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A multicentre stewardship initiative to decrease excessive duration of antibiotic therapy for the treatment of community-acquired pneumonia

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Background: The increased emphasis on pneumonia-related performance measures and patient outcomes has led hospitals to implement multifaceted approaches to quickly identify patients with community-acquired pneumonia (CAP), start timely therapy and reduce readmission. However, there has been minimal focus on duration of therapy (DOT) and patients often receive prolonged antibiotic courses. The IDSA and American Thoracic Society (IDSA/ATS) CAP guidelines recommend 5 days of therapy for clinically stable patients that quickly defervesce and stewardship teams are well positioned to influence prescribing practices.

Objectives: Determine the impact of a prospective stewardship intervention on total antibiotic DOT and associated clinical outcomes in hospitalized patients with CAP.

Methods: This multicentre, quasi-experimental study evaluated three concurrent interventions over a 6 month period to promote appropriate DOT. All centres updated institutional CAP guidelines to promote IDSA/ATS-concordant DOT, provided education and conducted daily audit and feedback with intervention to provide patient-specific DOT recommendations.

Results: A total of 600 patients with CAP were included (307 in the historical control group and 293 in the stewardship intervention group). The stewardship intervention increased compliance with DOT recommendations (42% versus 5.6%, $P < 0.001$) and reduced the median DOT per patient (6 versus 9 days, $P < 0.001$). Clinical outcomes, including mortality, readmission with pneumonia, presentation to the emergency centre/clinic with pneumonia and incidence of *Clostridium difficile* infection within 30 days of discharge, were not different between groups.

Conclusions: This multicentre evaluation of a stewardship intervention in hospitalized CAP patients reduced the total antibiotic DOT and increased guideline-concordant DOT without adversely affecting patient outcomes.

Introduction

The timely identification and management of community-acquired pneumonia (CAP) has significantly improved patient care and pneumonia-related quality performance measures, largely due to implementation of regulations by the Centers for Medicare and Medicaid Services (CMS) linked to reimbursement.[1,2] In response to these regulatory standards, hospitals have implemented multifaceted approaches to quickly identify CAP, start timely appropriate therapy, obtain cultures and assess need for vaccination.[1–3] Notably, however, there are no regulatory requirements surrounding duration of therapy (DOT). To date, only a limited number of studies have evaluated the ability of stewardship programmes to impact DOT and associated outcomes and complications.

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The 2007 IDSA and American Thoracic Society (IDSA/ATS) CAP guidelines recommend 5 days of therapy if patients are afebrile for 48–72 h and exhibit no more than one sign of clinical instability.[4] Longer durations of antibiotic therapy are recommended for patients with delayed clinical response, complications and extrapulmonary infections. Treatment with a β-lactam agent plus azithromycin or a fluoroquinolone alone are generally front-line treatment options for patients with non-severe CAP, as recommended by the IDSA/ATS guidelines. Fluoroquinolones and cephalosporins, particularly third-generation cephalosporins such as ceftriaxone, are frequently utilized for this indication due to ease of dosing and administration, yet use of these agents has been associated with increased risk for *Clostridium difficile* infection (CDI).[5–9] In addition to increased antibiotic exposure, prolonged antibiotic courses have also been linked to the development of antimicrobial resistance and acquisition of superinfections, including CDI.[5,10] Adherence to IDSA/ATS DOT guidelines has been shown to be safe for patients with CAP,[11] yet compliance with recommendations for DOT appears to be suboptimal and unnecessarily long antibiotic DOT appears to be common,[12] putting patients at risk for adverse outcomes. Therefore, the objective of this study was to assess the impact of a multicentre, multifaceted stewardship initiative to promote compliance with IDSA/ATS CAP recommendations regarding DOT in hospitalized CAP patients and its impact on patient outcomes.

Methods

This was a multicentre, pre-post quasi-experimental study evaluating patients before (November 2014–April 2015; historical control group) and after (November 2015–April 2016; intervention group) the implementation of a multifaceted CAP-focused stewardship initiative. The study was conducted at three large, academic medical centres: Michigan Medicine (Ann Arbor, MI, USA), Froedtert Hospital (Milwaukee, WI, USA) and Ochsner Medical Center (New Orleans, LA, USA). All three centres have integrated primary care and specialty clinics that operate within the healthcare system and utilize Epic (Epic Systems Corporation; Verona, WI, USA) as the electronic health record for inpatients and outpatients.

Patients were included if they were ≥18 years old and admitted to a medical service for CAP, defined as the presence of signs and/or symptoms of pneumonia at admission or within 48 h of hospital presentation. This included endorsement of symptoms associated with pneumonia by the patient (such as cough, shortness of breath etc.), suggestive radiographic imaging and consideration of the clinician assessment of the patient. Patients were excluded if they were diagnosed with any of the following: healthcare-associated pneumonia (HCAP), ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), empyema, necrotizing pneumonia, bacteraemia or any concomitant infection that required additional antimicrobial therapy beyond CAP therapy. Patients were also excluded if they had or experienced any of the following: cystic fibrosis, admission to the ICU, transfer from an outside hospital, respiratory culture with a non-fermenting Gram-negative bacillus or *Staphylococcus aureus*, or died during treatment of pneumonia. Historical control group patients were identified retrospectively by ICD-9 and ICD-10 codes indicative of pneumonia or any respiratory diagnosis, such as shortness of breath or asthma exacerbation, and individual charts were screened thoroughly by investigators for diagnosis of CAP, confirmed by positive radiographic results plus signs and symptoms consistent with pneumonia.

The primary objective was to assess the impact of stewardship intervention on CAP antimicrobial DOT. Secondary objectives included evaluating the impact of the intervention on patient outcomes, including mortality, readmission or presentation to a clinic or emergency centre for pneumonia, and incidence of CDI at 30 days post-encounter discharge. Additional endpoints included measuring compliance with IDSA/ATS duration recommendations before and after implementation of the stewardship initiative.

Actual DOT was defined as the total duration of antibiotics received by a patient, including inpatient administration and outpatient prescription. Appropriate DOT was defined as the DOT a patient should have received based on IDSA/ATS recommendations. Patients whose actual DOT matched appropriate DOT were considered to have received guideline-concordant durations of therapy.

Stewardship intervention

The Antibiotic Stewardship Team (AST) at each institution employed a multifaceted approach to promote appropriate antibiotic DOT in concordance with IDSA/ATS guidelines. Although institution-specific empirical CAP guidelines already existed at each institution, as part of the intervention each AST updated the guidelines to provide and emphasize appropriate DOT recommendations based on IDSA/ATS recommendations. Pocket cards highlighting these updates were created and distributed throughout the medicine services. The guidelines and pocket cards were made available on the hospital intranet sites for reference. Immediately prior to the initiation of the intervention, AST members led multiple educational sessions for pharmacists and prescribers, including interns, residents, advanced practice providers and attending physicians, on management of CAP, the institutional guideline updates and the stewardship initiative.

During the intervention study period (November 2015–April 2016), Infectious Diseases pharmacists performed prospective audit with feedback and intervention on identified CAP patients admitted to medicine services Monday–Friday. Potential patients were identified via an Epic report that utilized a combination of admitting diagnosis and antibiotic therapy. The AST pharmacists contacted primary team prescribers and made direct, verbal recommendations regarding appropriate DOT based on individual patient evaluation. The ASTs made recommendations that antibiotic therapy be discontinued 72 h after patients were afebrile and had no more than one sign of CAP-associated clinical instability (see criteria in Table 1). Patients with chronic baseline conditions that are defined as CAP-associated signs of clinical instability were deemed to be clinically stable when the condition returned to baseline status. The minimum appropriate DOT for CAP was 5 days. If patients were not afebrile for at least 72 h or had more than one sign of clinical instability on day 5, the duration was extended until those criteria were met. As the AST pharmacists provided specific stop dates for CAP antimicrobial therapy, recommendations were only made once criteria were met.

Ethics

This study was approved by the institutional review board at all three institutions. As the intervention was promoting standard of care as per the IDSA/ATS guidelines, no written informed consent was required.

Statistical analysis

All outcomes compared the stewardship intervention group with the historical control group. Descriptive statistics included median (IQR). Clinical outcomes were evaluated through 30 days post-discharge. The binary variables were compared using ORs and the ordinal variables were compared with the Wilcoxon Rank-Sum test. All statistical analysis was done using R Core Team (2017, Vienna, Austria) and EpiTools: Epidemiology Tools (2012, Tomas J. Aragon Developer). Effects were considered significant if the P value was <0.05.

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Table 1. IDSA/ATS DOT recommendations

Appropriate DOT	CAP-associated clinical signs of instability
• Five days of therapy if patients are afebrile for 48–72 h and exhibit no more than one sign of clinical instability • Longer durations of antibiotic therapy are recommended for patients with delayed clinical response, complications and extra-pulmonary infections	• Heart rate ≥100 beats per min • Respiratory rate ≥24 breaths per min • Systolic blood pressure ≤90 mmHg • Arterial O_2 saturation ≤90% or pO_2 ≤60 mmHg on room air • Altered mental status

Results

A total of 600 patients were included in the study (307 in the historical control group and 293 in the stewardship intervention group). Baseline characteristics between groups were similar, with a few exceptions (Table 2). Patients in the intervention group were more likely to have a prior myocardial infarction (7.8% versus 3.9%, $P = 0.042$) and chronic pulmonary disease (37.5% versus 29.3%, $P = 0.033$), and more patients in the historical group were receiving chronic systemic steroids (15.3% versus 7.2%, $P = 0.002$). Overall, patients in the intervention group had numerically higher Charlson comorbidity index scores, although the difference was not significant [median score (IQR) 2 (0–3) versus 1 (0–3), $P = 0.275$]. The severity of pneumonia at presentation, as indicated by CURB-65 scoring, showed a similar severity of disease in both groups [median score (IQR) 1 (1–2) versus 1 (1–2), $P = 0.35$].

The median (IQR) DOT received by patients was significantly lower in the intervention group compared with the historical group [6 (5–7) versus 9 (7–10) days, $P < 0.001$] (Table 3). The historical group had a median of 3 days excess antibiotic treatment from IDSA/ATS appropriate duration and this was reduced significantly to 1 day in the intervention group ($P < 0.001$). Thus, a total of 586 days of unnecessary antibiotics were avoided over the 6 month intervention period. Based on IDSA/ATS DOT recommendations, 96.4% of the historical control group and 91.5% of the intervention group met criteria for and should have received 5–6 days of therapy for CAP treatment (Table 4). Only one patient in the historical group and four patients in the intervention group should have received more than 10 days of therapy per IDSA/ATS guidelines. Guideline-concordant DOT increased from 5.6% in the historical group to 42% in the stewardship intervention group ($P < 0.001$). More patients in the intervention group received 5 days of therapy [103 (35.2%) versus 15 (4.9%) patients, $P < 0.001$] (Figure 1). There was a decrease in longer durations of therapy (8–14 days) in the intervention group.

Within 30 days post-discharge, 58.1% of patients in the historical control group and 57.2% in the intervention group had documented follow-up within the health systems. The incidence of readmission to the hospital for pneumonia (7.1% versus 3.8%) and presentation to a clinic or emergency centre for pneumonia (6.8%

Table 2. Baseline demographics

	Historical control group ($N = 307$)	Intervention group ($N = 293$)	P
Age (years), median (IQR)	67 (53–78.5)	66 (54–80)	0.703
Age >65 years, *n* (%)	158 (51.5)	154 (52.6)	0.789
Male, *n* (%)	146 (47.6)	152 (51.9)	0.292
Comorbidities			
Charlson comorbidity index, median (IQR)	1 (0–3)	2 (0–3)	0.275
cerebrovascular accident, *n* (%)	21 (6.8)	18 (6.1)	0.734
congestive heart failure, *n* (%)	56 (18.2)	58 (19.8)	0.629
myocardial infarction, *n* (%)	12 (3.9)	23 (7.8)	0.042
peripheral vascular disease, *n* (%)	12 (3.9)	16 (5.5)	0.377
connective tissue disease, *n* (%)	1 (0.3)	2 (0.7)	0.598
chronic pulmonary disease, *n* (%)	90 (29.3)	110 (37.5)	0.033
chronic liver disease or cirrhosis, *n* (%)	7 (2.3)	10 (3.4)	0.417
liver disease (moderate/severe), *n* (%)	6 (2)	4 (1.4)	0.595
kidney disease (moderate/severe), *n* (%)	45 (14.7)	46 (15.7)	0.724
dementia, *n* (%)	18 (5.9)	15 (5.1)	0.696
previous CDI (last 90 days), *n* (%)	2 (0.7)	0 (0)	NA
Immunocompromised patients, *n* (%)			
AIDS	3 (1)	2 (0.7)	0.723
diabetes	95 (30.9)	86 (29.4)	0.722
leukaemia or lymphoma	17 (5.5)	11 (3.8)	0.337
solid tumour	46 (15)	56 (19.1)	0.193
Laboratory test results on admission			
WBCs (10^3/μL), median (IQR)	11.6 (8.5–15.7)	11.2 (8.1–15.5)	0.502
ANC <500 cells/mm^3, *n* (%)	4 (1.3)	1 (0.3)	0.236
CD4 <200 cells/mm^3, *n* (%)	4 (1.3)	2 (0.7)	0.485
Medication exposures, *n* (%)			
antibiotics (last 30 days)	64 (20.8)	62 (21.2)	0.925
antirejection medications	22 (7.2)	17 (5.8)	0.505
chemotherapy (last 30 days)	5 (1.6)	3 (1)	0.547
proton pump inhibitors	101 (32.9)	96 (32.8)	0.972
steroids (chronic, systemic)	47 (15.3)	21 (7.2)	0.002
TNF-α inhibitors	1 (0.3)	2 (0.7)	0.598
Factors associated with admission			
CURB-65 score, median (IQR)	1 (1–2)	1 (1–2)	0.35
suspected/witnessed aspiration, *n* (%)	19 (6.2)	31 (10.6)	0.054

WBCs, white blood cells; ANC, absolute neutrophil count.

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versus 4.4%) were similar between the historical and intervention groups, respectively. There was no difference in mortality identified at 30 days post-discharge (2.3% historical control versus 1% intervention group, $P = 0.233$). There were no episodes of CDI identified in either the historical group or the intervention group throughout hospital stay or at 30 days post-discharge (Table 5).

Discussion

To our knowledge, this is the largest study evaluating the impact of stewardship intervention on DOT and clinical outcomes for CAP. In our study, a multifaceted stewardship intervention targeting compliance with IDSA/ATS DOT recommendations through guideline expansion and education as well as patient-specific prospective audit and feedback resulted in significantly decreased durations of antimicrobial therapy. Importantly, this decrease was not associated with any increases in adverse outcomes, including mortality and readmission. Given that inappropriately prolonged durations of therapy with high-risk antimicrobial agents is common in the setting of pneumonia treatment, optimizing CAP therapy is an opportune initiative for stewardship programmes.

A short course of therapy for CAP has been shown to be safe in several randomized trials.[13] Additionally, a duration based on IDSA/ATS guidelines has been recently validated in a multicentre randomized trial of over 300 patients by Uranga *et al.*[11] Patients were randomized to a control group where DOT was based on physician discretion or an intervention group where IDSA/ATS recommendations were followed. Patients in the control group received a median of 10 days of antibiotic therapy compared with 5 days in the intervention group. Despite this difference in DOT, clinical success was similar between both groups at both 10 days (48.6% versus 56.3%) and 30 days (88.6% versus 91.9%) from admission. There were no differences in antibiotic adverse effects and rates of CDI were not noted. They concluded that the IDSA/ATS recommendations can be safely implemented in hospitalized patients with CAP. The study by Uranga *et al.*[11] provides

Table 3. DOT comparisons

	Historical control group ($N = 307$)	Intervention group ($N = 293$)	*P*
Total duration of antibiotic therapy, median (IQR)	9 (7–10)	6 (5–7)	<0.001
Guideline-concordant therapy[a], *n* (%)	17 (5.6)[c]	120 (42)[d]	<0.001
Guideline-concordant therapy +1 day[b], *n* (%)	28 (9.2)[c]	121 (42)[d]	<0.001
Excess antibiotic days, median (IQR)	3 (2–5)	1 (0–2)	<0.001

[a]Actual DOT matched appropriate DOT based on IDSA/ATS duration recommendations.
[b]Actual DOT matched appropriate DOT or within +1 day of appropriate therapy.
[c]304 patients.
[d]287 patients.

Table 4. Appropriate DOT patients should have received based on IDSA/ATS guidelines

Appropriate DOT (days)	Historical control group ($N = 307$), *n* (%)	Intervention group ($N = 293$), *n* (%)	*P*
5–6	296 (96.4)	268 (91.5)	0.011
7–10	10 (3.3)	21 (7.2)	0.03
11–14	1 (0.3)	1 (0.3)	0.972
>14	0 (0)	3 (1)	–

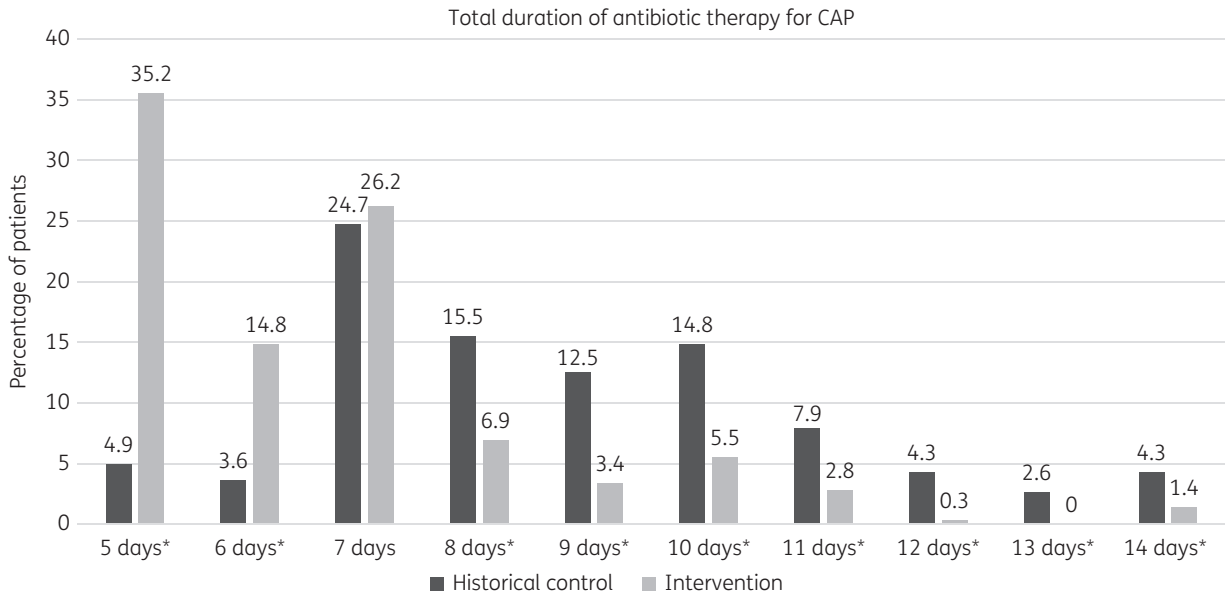

Figure 1. Actual DOT in the historical control group versus stewardship intervention. An asterisk denotes a significant difference.

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Table 5. Clinical outcomes

	Historical control group ($N = 294$), *n* (%)	Intervention group ($N = 293$), *n* (%)	*P*
CDI	0 (0)	0 (0)	–
Re-presented to emergency centre or clinic with pneumonia	20 (6.8)	13 (4.4)	0.22
Readmission with pneumonia[a]	21 (7.1)	11 (3.8)	0.075
Mortality[b]	7 (2.3)	3 (1)	0.233

CDI outcome evaluated from CAP diagnosis to 30 days post-discharge; all other outcomes evaluated from discharge to 30 days post-discharge.
[a]Historical control group with 295 patients in analysis.
[b]Historical control group with 298 patients in analysis.

support for adherence to IDSA/ATS recommendations in order to limit unnecessarily prolonged antimicrobial exposure for CAP patients.

Several other ASTs have targeted CAP for disease-based stewardship efforts. Avdic *et al.*[12] implemented an intervention similar to ours, utilizing education and prospective audit with feedback and intervention, with the goal of optimizing DOT for patients admitted with CAP. With their intervention, a significant reduction in the median DOT was achieved (7 versus 10 days, $P < 0.001$), which is similar to the reduction in DOTs noted in this study (6 versus 9 days, $P < 0.001$). However, Avdic *et al.*[12] published a single-centre study and included only 63 patients in the intervention group, making it difficult to evaluate the impact of the decrease in DOT on outcomes. Three other studies evaluated DOT as part of a multifaceted approach to optimize the management of CAP. Marcos *et al.*[14] evaluated the utilization of a CAP team to actively promote concordance with IDSA/ATS guidelines. They reported a shorter length of hospitalization and shorter duration of antibiotic therapy (6 days less, $P < 0.001$) in patients managed by the CAP team compared with patients managed by a general pulmonary team. No differences in clinical outcomes were reported, although there were only 65 patients in the study. Capelastegui *et al.*[15] conducted a CAP study in Spain, which included implementation of a guideline focused on triage of patients for admission, appropriate antibiotic selection, intravenous to oral switch and criteria for hospital discharge. This intervention demonstrated a significant impact on 30 day mortality [OR 2.14 (95% CI 1.23–3.72)] and in-hospital mortality [OR 2.46 (95% CI 1.37–4.41)]. However, they reported a relatively small decrease in antibiotic DOT (12.9 to 11.4 days, $P < 0.001$) with the intervention, potentially due to the passive design of this initiative, which lacked patient-specific prospective audit and feedback. Finally, Haas *et al.*[16] implemented a quasi-experimental stewardship study with 84 intervention patients (255 total patients), which focused on decreasing unnecessary fluoroquinolone utilization, decreasing unnecessary CT scans and cultures, and optimizing DOT. Through guideline and order set development, the median DOT decreased from 10 to 7 days ($P < 0.0001$); significant decreases in levofloxacin use, CT chest imaging and sputum cultures were also reported.[16] All of the previous published studies highlight the benefits of the ability of CAP-targeted stewardship interventions to reduce unnecessary antibiotic DOT, utilizing active or passive stewardship methods. However, this is the first multicentre study with a large sample size aimed at assessing the relationship of antibiotic duration and patient outcomes.

In our study, prospective audit and feedback by the stewardship teams in addition to robust education and dissemination of clinician tools resulted in increased compliance with IDSA/ATS duration recommendations. Prior to our intervention, guideline-concordant therapy was received by only 5.6% of admitted CAP patients. A recent Veterans Affairs study demonstrated a similar baseline compliance rate of 6.9%, suggesting guideline-discordant DOT is common at many institutions.[17] In our intervention group, guideline concordance increased to 42%, a significant improvement from baseline. While our improvement was robust, many patients still received guideline-discordant therapy. This compliance rate was lower than anticipated and may be due to numerous factors. Recommendations were made by the stewardship team upon documentation of patient clinical stability and not necessarily at time of discharge or on the last day of appropriate therapy. As a result, if the appropriate DOT was not documented within progress notes in the medical record, the stop date for antimicrobial treatment may have been forgotten or not passed on to the clinician caring for the patient at discharge and responsible for writing the discharge prescriptions. Furthermore, often a discharge prescription for 1–3 days of therapy would have been sufficient to complete the recommended course of therapy. Clinicians may have felt hesitant writing prescriptions for short durations with only a few tablets. These results and observations suggest further room for duration optimization.

As discussed, a variety of tactics have been utilized in disease-based efforts for CAP. Active disease-based stewardship strategies, such as the one utilized in our study, are labour-intensive and require daily dedicated AST time and resources. However, the multicentre nature of our initiative allowed for pooling of certain resources. Information and tools were shared between the centres, including educational slide decks, pocket cards and stewardship monitoring tools. This collaboration reduced the burden on each individual site, making implementation of the intervention more feasible. Further evaluations of inter-hospital partnerships for stewardship efforts are worthwhile.

Our study is with some notable limitations. First, we excluded all patients with CAP admitted to the ICU and with complications, such as empyema, limiting the applicability of our results to these populations. Furthermore, our follow-up period for clinical outcomes was 30 days post-discharge, a time period that may not capture all outcomes; however, it should be noted that the majority of disease-related outcomes would have occurred during this period. Our prospective audit and feedback component was conducted Monday–Friday, potentially omitting CAP patients treated outside those times. Lastly, our educational sessions were not repeated, potentially missing new, rotating clinicians at these three large teaching institutions.

In summary, in the largest CAP-targeted stewardship study to date, implementation of a multifaceted stewardship intervention targeted at optimizing the DOT for CAP patients admitted to

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medicine services resulted in a significant reduction in the duration of antimicrobial therapy, with increased compliance with IDSA/ATS recommendations and guideline-concordant therapy. Shorter durations of therapy in the intervention group did not result in increased adverse events, including recurrence of pneumonia, readmission and mortality, supporting that shorter durations of therapy are safe and appropriate for CAP management. As days of antimicrobial therapy were significantly reduced, future exploration into the economic impact of a CAP-targeted DOT initiative would be of great interest. Further studies into inter-hospital collaboration for stewardship efforts and methods to further increase compliance with IDSA/ATS recommendations are also warranted.

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Transparency declarations

None to declare.

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