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ORIGINAL RESEARCH

Antimicrobial Stewardship Meets Transitions of Care: Defining Length of Therapy for Community-Acquired Pneumonia (CAP)

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Abstract

Introduction: Hospital-based antimicrobial stewardship efforts have traditionally focused on inpatient settings. Antibiotic prescribing at discharge is often an overlooked area of focus for antimicrobial stewardship programs. Discharge prescribing optimization is necessary to combat antibiotic overuse.

Methods: This was an observational, retrospective cohort study at a four–adult community hospital system. Four hundred adult patients admitted with community-acquired pneumonia and discharged with antibiotics were included. The primary outcome was overall (inpatient and discharge) antibiotic length of therapy. The secondary outcome was percentage of patients discharged on a fluoroquinolone who had not received one in the hospital. Descriptive statistics were utilized.

Results: The median total antibiotic length of therapy was 9.5 days (IQR 8, 11). The median inpatient and discharge antibiotic lengths of therapy were 4 days (IQR 3, 5) and 5 days (IQR 5, 7), respectively. Of the 108 patients prescribed a fluoroquinolone at discharge, 43% (46/108) had not previously received a fluoroquinolone while hospitalized.

Conclusion: Both length of therapy and fluoroquinolone stewardship at discharge may represent possible antimicrobial stewardship targets in community-acquired pneumonia patients.

Introduction

Antimicrobial stewardship programs (ASPs) seek to optimize antimicrobial use to reduce the risk for *Clostridioides difficile* infection, drug toxicities, and the emergence of drug-resistant pathogens.[1, 2] ASP interventions have historically focused on antibiotic use during hospitalization. A common target for hospital-based ASPs is community-acquired pneumonia (CAP) since it accounts for an estimated 1.6 million hospitalizations annually in the United States and is one of the top ten causes of mortality.[3, 4] Additionally, the Centers for Disease Control and Prevention (CDC)'s Core Elements of Hospital Antimicrobial Stewardship Programs specifically designate duration of therapy at discharge in CAP patients as an important target.[5] Contrary to guideline recommendations, many patients hospitalized with CAP receive greater than five days of antibiotics with the outpatient duration often exceeding the inpatient length of therapy.[6-11]

Additionally, increases in discharge fluoroquinolone prescribing rates relative to inpatient settings have been previously described; this is particularly concerning given the myriad of toxicities associated with fluoroquinolones and the U.S. Food & Drug Administration (FDA)'s caution against their use.[6, 8, 12] This has prompted a focus on antimicrobial stewardship efforts at transitions of care to decrease suboptimal antibiotic choice and duration at hospital discharge.[13] Discharge prescription data can be challenging to capture, limiting the amount of data reported regarding the total duration of therapy for hospitalized patients with CAP.[6-8] Therefore, in order to determine current discharge prescribing practices in a health system, manual review may be necessary. The purpose of this study was to quantify antimicrobial stewardship opportunities at hospital discharge in patients admitted for CAP.

Methods

Study setting and population

This was a retrospective, observational study conducted at Norton Healthcare, a not-for-profit community healthcare system, in Louisville, Kentucky. The system includes four adult hospitals with approximately 1,600 licensed beds. All hospitals are within the Louisville metropolitan area and are served by a central ASP comprising four full-time infectious diseases pharmacists, one infectious diseases physician, and one infectious diseases pharmacy resident. Antimicrobial stewardship staff perform prospective audit and feedback. Specifically regarding pneumonia, the ASP has a local guideline in place, which recommends 5 days as an appropriate length of therapy in CAP patients who are clinically stable and have been afebrile >48 hours. Though not explicitly recommended in the guideline, procalcitonin is mentioned as a possible guide in determining length of therapy, and discontinuation of antibiotics is encouraged if procalcitonin is $\leq$0.5 ng/mL or has decreased $\geq$80% from a baseline >10 ng/mL. The ASP currently has no defined process for addressing discharge antibiotic prescribing.

Patients $\geq$18 years of age were included if they were admitted with a diagnosis-related group code for CAP (177, 178, 179, 193, 194, or 195) between June 2018 and June 2019 and were discharged on an antibiotic for CAP. Patients were excluded if they had any of the following complicating factors: cystic fibrosis, lung transplant, empyema, lung abscess, receiving chemotherapy, HIV, a respiratory culture with Pseudomonas spp., pregnancy, incarceration, inpatient mortality, or if they were discharged on parenteral antibiotic therapy or systemic antifungals other than fluconazole. Patients could be included more than once in the study period. Patients meeting inclusion and exclusion criteria were randomized, and samples of 100 patients from each of the four hospitals were included in the final cohort. The study was exempted from informed consent by the University of Louisville Institutional Review Board (IRB 19.1072).

Study outcomes

The primary outcome was the total antibiotic length of therapy for CAP. The secondary outcome was the percentage of patients discharged on a fluoroquinolone when a fluoroquinolone was not administered during the hospitalization. Post-hoc exploratory analysis included the distribution of discharge antibiotic days of therapy. Data were characterized with descriptive statistics.

Definitions

Inpatient antibiotic length of therapy was defined as the number of calendar days for which CAP antibiotics were administered. CAP antibiotics included penicillin, amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, cefazolin, cephalexin, cefuroxime, ceftriaxone, ceftazidime, cefdinir, cefpodoxime, azithromycin, doxycycline, ciprofloxacin, levofloxacin, moxifloxacin, linezolid, and vancomycin. Discharge antibiotic length of therapy was determined based on the prescribed duration from the discharge prescription. If more than one antibiotic was prescribed at discharge, length of therapy for both agents was considered, and the longer duration based on calendar days of either agent was utilized. For example, if a patient was prescribed one day of azithromycin and five days of amoxicillin/clavulanate, the discharge length of therapy was considered to be five days. Hospital length of stay was collected based on calendar days for which the patient was hospitalized.

In addition to antibiotic therapy information, age, sex, first procalcitonin, admission to the intensive care unit (ICU), and blood culture information were collected if available.

Results

To reach the target sample size, 445 hospital admissions were screened. Forty-five patients were excluded, with the most common reason being the receipt of chemotherapy (n=31), followed by lung abscess (n=4), Pseudomonas spp. infection (n=3), HIV (n=3), empyema (n=2), lung transplant (n=1), and being discharged on parenteral antibiotics (n=1). The median age was 68 years (interquartile range [IQR] 56, 79), and 53% of the cohort was female. The median hospital length of stay was 3 days (IQR 2, 4).

The median total antibiotic length of therapy was 9.5 days (IQR 8, 11). The distribution of the total antibiotic length of therapy is represented in **Figure 1**. Most patients (97%) received more than 5 days of antibiotic therapy. The median inpatient and discharge antibiotic lengths of therapy were 4 days (IQR 3, 5) and 5 days (IQR 5, 7), respectively. At hospital discharge, 76% of patients received either 5 days, 7 days, or 10 days of additional antibiotic therapy (**Figure 2**).

At least one dose of a fluoroquinolone was administered in 22% (n=86) of all patients during hospital admission. Thirty-one percent (27/86) of those patients received only a single dose of a fluoroquinolone prior to switching to an alternative antibiotic. Of 108 patients (27%) who were prescribed a fluoroquinolone at discharge, 43% (46/108) had not previously received a flu-

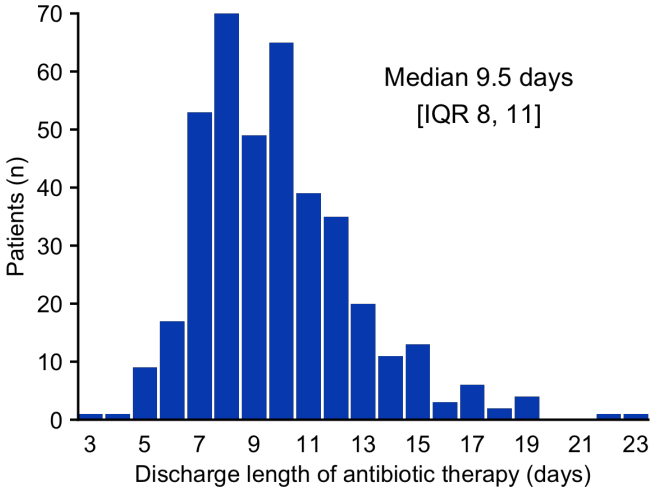

Figure 1. Distribution of total antibiotic length of therapy for community-acquired bacterial pneumonia.

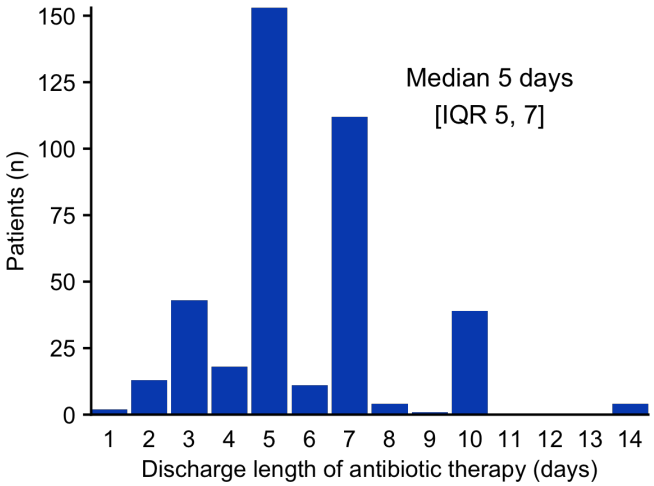

Figure 2. Distribution of discharge antibiotic length of therapy for community-acquired bacterial pneumonia

oroquinolone while inpatient, translating to a new start rate of 11.5% (46/400) among the entire cohort. Antimicrobials utilized at hospital discharge can be found in **Table 1**.

Procalcitonin was collected in 217 patients, with 24.4% of initial values resulting $\geq$0.5 ng/mL. Procalcitonin was ordered at a median of hospital day 2. A small number (n=10, 2.5%) of patients were admitted to the ICU. Blood cultures were collected in 86.5% of patients. Growth from blood cultures with was observed in 2 patients. In both cases *Streptococcus pneumoniae* was isolated.

Table 1. Choice of discharge antimicrobial.

Discharge antibiotic*	*n* (%)
Total	400
Penicillin	0 (0.0)
Amoxicillin	8 (2.0)
Amoxicillin/clavulanate	140 (35.0)
Cephalexin	7 (1.8)
Cefuroxime	4 (1.0)
Cefdinir	72 (18.0)
Cefpodoxime	0 (0.0)
Azithromycin	65 (16.3)
Doxycycline	23 (5.8)
Ciprofloxacin	3 (0.8)
Levofloxacin	105 (26.3)
Moxifloxacin	0 (0.0)
Linezolid	1 (0.3)

* If patients received multiple antibiotics at discharge, this was collected.

Discussion

We found that patients hospitalized for CAP who completed their antibiotic course after hospital discharge received a median 9.5 days of total antibiotic therapy. The 2019 American Thoracic Society and Infectious Diseases Society of America guidelines recommend that antibiotic therapy should be continued until patients achieve clinical stability and for a minimum 5 days.[11] A total duration of 5 days is likely adequate for most patients discharged on oral antibiotics as most achieve clinical stability within 48 to 72 hours.[10] In this cohort, the median length of stay was 3 days. Using hospital discharge as a surrogate for clinical stability, shorter durations likely could have been appropriate in many patients. Additionally, relatively few patients had documented elevations in procalcitonin or required ICU admission, possibly indicating that prolonged durations of therapy were likely unnecessary in the overall cohort.[14] Despite these assumptions, 97% of patients received longer than 5 days of antibiotic therapy.

Excessive duration of therapy for CAP has also been observed in other studies.[8, 9, 12] Yi *et al.* found that more than 67% of patients with CAP received >7 days of therapy.[8] More recently, Vaughn *et al.* described a large cohort, in which 63% of antibiotic overuse days were after discharge.[9] A large retrospective Veteran's Affairs study, which also included assessment for clinical stability at discharge, also found that 86.1% of CAP patients received treatment that was discordant with guidelines.[6] Overall, excessive prescribing has been observed in both regional and national studies.

The majority of antibiotic exposure occurred in the outpatient setting, and the duration of antibiotic therapy at

discharge appeared to be selected based on fixed durations. This was also observed in a large study in Michigan, where authors found prescribers "resetting the clock" and ordering 5, 7, or 10 days of therapy in 45% of patients at discharge.[7] These same fixed outpatient durations were selected in an even larger percentage of our cohort (76%). This phenomenon may speak to prescribing convention driving decision-making rather than a patient-specific assessment.[15]

A recent report from the Michigan Hospital Medicine Safety Consortium described targeted efforts to decrease antimicrobial length of therapy in uncomplicated CAP patients, as this had previously been identified as an area of opportunity to improve care within the state.[16] The group provided data, education, and pay incentives to participating hospitals and demonstrated an increase in guideline-compliant five-day treatment courses from 22.1% to 45.9%.[16] Additionally, a decrease in short-term antibiotic-associated adverse effects was observed, demonstrating another potential advantage of shorter durations of antibiotic therapy.[16] Though these results are impressive, the authors point out that their financial support from an insurance company made the program possible, and this may not be a viable strategy for all institutions.

Fluoroquinolones are key targets for antimicrobial stewardship programs given their FDA safety warnings, association with *C. difficile* infection, and propensity for inducing antimicrobial resistance.[12, 17, 18] Despite associated risks, many patients were transitioned to a fluoroquinolone at hospital discharge. The rate of new fluoroquinolone starts (11.5%, 46/400) was comparable to that found by Vaughn *et al.* for hospitals with fluoroquinolone stewardship programs (17%), but less than the increase in fluoroquinolone prescriptions at discharge reported by Yi *et al.* (22–24%).[8, 12] The lower rates in our cohort were surprising given that outpatient fluoroquinolone prescribing rates in Kentucky are among the highest in the nation.[19] Still, even a modest rise in fluoroquinolone prescriptions at discharge is concerning as non-fluoroquinolone alternatives were utilized in the inpatient setting. Our data add to the growing body of literature emphasizing the need for fluoroquinolone stewardship interventions at hospital discharge. The overall impact of reductions in inpatient fluoroquinolone use may be offset by new fluoroquinolone starts at hospital discharge.

Our data are consistent with previous reports that antimicrobial stewardship opportunities in discharge prescribing appear to be numerous, in regard to both length of therapy and choice of antimicrobial. This mirrors the results of previous studies and confirms that this wide-spread issue of overprescribing exists within a community health settings. The southern region of the United States has a higher rate of prescribing than other areas of the United States, and describing specific areas of antimicrobial stewardship opportunities may be an aid to providers or antimicrobial stewardship programs.[20] Limitations include the retrospective nature of the study and inclusion based on diagnostic codes, rather than criteria, though this is consistent with methodology used in other studies.[6-10] Additionally, there was no individual assessment of comorbidities or clinical stability at discharge; thus, it is unknown whether these factors may have contributed to prescribing trends.

Future studies should investigate the impact of interventions to optimize discharge prescribing, which could include clinician education, institutional guidelines, electronic health record support, or prospective audit-and-feedback.

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