reservoirs. When a patient with nosocomial *C. difficile* was identified on a ward, high touch areas in all patient rooms, nurse's station and shared equipment that was on the ward was cleaned with a bleach-based product. The cleaning program was named "Scrub Club," (comprehensive cleaning using a sporicidal agent). Departments involved in "Scrub Club" included Housekeeping, Nursing and Patient Care Equipment staff. The purpose was to enhance cleaning on the ward in case there was inadvertent environmental contamination.

Bedpans and commode liners/blood pressure cuffs

Bedpans and commodes, particularly those used by patients with diarrhea, can lead to splashing and contamination of the environment. Bedpan/commode liners were purchased, and their use was encouraged for all patients with loose stools. These liners absorbed the liquid to eliminate splashing. Additionally, disposable blood pressure cuffs were purchased and used in all in-patient rooms, replacing the need to clean the blood pressure cuff when a patient was discharged.

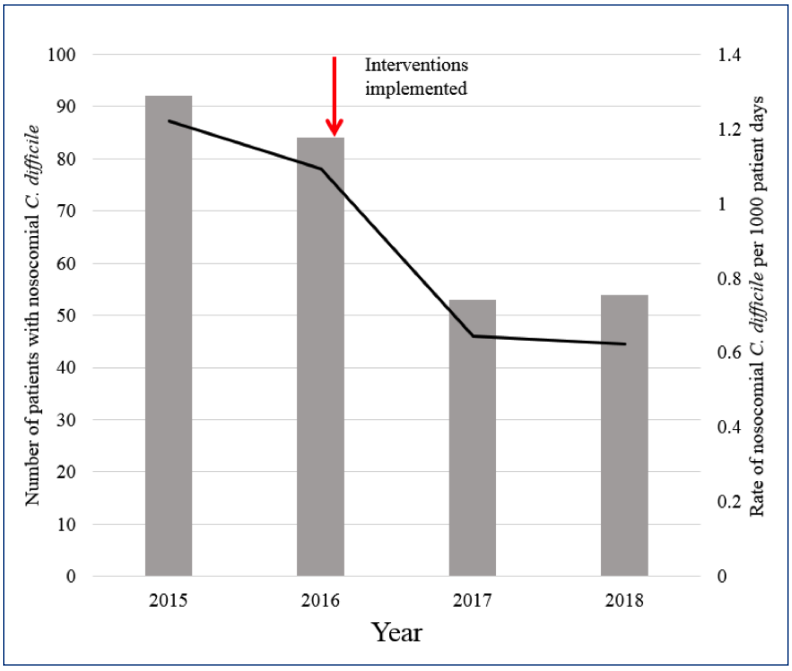
Antibiotics

Another factor associated with *C. difficile* infection is exposure to antibiotics. Unnecessary exposure to antibiotics could be decreased or eliminated to decrease the rate of *C. difficile* infections. During 2014 a formal Antimicrobial Stewardship program was started; its activities and interventions increased over time.

RESULTS

The number of patients with nosocomial *C. difficile* decreased from 92 in 2015 to 84 in 2016 to 53 in 2017 and 54 in 2018. There was a 42% reduction in the number of cases when comparing 2017 to 2015. (**Figure 1**)

Figure 1. Number of patients with nosocomial *C. difficile* and rate of nosocomial *C. difficile* per 1,000 patient days by year.



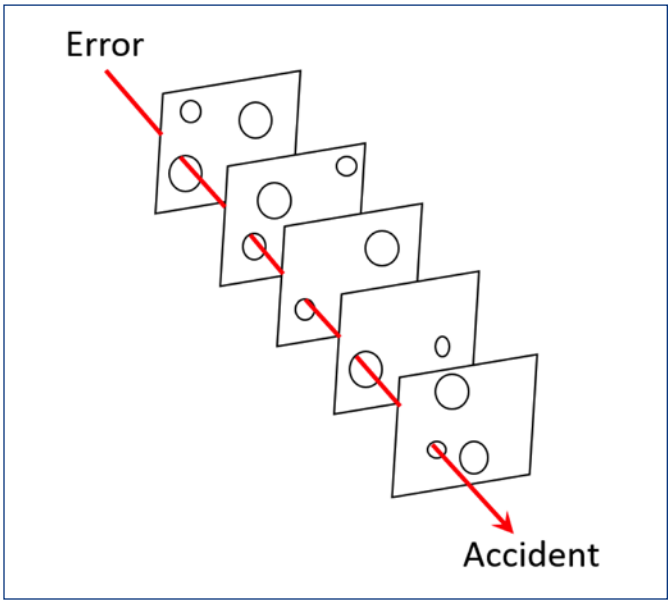
DISCUSSION

Transmission of *C. difficile* may occur in a healthcare setting when the organism is transferred from patient-to-patient via the hands of healthcare workers or from a contaminated environment. The development of nosocomial *C. difficile* in various patient populations on different wards throughout the hospital was not necessarily due to an individual safety error, but suggested potential systemic, hospital-wide deficiencies in infection control. Previous efforts to eliminate specific sources of infection were unsuccessful in reducing nosocomial *C. difficile* infections. Instead, a collaborative, interdisciplinary approach involving multiple intervention points and several departments resulted in a reduction in nosocomial *C. difficile* infections.

There may have been unrecognized improvements in other processes due to the Hawthorne effect. Other unmeasured processes may have also contributed to the reduction such as increased thoroughness of cleaning by Housekeeping.

Cases of nosocomial *C. difficile* can be explained by the Swiss cheese model of accident causation (**Figure 2**).[9] For an accident to take place, alignment of the holes in the Swiss cheese must occur such that an error will flow through all the holes emerging from the other end producing an accident. This model shows the defenses as pieces of Swiss cheese which have holes or flaws (latent defects) in them. Some examples of latent factors include equipment design, equipment choice, equipment maintenance, procedures, policies, training, communication, resources, staffing, workload, physical environment, noise, interruptions, roles, responsibilities and supervision. In order to reduce *C. difficile* on the wards, some of these factors were addressed. Appropriate testing, early identification of infected patients, initiation of contact precautions, bleach cleaning of patient rooms, shared equipment and the nursing ward, use of bedpan liners, as well as other improved compliance may have protected against the development of nosocomial *C. difficile*. The numerous interventions involving multiple hospital departments resulted in the reduction in the rate of nosocomial *C. difficile*. The goal will be to not only sustain these improvements but to further reduce the rate of nosocomial *C. difficile*.

Figure 2. The Swiss cheese model of accident causation illustrates that there are many layers between an error and an accident. Holes, in each slice, represent flaws (latent failures) that if aligned can allow the accident to occur.



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Authors

Susan Steeves, MSN, RN; Infection Control and Epidemiology, The Miriam Hospital, Providence, RI.

Nancy Vallande, MS; Infection Control and Epidemiology, The Miriam Hospital, Providence, RI.

John R. Lonks, MD; Infection Control and Epidemiology, Division of Infectious Diseases, The Miriam Hospital; The Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

John R. Lonks, MD
The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906
401-793-4620, Fax 401-793-4534
jlonks@lifespan.org

Antibiotics and Nosocomial *Clostridioides difficile*, a Retrospective Chart Review

KELLY A. SKRABLE, MD, MPH; JOHN R. LONKS, MD

ABSTRACT

C. difficile is a complication of antibiotic therapy. Certain antibiotics are associated with a higher rate of developing *C. difficile*. The charts of 54 patients with nosocomial *C. difficile* were reviewed and very few had received a high-risk antibiotic. Seven (13%) of 54 patients had not received any antibiotics in the hospital prior to the positive stool test for *C. difficile*. Moreover, 6 of the 7 had no documentation of receiving an antibiotic in the 56 days prior to admission suggesting that they might be colonized with *C. difficile*.

KEYWORDS: *Clostridioides difficile*, antibiotics, healthcare-associated infections

INTRODUCTION

Clostridioides difficile (formerly Clostridium difficile) infection is a rare, but potentially devasting, complication of antibiotic therapy. Since about one-half of all hospitalized patients receive an antibiotic, a rare complication can affect many patients.[1] In 2017 there were 223,900 people hospitalized with *C. difficile* in the United States with 12,800 deaths.[2]

Certain antibiotics such as clindamycin and cefotaxime, a third-generation cephalosporin, are associated with a higher risk of developing *C. difficile* infection.[3] Doxycycline, penicillin, macrolides, trimethoprim/sulfamethoxazole and cefazolin, a first-generation cephalosporin, are low-risk antibiotics. Ciprofloxacin, levofloxacin, meropenem (a carbapenem) and certain cephalosporins are medium risk. In addition to antibiotics, proton pump inhibitors may increase the risk of developing *C. difficile* infection.

The rate of nosocomial *C. difficile* in the state of Rhode Island is among the highest in the country. At The Miriam Hospital, a 247-bed teaching hospital in Providence, RI, numerous interventions were used to decrease the rate of nosocomial *C. difficile* (See accompanying article, "Safety and Nosocomial *Clostridioides difficile* Infections", Steeves S, et al). As part of a quality improvement project to further reduce the rate of nosocomial *C. difficile*, a retrospective chart review was performed to determine which antibiotics were received by patients with nosocomial *C. difficile*. This data may help to determine if antibiotic use could be optimized to reduce the rate of nosocomial *C. difficile* infection.

METHODS

This descriptive study includes data from persons admitted to The Miriam Hospital (TMH) in Providence, RI who developed hospital onset *C. difficile* infection using National Healthcare Safety Network (NHSN) Laboratory-identified data from January 1, 2018 through December 31, 2018. Electronic medical records were reviewed. This study was a retrospective chart review conducted for internal quality improvement at TMH and thus was exempted from needing Institutional Review Board approval.

Case Definition

A case of hospital onset *C. difficile* was defined as per the NHSN criteria of a positive laboratory diagnostic test >3 days after admission. The date of admission to an inpatient unit was coded as hospital day 1. The Microbiology laboratory uses a PCR-based diagnostic test. As per NHSN, an incident case was defined as a patient without symptom onset or a positive laboratory test in the previous eight weeks (56 days). A recurrent case was defined as a patient with a positive *C. difficile* test within the previous 56 days. Patients diagnosed with a second hospital-onset *C. difficile* infection >56 days after their first infection during the period of study were counted as separate incident cases.

Variables of Interest

Patient data were de-identified and patients were assigned a code for analysis. All data were extracted from patients' electronic medical record unless otherwise noted. Age was recorded in years as the age of the patient at the time of *C. difficile* diagnosis. Sex was defined as male or female per patient chart. The admission date was defined as the admission date of the hospitalization to an inpatient unit during which the patient was diagnosed with *C. difficile*. The location from which the patient was admitted was defined as the location in which the patient had spent the previous 24 hours and was coded as home, nursing home or transfer from another hospital. Home included any private residence. Nursing home included patients who were admitted from rehabilitation facilities and skilled nursing facilities. Patient charts were also reviewed to identify if patients had undergone a surgical procedure or been hospitalized during the eight weeks prior to the index admission. Hospitalization was defined as an overnight admission of a minimum of

one day; emergency department visits that did not result in admission were excluded. Surgical procedures were defined as invasive surgical procedures done in the operating room and excluded procedures such as bedside central line/PICC line placement, suturing of wounds, etc. Hospitalizations and surgical procedures that were performed outside of The Miriam Hospital but documented in patients' electronic medical record were included.

Previous antibiotic use was defined as any antibiotic for which the patient was prescribed at least one dose in the previous 56 days. Antimicrobial agents during hospitalization were defined as any antibiotic of which patient received at least one dose prior to the patient's *C. difficile* diagnosis during the hospitalization of interest. Number of days received was defined as the number of days patient received each antibiotic prior to diagnosis with *C. difficile*. The day the *C. difficile* specimen was collected was not counted as a "day received" for antimicrobial agents. One dose of antibiotic was counted as one day independent if patient received the full therapeutic amount of antibiotic for that day.

Proton pump inhibitor (PPI) use was coded as "yes" if patients had one or greater doses of PPI documented in the chart at any time in the six months prior to *C. difficile* infection. Site of infection was defined as the documented infection site for which antimicrobials were prescribed. The culture site was the site from which positive cultures were obtained. Negative cultures were not recorded. Culture organism was the organism(s) that grew from the positive culture sites; some sites grew more than one organism and all organisms were recorded. Sepsis was defined as "yes" when patients had a diagnosis of sepsis recorded during the hospitalization in which they were diagnosed with *C. difficile*. Other positive tests were defined as other positive microbial tests, including, MRSA/VRE screen positive patients and positive respiratory pathogen panels.

Data Quality

Charts were reviewed in a standardized manner and data were extracted from the same location in the chart when possible. In addition, outpatient records were reviewed for all patients with such data included in their electronic medical record to ensure that all possible information on prior hospitalizations, surgical procedures, antibiotic and PPI use, etc. was recorded. A list of operational definitions for each variable was created to ensure standardization in the interpretation and documentation of all variables. Any discrepancies or ambiguities were reviewed with the senior author, who made a final decision.

Data Analysis

Data were entered into a spreadsheet and descriptive statistics were run. The mean, minimum and maximum values were calculated for patient age and days between admission and *C. difficile* diagnosis. Percent distributions were calculated for all other variables.

RESULTS

Demographics

There were a total of 54 hospitalizations with hospital onset incident *C. difficile* cases from January 1, 2018–December 31, 2018 representing 52 unduplicated patients. Two patients were diagnosed with *C. difficile* twice in separate hospitalizations >56 days apart during the study period. Thus, each *C. difficile* diagnosis was counted as a separate incident case for the purposes of this analysis. Of the 54 incident cases, 26 (48%) were male and 28 (52%) were female. The average age of patients was 72.6 years (range 42 – 94 years) at the time of *C. difficile* diagnosis. The majority (n=43; 80%) of patients were admitted from home with ten (19%) admitted from a nursing home and one patient (2%) transferred from another hospital.

Forty-three percent (n=23) of patients were neither hospitalized nor had a surgical procedure in the eight weeks prior to their *C. difficile* diagnosis. A total of 41 percent were hospitalized and almost a quarter (n=12; 22%) had a surgical procedure in the previous eight weeks. Eight patients (15%) had a previous *C. difficile* infection >56 days prior to the incident case; the remaining 46 (85%) had no previous *C. difficile* infection documented in their electronic medical records. One half (n=27) had taken a proton pump inhibitor in the six months prior to diagnosis.

Almost sixty percent (n=33; 61%) of patients did not have documented antibiotic use in the eight weeks (56 days) prior to admission. Of those who did receive antibiotics, the most commonly used were intravenous vancomycin (15%), followed by ceftriaxone (13%) and piperacillin/tazobactam (11%). The remaining antibiotics used were taken by less than ten percent of patients (**Table 1**).

Admission Clinical Data

The average number of days between admission and *C. difficile* diagnosis was seven (range 3 – 25; median 5 days). The vast majority (n=47; 87%) of patients took at least one antibiotic during admission prior to being diagnosed with *C. difficile*. Of those who used antibiotics, the most common site of infection for which the antibiotics were prescribed was the lower respiratory tract (22%) followed by the urinary tract (19%) and the bloodstream (15%). Approximately ten percent of infections were in the skin and soft tissue (9%), gastrointestinal tract (11%) or undetermined/empirical (11%) respectively. Of note, the undetermined/empirical category included peri-operative antibiotic administration. Seven (13%) patients had a documented diagnosis of sepsis during the admission. Five patients had more than one site of infection (**Table 2**).

A total of twenty-six patients had a positive infection site culture. Eleven patients (20%) had positive urine cultures, seven (13%) had positive blood cultures, four (7%) had positive abscess site cultures and four (7%) had positive sputum cultures.

The most commonly used antibiotics during admission

Table 1. Antibiotics used in the 56 days prior to admission of patients diagnosed with *C. difficile*, January 1–December 31, 2018.

Antibiotic	Number (percent)
Vancomycin (intravenous)	8 (15)
Ceftriaxone	7 (13)
Piperacillin/tazobactam	6 (11)
Cefazolin	4 (7)
Levofloxacin	4 (7)
Amoxicillin/clavulanate	3 (6)
Ampicillin/sulbactam	2 (4)
Cefepime	2 (4)
Ciprofloxacin	2 (4)
Metronidazole (intravenous)	2 (4)
TMP/SMX	2 (4)
Metronidazole (oral)	1 (2)
Cefuroxime axetil	1 (2)
Azithromycin	1 (2)
Meropenem	1 (2)
Penicillin	1 (2)

Table 2. Admission clinical data of patients diagnosed with *C. difficile*, January 1–December 31, 2018

Site of infection*	Number (percent)
Lower respiratory tract	12 (22)
Urinary tract	10 (19)
Bloodstream	8 (15)
Sepsis	7 (13)
None	7 (13)
Gastrointestinal tract	6 (11)
Undetermined/empirical**	6 (11)
Skin and soft tissue	5 (9)
Bone and joint	1 (2)
Hepatobiliary system	1 (2)
Asymptomatic bacteriuria	1 (2)
Fever and neutropenia	1 (2)
Other***	1 (2)

* Five patients had more than one site of infection
** Includes empiric peri-operative antibiotics
*** Respiratory pathogen panel positive for Coronavirus HKU1

Table 3. Antibiotics used during hospitalization of patients diagnosed with *C. difficile*, January 1–December 31, 2018.

Antibiotic	Number (percent)	Average Number of Days Used
Piperacillin/tazobactam	27 (50)	4.1
Vancomycin (IV)	25 (46)	3.4
Ceftriaxone	11 (20)	2.8
Cefazolin	8 (15)	3.0
Cefepime	8 (15)	3.5
Azithromycin	6 (11)	3.5
Metronidazole I.V.	4 (7)	1.3
Aztreonam	3 (6)	2.3
TMP/SMX	2 (4)	2.0
Doxycycline	2 (4)	2.0
Ciprofloxacin	2 (4)	1.5
Levofloxacin	2 (4)	3.0
Ertapenem	2 (4)	7.0
Meropenem	2 (4)	3.0
Ampicillin/sulbactam	1 (2)	4.0
Amoxicillin/clavulanate	1 (2)	2.0
Clindamycin	1 (2)	1.0

were piperacillin/tazobactam (50%), followed by vancomycin IV (46%), ceftriaxone (20%), cefazolin (15%), cefepime (15%) and azithromycin (11%). All other antibiotics administered were used in less than ten percent of the patients *C. difficile* (**Table 3**).

Seven (13%) patients did not receive any antibiotics during their hospital stay prior to the positive test for *C. difficile*. One patient recently completed an outpatient course of amoxicillin/clavulanate prior to admission. Three of the seven had a prior positive test 22, 297 and 682 days prior to admission. The patient with the positive test 22 days earlier was an inpatient at an outside hospital. One patient received oral magnesium oxide which can cause diarrhea.

DISCUSSION

C. difficile infection is a complication of antibiotic therapy. Certain antibiotics, such as clindamycin, are associated with a higher risk for developing *C. difficile* infection. One strategy to reduce the rate of nosocomial *C. difficile* is to reduce the use of high-risk antibiotics. At The Miriam Hospital during 2018 very few patients with nosocomial *C. difficile* received a high-risk antibiotic.

Approximately 30-50% of prescribed antibiotics may be inappropriate or unnecessary.[4] In this study of patients with nosocomial *C. difficile*, very few received unnecessary antibiotics.

If *C. difficile* is solely a complication of antibiotic therapy, then it is remarkable that seven patients (13%) classified by NHSN as having hospital-acquired *C. difficile* did not receive any antibiotics while in the hospital. Moreover, six of the seven did not receive any antibiotics in the 56 days prior to their admission. Three of the seven had a prior positive stool test for *C. difficile*. Hence, they may be chronically colonized and did not acquire *C. difficile* while in the hospital. Four-percent to 15% of healthy adults are colonized with *C. difficile*.[5] Hence, if a colonized patient is admitted to the hospital and develops diarrhea for some other reason, when a stool sample is tested it will be positive for *C. difficile* even though the diarrhea is not due to *C. difficile*.

This study has several limitations. The data were collected via retrospective chart review. While every effort was made to extract data for each variable in a systematic manner, the data completeness and quality for each patient was limited by what was documented. Additionally, some variables, such as antibiotic use and surgery/hospitalization in the prior 56 days depended on access to and completeness of outpatient records. For the sake of consistency in operational definitions and analytical purposes, "PPI use" was coded as a dichotomous variable with one recorded use of any PPI coded as "yes". This is not, however, representative of how these medications are used in clinical practice, with the vast majority of conditions requiring multi-day/week courses.

C. difficile infection is a complication of antibiotic therapy. At The Miriam Hospital during 2018 use of high-risk antibiotics or unnecessary use of antibiotics was found in very few of the cases of nosocomial *C. difficile*. Moreover, 13 percent of patients did not receive an antibiotic in the hospital. Hence, some of the patients classified as having nosocomial *C. difficile* may be colonized but not infected.

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Authors

Kelly A. Skrable, MD, MPH; The Warren Alpert Medical School of Brown University, Providence, RI; Brigham and Women's Hospital, Boston, MA.

John R. Lonks, MD; Infection Control and Epidemiology, Division of Infectious Diseases, The Miriam Hospital; The Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

John R. Lonks, MD
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906
401-793-4620
Fax 401-793-4534
jlonks@lifespan.org

Rate of *Clostridioides difficile* Culture Positivity Among Hospitalized Patients

JOHN R. LONKS, MD; ERIC NOLETTE, BS; JENNIFER L. CADNUM, BS; CURTIS J. DONSKEY, MD

ABSTRACT

The rate of nosocomial *C. difficile* in Rhode Island is among the highest in the country. Colonization with *C. difficile* is uncommon but can lead to falsely identifying a patient as having *C. difficile* infection. Additionally, unrecognized *C. difficile* colonization may act as a reservoir in the hospital. During a 19-day period, rectal swabs obtained for routine VRE surveillance were cultured for *C. difficile*. Overall, 51 (7.9%) of 649 patients had *C. difficile* by culture. The majority (n=36, 71%) of patients from whom a rectal swab grew *C. difficile* did not have a sample sent to the clinical laboratory. Hence, at least 5.5% of the 649 patients were colonized. One patient was classified as having hospital-acquired *C. difficile* since the clinical specimen was sent to the clinical laboratory on hospital day 4. This patient was culture positive on admission and hence misclassified as having hospital-acquired *C. difficile*.

KEYWORDS: *Clostridioides difficile*, health care-associated infections, microbial colonization

INTRODUCTION

In January 2013, the Centers for Medicare and Medicaid Services (CMS) began requiring acute-care hospitals to submit any laboratory-identified (LabID) *Clostridioides difficile* cases to the Centers for Disease Control and Prevention's surveillance system, the National Healthcare Safety Network.[1] Data from the first quarter of 2013 demonstrated Rhode Island ranked 51st among the 50 states and the District of Columbia for *C. difficile* LabID standardized infection ratios (SIRs).[2] It has been proposed that the high rate of *C. difficile* in Rhode Island might be explained in part by the relatively high proportion of the population that is elderly and by the fact that hospitals in the state may have switched more rapidly and uniformly to nucleic acid amplification testing methods for *C. difficile* than other states.[2] However, the high rate of *C. difficile* in Rhode Island also suggested a need to re-assess infection control strategies in hospitals and nursing homes and to consider other contributing factors.

Several recent studies suggest that a substantial proportion of *C. difficile* cases classified as healthcare-associated *C. difficile* infection (CDI) were colonized on admission.[3-12] For example, Gonzalez-Orta et al.[3] reported that 14% of patients admitted to an acute care hospital were asymptomatic carriers of toxigenic *C. difficile* on admission and 9% of the carriers subsequently were diagnosed with healthcare-associated *C. difficile* versus only 1% of those with negative admission cultures. Such studies raise concern that patients with asymptomatic carriage on admission are often falsely diagnosed with *C. difficile* when they develop diarrhea for other reasons.[13] However, most prior studies evaluating carriage on admission have been small studies often involving single wards. Therefore, we conducted an Infection Control quality improvement project to determine the frequency of *C. difficile* carriage at an acute care teaching hospital in Rhode Island.

METHODS

The study was conducted at The Miriam Hospital, a 247-bed teaching hospital in Providence, RI. Rectal swabs are obtained as part of the routine Infection Control surveillance for vancomycin-resistant enterococci (VRE) on hospital admission or admission/discharge from ICUs. For 19 consecutive days during 2014, the rectal swabs obtained for VRE culture were also cultured for *C. difficile*. The swabs were kept frozen at -80 until shipped on dry ice for *C. difficile* culture.

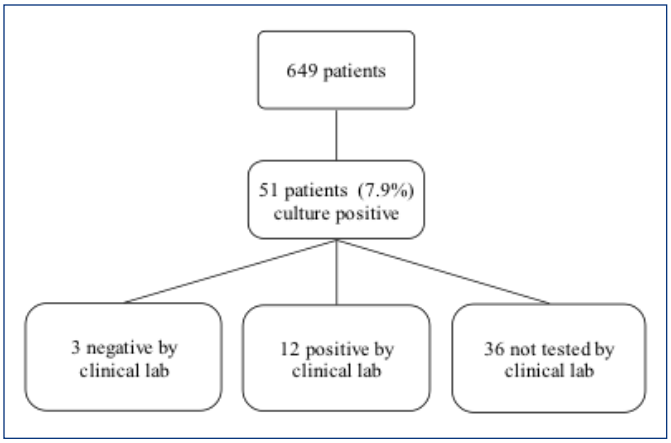
The rectal swabs were plated directly onto selective media for culture of toxigenic *C. difficile* as previously described.[14] After plating, the swabs were submersed in *C. difficile* brucella broth with thioglycolic acid and l-cystine (CDBB-TC) and incubated for up to 72 hours to identify low-level colonization.[15] All *C. difficile* isolates were tested for *in vitro* cytotoxin production using *C. difficile* Tox A/B II (Wampole Laboratories) and isolates that did not produce toxin were excluded from the analysis. For a subset of isolates, polymerase chain reaction (PCR) analysis for the binary toxin gene *cdtB* and fluorescent PCR ribotyping was performed as previously described.[16] For the directly plated swabs, the number of colonies recovered per swab was counted.

The percentage of directly plated swabs with greater than 25 colony-forming units (CFUs) per swab was calculated as this level of contamination has previously been associated with increased frequency of skin and/or environmental contamination in asymptomatic carriers.[14]

RESULTS

A total of 754 swabs were cultured from 649 patients. 86 patients were cultured twice, 8 cultured 3 times and one patient was cultured 4 times during the 19 days. Patients were considered positive if they had one or more positive cultures. Overall, 51 (7.9%) patients had cultures positive for toxigenic *C. difficile*, including 28 (4.3%) on directly plated agar culture and 23 (3.5%) in broth culture only. (**Figure 1**)

Figure 1. C. difficile cultures and clinical laboratory testing.



A chart review of the 51 culture positive patients demonstrated that 15 had a clinical laboratory test for *C. difficile*; 12 were positive and 3 were negative. The three negative test results from the clinical laboratory test were 2 days prior to the positive culture, 10 days after the culture and 11 days after the culture. Twenty-eight patients (54.9%) had positive cultures on agar culture plates and 23 (45.1%) patients had low-level carriage only detected by broth enrichment cultures. Culture positivity by the broth method only occurred more frequently (53%) among patients who did not have a specimen sent to the clinical lab compared to those who were *C. difficile* positive by the clinical lab (25%). (**Table 1**)

Table 1. Recovery of toxigenic Clostridioides difficile on agar culture plates versus only in broth enrichment cultures, stratified by clinical laboratory testing results.

Clinical Lab	Agar Number (%)	Broth Only Number (%)
Not tested	17 (47)	19 (53)
Positive test	9 (75)	3 (25)
Negative test	2 (66)	1 (33)

There was one patient among the 51 culture positive patients who was classified as having hospital-acquired *C. difficile* since the clinical specimen was sent to the clinical laboratory on hospital day 4. This patient was culture positive by directly plated agar on admission and hence misclassified as having hospital-acquired *C. difficile*.

DISCUSSION

We found that 51 (7.9%) of 649 patients admitted to The Miriam Hospital were culture-positive for toxigenic *C. difficile*. Most of these culture-positive patients (71%) did not have a specimen sent to the clinical laboratory for *C. difficile* testing suggesting that they were colonized rather than infected. Fifteen of 51 (29%) patients with a positive culture had a specimen sent to the clinical laboratory and 12 (80%) had positive PCR tests for toxigenic *C. difficile*. Of these 12 patients, 11 (91.7%) had positive tests during the first 3 days of admission and were classified as community-acquired cases. The three negative clinical laboratory results were 2 days prior and 10–11 days after the positive culture. As the cultures and clinical laboratory *C. difficile* tests were several days apart, it is possible that these patients cleared colonization during their hospital stay. Factors such as receipt of antibiotics with inhibitory activity against *C. difficile* may contribute to clearance of colonization.[13]

One patient was colonized with *C. difficile* on admission and subsequently was diagnosed with hospital-acquired *C. difficile*, using National Healthcare Safety Network (LabID) criteria, based on a stool specimen submitted to the clinical laboratory on hospital day 4. As noted previously, positive tests in patients colonized on admission could result in a false-positive diagnosis of *C. difficile* if factors such as laxatives are the cause of diarrhea.

In summary, this quality improvement project was undertaken to determine the rate of colonization with *C. difficile* in an acute care hospital in Rhode Island. At least 5.5% and possibly 6.0% of patients are colonized with *C. difficile*, a rate consistent with previous studies.[13] Although a minority of new admissions were colonized, these patients could potentially be a source of transmission as they are not isolated and inappropriate testing could result in false-positive diagnosis of *C. difficile*.

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Authors

John R. Lonks, MD; The Warren Alpert Medical School of Brown University, Division of Infectious Diseases and Department of Infection Control and Epidemiology, The Miriam Hospital, Providence, RI.

Eric Nolette, BS; Division of Infectious Diseases and Department of Infection Control and Epidemiology, The Miriam Hospital, Providence, RI; Citadel Enterprise Americas LLC, Chicago, Ill.

Jennifer L. Cadnum, BS; Research Service, Cleveland VA Medical Center, Cleveland, OH.

Curtis J. Donskey, MD; Cleveland Veterans Affairs Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH.

Correspondence

John R. Lonks, MD
164 Summit Avenue
Providence, RI 02906
401-793-4620
Fax 401-793-4534
jlonks@lifespan.org

To Treat or Not to Treat: UTI or Bacteriuria?

RAUL MACIAS-GIL, MD; EMILY O'NEILL, PharmD; MELISSA M. GAITANIS, MD

INTRODUCTION

An 85-year-old male nursing home resident with dementia is admitted with altered mental status and decreased oral intake in the last 3 days. There has been a recent medication change and his dose of quetiapine had to be decreased due to a prolonged QT interval. He was afebrile and hemodynamically stable. On exam, he was found disoriented to time and place. He had no costovertebral or suprapubic tenderness on palpation. His complete blood count showed a WBC of 7000 per microliter. The staff noted some cloudiness in the urine the day prior to admission. Urine was sent for urinalysis (UA) showing +Leukocyte esterase (LE), pyuria [40–60 white blood cells (WBCs)], and few bacteria. Reflex urine culture grew >100,000 colony-forming units (CFU)/mL of *E. coli*.

a. Start ciprofloxacin for *E. coli* UTI
b. Start broad-spectrum antibiotics pending infectious work-up
c. Restart the higher dose of quetiapine and give Haldol to calm the patient down
d. Hold antibiotics, hydrate and continue a careful work-up for metabolic issues and medication side effects.

This case may seem familiar to many of us in medicine. When we see a patient with a positive urine test, there is an automatic need to react to it. As a result, many patients like the one described above end up receiving unnecessary antibiotics. Inappropriate use of antibiotics is associated with an increased risk for complications affecting not only our patients but also healthcare systems.

This article provides a summary of UTIs, catheter-associated UTIs, and asymptomatic bacteriuria. Understanding the difference between these etiologies is crucial for appropriate diagnosis and management.

URINARY TRACT INFECTIONS (UTIS)

To accurately diagnose a UTI, patients must have symptoms with or without a positive urine culture. Symptoms of UTI include dysuria, urgency, hesitance, frequency, new incontinence. Other constitutional symptoms such as fever, chills, can also be present in the acute setting. An infection of the lower urinary tract can progress in an ascending fashion until reaching the kidneys, causing pyelonephritis. Patients with significant constitutional symptoms and hemodynamic instability may present with changes in mental status. However, altered mental status, change in urine color, cloudy urine or foul-smelling urine alone should NOT be used to diagnose a UTI.[1]

Urine is often easy to collect and is often "positive." The bladder is not as sterile as we are taught, particularly in the elderly. We have relied on using pyuria for the definition of UTI and although its absence is associated with a 96% negative predictive value (NPV) for bacteriuria, its presence has a low (39%) positive predictive value (PPV) for bacteriuria. About 75–90% of patients with asymptomatic bacteriuria (ASB) do not develop a systemic inflammatory response or other signs or symptoms to suggest infection. Treatment of ASB does not effectively prevent symptomatic UTI.

The clinical significance of asymptomatic bacteriuria in catheterized patients is undefined. A significant proportion, 15-25% of hospitalized patients, may receive indwelling catheters. In many cases, catheters are placed for inappropriate indications and healthcare providers are often unaware that their patients have catheters, leading to prolonged unnecessary use. National data from NHSN acute care hospitals in 2006 showed a range of a pooled mean CAUTI rates of 3.1–7.5 infections per 1000 catheter days. The highest rates of CAUTIs were in burn ICUs followed by inpatient medical wards and neurosurgical wards. The lowest rates are in med-surg ICUs. An estimated 17–69% of CAUTI may be preventable with recommended infection control measures, up to 380,000 infections and 9000 deaths related to CAUTI per year could be prevented.

In addition, catheters may be used disproportionately in long-term care (LTC) facilities. The rate of catheter use for managing chronic voiding dysfunction in LTC residents ranges from 7–10%.[2] In non-catheterized residents, asymptomatic bacteriuria has been estimated at 18% to 57% for women and 19% to 38% for men.

ASYMPTOMATIC BACTERIURIA (ASB)

Asymptomatic bacteriuria (ASB) is defined as the absence of clinical symptoms suggesting a UTI in the setting of presence of at least one type of bacteria in the urine at a concentration of >10^5 cfu/mL or >10^8 cfu/mL, independent of the presence of white blood cells.

The estimated prevalence of ASB varies based on the age

cohort and patient population. ASB is more prevalent in men and women living in a long-term care facility (up to 50%) followed by elderly persons (>70 years old) living in the community (10.8 to 16% in women and 3.6 to 19% in men).[3] Persons with spinal cord injury requiring intermittent catheterization and sphincterotomy/condom catheter was as high as 69% and 57%, respectively.[4,5] One study has even reported a 100% prevalence of asymptomatic bacteriuria in persons with indwelling catheters.[6]

The risk of developing bacterial colonization in patients with indwelling catheters is directly proportional to the length of time the catheter will remain in place. Bacteriuria due to catheterization is acquired at a rate of 3–10% per day, the majority of whom are asymptomatic.[7] By 30 days, 100% of patients with a catheter will show bacteria in a urine specimen. The duration of catheterization and antibiotic use also influences the incidence of bacteriuria and candiduria.

As we describe in the recommendations below, the vast majority of people with asymptomatic bacteriuria do not need screening or treatment, except for two groups: pregnant women (rates of asymptomatic bacteriuria can be as high as 9.5%)[8] and patients undergoing invasive urological procedures. Urological procedures can be classified as low, intermediate and high risk, depending on mucosal irritation, length of procedure, or potential invasion of colorectal space (class III/contaminated procedures as transrectal prostate bx).

IDSA RECOMMENDATIONS FOR MANAGEMENT OF ASB

The Infectious Diseases Society of America (IDSA) guidelines for asymptomatic bacteriuria were released in March 2019. These guidelines highlight the importance of identifying patients in whom screening for ASB is needed in order to prevent UTIs. Most importantly, they provide recommendations regarding which groups should or should not be screened for the presence of bacteria in the urine.

Table 1 summarizes these recommendations, which include different groups of adults with asymptomatic bacteriuria. In regard to the management of asymptomatic candiduria, which are not included in these guidelines, IDSA guidelines for the management of candidiasis,[9] recommends removal of predisposing factors (ie indwelling catheter), when feasible. No antifungal treatment is recommended unless patient is at risk for disseminated infection (neutropenic patients or patients undergoing urologic invasive procedure).

Compared to 2005 guidelines, current guidelines highlight the importance of recognizing non-focal symptoms that historically have been attributed to a UTI. Many patients, especially the elderly, are at higher risk for delirium, changes in mental status, and falls. Similarly, these people are at higher risk for having bacteriuria. This association has led to many overdiagnosis of UTIs, thus overutilization of antibiotics and higher likelihood for patients to develop complications.

Table 1.

Group	Recommendation	
	Screening	Treatment
Healthy, premenopausal, non-pregnant women	NO screen	NO
Pregnant women	YES, screen with urine culture (UCX)	YES
Older person (men or women) functionally impared or living in long-term care facilities	NO screen	NO
Older person (men or women) functionally or cognitively impaired and non-localizing symptoms for UTI	NO screen -->Look for other causes of delirium	NO
Diabetic patients	NO screen	NO
Patients who have received a kidney transplant (>1 month prior)	NO screen	NO
Patients s/p non-renal solid organ transplant	NO screen	NO
Patients with high-risk neutropenia [absolute neutrophil count (ANC) <100 cells/mm3, ≥7 days' duration following chemotherapy]	Recommendation deferred	Recommendation deferred
Patients with spinal cord injury (SCI) leading to impaired voiding	NO screen	NO
Patients with a short-term (<30 days) indwelling urethral catheter	NO screen	NO
Patients undergoing elective non-urologic surgeries	NO screen	NO
Patients undergoing endoscopic urinary tract procedures/manipulation (Prior to transurethral resection of the prostate (TURP) or any other urologic procedure with a risk of mucosal bleeding)	YES, screen with UCX	YES Short course (1-2 doses) of targeted antimicrobial therapy 30-60 min prior to procedure
Patients planning to undergo surgery for an artificial urinary sphincter or penile prosthesis implantation	NO screen	NO

Outcomes or concerns include but are not limited to adverse drug reactions (ADRs), drug-to-drug interactions, polypharmacy, increased risk for antimicrobial resistance, and other (sometimes lethal) complications such as *Clostridioides difficile* infection.

With increasingly complex patients having multiple comorbidities and polypharmacy, it may be difficult to tell whether patients are symptomatic for UTI. Previous studies have tried to tease out antibiotic appropriateness. One study showed that 54% (224/414) of patients treated on an acute medical ward with antimicrobials showed that UTI was the most common diagnosis (N=49). Of those who were treated for a UTI, 32.6% had no symptoms suggestive of a UTI.[10] Catheterized patients were looked at in another study at a VA hospital. More than 50% of these patients were considered to have bacteriuria but 32% of these received inappropriate treatment.[11] Another observational study found that the average length of inappropriate treatment for ASB was around 6.6 days, resulting in two cases of C. *difficile* infection and one case of QT prolongation.[12] Treating patients who do not need to be treated could result in colonization with increasingly resistant urinary bacteria, untoward patient adverse events or hospital-acquired infections.

PHARMACOLOGICAL MANAGEMENT OF UTIS

When a patient does have urinary symptoms or a medical presentation consistent with a UTI, goal-directed therapy is aimed at evaluating and relieving urinary stasis or obstruction, removing unnecessary devices (i.e. indwelling catheters) and choosing antibiotic therapy to treat typical urinary pathogens. Urinary bacteria are most often coliform gram-negative organisms in the community at large. *E coli* causes 70–95% of both upper and lower UTIs. Other organisms to consider are *S saprophyticus* (younger women), *Proteus species* (spp), *Klebsiella spp*, *Enterococcus faecalis* (older men), and other enterobacteriaceae. For purposes of a concise overview, we will focus on treatment of community-acquired bacterial pathogens.

Current first-line recommendations for the treatment of acute uncomplicated cystitis includes nitrofurantoin monohydrate/macrocrystals 100 mg BID for 5 days or trimethoprim-sulfamethoxazole (TMP/SMX) 160/800 mg BID for 3 days. TMP/SMX use is restricted to facilities with local uropathogen resistance rates less than 20%.[13] Fosfomycin, typically dosed as a one-time 3 g sachet, is a novel antibiotic that can be considered for treatment of uncomplicated cystitis. It boasts limited collateral damage and low reported resistance due to its unique mechanism of action. Use of fosfomycin should be restricted to patients with allergies to first-line antimicrobial agents or infections with multi-drug resistant organisms.[14] Complicated cystitis that extends beyond the bladder should raise concerns for pyelonephritis. In these patients, duration of therapy can be extended to 10 or 14 days. The preferred antibiotic should have high bioavailability and great penetration. In these scenarios, fluoroquinolones are frequently preferred by many providers due to their extensive spectrum of activity, its excellent bioavailability (near 100%), and high penetration into the prostate.

Commonly used agents have risks for adverse drug reactions (ADRs) and/or drug interactions. Elderly patients who are most likely to receive treatment, are particularly at higher risk to develop antibiotic associated ADRs.[15] This risk is most likely due to decreased clearance of the drug (reduced renal or hepatic metabolism), drug interactions from polypharmacy, and increased pharmacodynamic sensitivity.[16]

Fluoroquinolones can prolong the QT interval, especially in patients receiving other QT-prolonging medications such as antipsychotics or antifungals. More concerning is the extensive list of black box warnings associated with this drug class. These warnings include hypoglycemia, tendonitis and tendon rupture, peripheral neuropathy, CNS effects, and potential myasthenia gravis exacerbations. In late 2018 the FDA warned for increased risk of life-threatening aortic aneurysms or dissections, especially in the elderly and patients with hypertension or vessel abnormalities.[17] Prescribers should be aware of the association between fluoroquinolone use and risks for adverse outcomes. Thus, careful evaluation of patients, their comorbidities, and review of active medications is highly recommended prior to initiating treatment with fluoroquinolones.

Alternative agents to fluoroquinolones are not without associated ADRs and drug interactions. TMP/SMX can cause dermatological reactions (including life-threatening Stevens Johnson Syndrome), acute kidney injury, and hyperkalemia; the latter two being most common in the elderly or when compounded with potassium sparing diuretics, ACE inhibitors, and other nephrotoxic agents. TMP/SMX also influences INR levels in patients on warfarin therapy by increasing the levels of warfarin, thus, increasing the risk of bleeding. Frequent INR monitoring along with a reduction of warfarin dosing is recommended in these patients.

Nitrofurantoin is contraindicated in patients with impaired renal functions. Previously, the creatinine clearance cut-off for use of nitrofurantoin was below 60 mL/min. In 2015, the American Geriatric Society decreased the threshold of creatinine clearance cut-off to less than 30 mL/min.[18] Risks associated with nitrofurantoin use include pulmonary and hepatic toxicity, hemolytic uremia, and peripheral neuropathy.

Beyond ADRs and potential side effects associated with antimicrobial use, inappropriate prescribing of these agents potentiates antibiotic resistance. Common uropathogens such as *E. coli* and *K. pneumonia* have been associated with the development of extended spectrum beta lactamase (ESBL) and even Carbapenemase-producing conferring resistance to the most commonly used "broad-spectrum

antibiotics." Increased exposure to these antibiotics is also associated with secondary opportunistic infections such as *Clostridioides difficile* (*C. difficile)* and yeast infections. The potential of ADRs, antibiotic resistance, and secondary infections associated with antibiotic use should reinforce judicious prescribing practices when considering antibiotics for a patient presenting with a low suspicion for UTI.

OTHER INTERVENTIONS TO IMPROVE OUTCOMES

Two-Step Urine Culture Ordering[19]

Alongside careful clinical judgement, one large academic medical center implemented a "two-step process" to justify treatment of UTI. Researchers utilized a specialized container to hold urine samples at room temperature for up to 48 hours at the time of presentation to the ED. Urine was not sent for culture until a validated diagnostic screen was completed by the ED physician with a subsequent order for culture.

Following implementation of this protocol, there was a decrease in the percentage of weekly ED visits associated with a processed urine cultures (UC) (5.97% vs 4.68%, p<0.001), a decrease in the percentage of monthly ED visits requiring callback for positive UC (1.84% to 1.12%, p<0.001), and a decrease in antimicrobial prescriptions for urinary indication among admitted patients (20.6% to 10.9%, p<0.01). The researchers reported a false omission rate of 1.35% (95% CI 0.7% to 2.2%), yet no identified cases of untreated urinary tract infection (UTI), or significant change in repeat ED visits or ED length of stay. Placing urinary specimens on hold (up to 48 hours) for further testing with urinary cultures may be a potential intervention to consider in medical centers to reduce the overuse of antimicrobials in the setting of ASB. The applicability of this intervention should be individualized as operational processes may differ at each medical center.

ANTIBIOTIC STEWARDSHIP AND EDUCATION

Data supporting the effectiveness of hospital antibiotic stewardship programs have been long-standing and voluminous. In 2017, the Joint Commission established inpatient AMS programs to be an accreditation standard for hospitals and expanded this standard to the outpatient arena in 2019.

Most of the studies on limiting treatment of asymptomatic bacteriuria have included participants from the community and healthy women. The excluded populations from many of these early studies are hospitalized or institutionalized patients, patients with chronic urinary tract conditions or stents, transplant patients, and spinal cord patients. Ironically these are the patients who need our attention and expertise. Education, combined with audit and feedback, can change clinician behavior. It is possible to incorporate interventions to guide providers toward thoughtful process and corrective action rather than reflex prescribing.[20] AMS programs led by physicians, pharmacists and nurses are able to offer educational guidelines, alternatives for prescribing (low likelihood cases), case-based learning for small group feedback, and evidenced-based lectures which can modify clinician practice.

HOSPITAL REIMBURSEMENT AND QUALITY STANDARDS

Antimicrobial stewardship goes hand in hand with infection control. Hospitals have an incentive to approach bacteriuria cautiously, testing only when needed, using antibiotics only when warranted, and removing unnecessary genitourinary catheters. In 2008 there was a significant policy change by which Medicare ceased reimbursement for hospital-acquired infections (HAIs), such as catheter-associated urinary tract infections (CAUTI). In 2015, *C. difficile* colitis was included in this HAI group. Treating HAIs proves to be more expensive than preventing them. As a result of monetary penalization, hospitals have implemented quality improvement initiations aimed at improving outcomes and reducing infection rates.

GOING BACK TO OUR CASE

In this 85-year-old gentleman, we may want to closely monitor clinical status, hydrate, assess for any metabolic abnormalities, and carefully evaluate what antipsychotics should be used (if any at all) in this elderly man with dementia. If he has urinary retention, this could be relieved and worked up, but if he has no systemic or localized signs of infection, his urine should not be tested or treated (unless he was going for cystoscopy with biopsy in the near future). Alternatively, you could consider a 2-step urine testing while continuing to monitor clinical status off antibiotics.

DISCUSSION AND CONCLUSION

Asymptomatic bacteriuria is defined as bacteria in the urine without symptoms referable to the urinary tract. Prevalence ranges from 1–5% of normal healthy women to 40–50% of those in long-term care facility. Diagnostic uncertainty in the institutionalized elderly leads to inappropriate antimicrobial use. The majority of patients with ASB require no treatment except pre-operative state for invasive urological procedure and in pregnancy.

Delirium or falls, especially in the elderly, should have a wide net cast for etiology of "mental status change." Mental status changes alone without symptoms referable to the urinary tract or systemic symptoms of infection does not accurately translate into UTI. In these instances, NO urine cultures or empiric antimicrobials for UTI are encouraged.

Antibiotics should be used judiciously for the treatment of UTIs. Targeted therapy is recommended when a causative organism has been identified.

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Authors

Raul Macias-Gil, MD; Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI.

Emily O'Neill, PharmD; Providence Veterans Affairs Medical Center, Providence, RI.

Melissa M. Gaitanis, MD; Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI; Providence Veterans Affairs Medical Center, Providence, RI.

Correspondence

Melissa M. Gaitanis, MD
Providence VA Medical Center
830 Chalkstone Avenue
Providence, RI 02908
401-273-7100 (x3609)
Fax 401-457-3364
melissa_gaitanis@brown.edu