**APPENDIX (SUPPLEMENTAL INFORMATION)**

**ANTIBIOTIC OVERUSE AFTER DISCHARGE FROM MEDICAL SHORT STAY UNITS**

Running Title: Antibiotic overuse in medical short stay units

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*Study Setting –* This retrospective cross-sectional study included patients hospitalized in either of two medical SSUs at a single academic medical center. The units care for patients requiring hospitalization with an anticipated stay of less than three days. In 2019, average length of stay was 50 hours. Neither SSU has dedicated antibiotic stewardship presence. However, many SSU physicians also round on the inpatient hospitalist service which has strong stewardship involvement, including rounding with clinical pharmacists to reinforce institutional antibiotic guidelines. Recent inpatient stewardship has targeted antibiotic overuse at discharge and excess antibiotic duration for community-acquired pneumonia (CAP) (1). Notably, the inpatient hospital medicine services performed in the top 25% of regional hospitals in both initiatives (2,3). All institutional guidelines related to antibiotic prescribing are accessible to SSU providers.

*Study Participants* – We included adult patients discharged from SSUs between May 2018 and September 2019 with one of four primary diagnoses: pneumonia, UTI, SSTI, or “other”. Patients with a diagnosis of pneumonia were identified using discharge diagnostic coding and included all patients treated for CAP, CAP with risk factors for drug resistance (healthcare-associated pneumonia [HCAP] under previously used guidelines), and those treated for pneumonia who did not meet guideline-based diagnostic criteria for pneumonia (4,5). Patients with a diagnosis of SSTI were identified using discharge diagnostic coding and included those treated for cellulitis, animal bite, and/or skin or soft tissue abscess. Patients with odontogenic involvement or preseptal/orbital cellulitis were included in the “other” category, along with cases of intra-abdominal infections (including acute uncomplicated diverticulitis, cholangitis with successful source control, and spontaneous bacterial peritonitis). Because ICD codes are neither sensitive nor specific for identifying UTI, we identified patients with a potential UTI based on presence of a positive urine culture, receipt of antibiotics, and no additional infectious diagnoses. Patients in this group included those with uncomplicated cystitis, complicated cystitis (male, immunosuppressed, or catheter-associated), pyelonephritis, and asymptomatic bacteriuria (ASB).

All potentially eligible patients received a random number and were reviewed in order of randomization until our target of 100 total patients were included (Appendix Figure 1).

The full list of exclusion criteria included: patients who did not receive antibiotics at discharge, patients being treated for an infection without a clear institutional guideline with respect to treatment duration or antibiotic selection (i.e. tenosynovitis, diabetic foot infection, bursitis, epididymo-orchitis, suppurative parotitis, bacteremia without clear source, deep traumatic SSTI with possible myositis, UTI with obstructing ureteral stone, SSTI with graft), patients on chronic suppressive antibiotics, patients diagnosed with multiple unrelated infections, severe immunosuppression (patients with AIDS [CD4 <0.200 x109 cells/L], neutropenia [ANC <0.500 x 109 cells/L], history of solid organ transplant or BMT, or receipt of two or more immunosuppressive agents), patients who were pregnant, those who failed to clinically improve within 72 hours of appropriate treatment (e.g., developed complication, required higher level of care, by day 3 still had >1 sign of clinical instability [heart rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, arterial saturation <90% on room air or oxygen requirement higher than at baseline, or altered mental status higher than at baseline]), those who were admitted from or discharged to hospice, and those admitted to or discharged from another service.

*Definition of Antibiotic Overuse after Discharge* - Antibiotic overuse was subdivided into categories that are common during care transitions based on prior studies (6-8): unnecessary antibiotic use, excess duration, and guideline discordant selection. The specific criteria for overuse was determined using prior guidelines (2,9,10). Unnecessary antibiotic use was defined as antibiotics prescribed for non-infectious disease states or non-bacterial infections (11), which included patients who did not meet guideline criteria for bacterial pneumonia (12) and patients with asymptomatic bacteriuria (9, 10). This was not assessed for SSTI due to the limitations of chart review and diagnoses were assumed to be correct. “Excess duration” was defined as antibiotics prescribed “beyond the indicated duration of therapy absent any clinical reason for a lengthened course” (11). This involved cases where the combined inpatient and outpatient duration of therapy was more than one day longer than recommended per internal institutional guidelines. Of note, though our institutional guidelines recommend 5-day treatment durations for patients with SSTI who are clinically improving, national guidelines allow for up to 7 days (13). Thus, we report the percentage of patients receiving an excess duration using a 7-day cutoff for SSTIs with clinical improvement. Any duration was considered appropriate for cases in which the patient had failed >72 hours of appropriate outpatient antibiotics. Guideline discordant selection was further categorized into suboptimal and inappropriate antibiotic use. Suboptimal use refers to antibiotics that, although potentially effective for the diagnosed infection, were inconsistent with institutional guidelines without documentation of or otherwise apparent rationale to avoid preferred agents. This includes suboptimal use of fluoroquinolone therapy defined as use of “fluoroquinolones (levofloxacin, ciprofloxacin, or [for pneumonia only] moxifloxacin) prescribed when a safer alternative was available after accounting for allergies, resistance, condition, and contraindications” (3). Inappropriate antibiotic selection includes antibiotics prescribed that did not cover the isolated or probable infectious organism(s). This included cases where the provider did not adjust treatment based on culture data when indicated.

Institutional treatment guidelines were considered the gold standard for antibiotic selection and treatment duration. A simplified form of institutional guidelines is available as a pocket-card to all providers (Appendix Figure 2) with complete guidelines accessible online (see Appendix Figure 2 footnote). A fully appropriate antibiotic regimen required a guideline-concordant antibiotic prescribed for an appropriate duration to treat a condition that was considered to be a bacterial infection. When evidence for appropriate treatment was conflicting, treatment was considered appropriate.

*Data Collection* – Patient data, including demographics, length of stay, Charlson comorbidity index, and primary care physician, were digitally extracted from the clinical data warehouse. Additional patient information manually collected by two independent reviewers in duplicate from the medical record included: diagnostic information, comorbidities, antibiotic prescriptions, culture results, clinical course details (e.g. source control procedures, consultations), and an assessment antibiotic appropriateness (see above). “Source control procedure” referred to patients who required a source control procedure (e.g. incision and drainage for purulent cellulitis or dental abscess) during their inpatient stay. For these cases, duration of treatment was calculated as beginning after this procedure occurred. Treatment duration was determined by manual review of the medication administration record and was rounded to the nearest half day.

The reviewers also evaluated for documented factors appearing to regularly influence antibiotic prescribing (“slow to respond”, “failure of outpatient therapy”) and lead to overuse including prescribing errors. “Slow to respond” was defined as patients documented by providers as demonstrating delayed clinical improvement despite having received less than 48-72 hours of appropriate therapy. “Failure of outpatient therapy” refers to patients who were documented as not clinically responding to preceding outpatient antibiotics despite having previously received an inappropriate regimen, less than 72 hours of appropriate therapy, or antibiotics without source control when indicated. This included patients with purulent cellulitis who had received seemingly appropriate antibiotics but had not yet undergone source control. “Miscalculation of duration” included cases where the provider documented duration of therapy differed from the duration received by the patient (e.g. stating 7 days were prescribed in discharge summary when 9 days were actually prescribed) as well as cases that failed to account for inpatient therapy in the total duration (e.g. giving the guideline recommended number of days as outpatient therapy but not including inpatient days of therapy already given).

Comorbidities recorded included moderately immunosuppressed (defined as HIV with CD4 count above 0.200 × 109 cells/L, chemotherapy within 30 days, treatment for leukemia or lymphoma within 6 months, long-term steroid use (≥10 mg of prednisone per day or equivalent), use of a biologic agent (such as a tumor necrosis factor inhibitor), or presence of a congenital or acquired immunodeficiency (for example, asplenia, nephrotic syndrome, or renal transplant >1 year prior), otherwise immunosuppressed (defined as immunosuppression not meeting definition for severe or moderate immunosuppression as previously described), type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), and cirrhosis.

*Data analysis -* Interquartile range for datasets were calculated using Microsoft Excel. This method varies from the more commonly used method of calculating quartiles. In this method, percentiles are assigned to each value in the array. Values before and after the specific percentile (25th and 75th) are identified, and the quartile is identified by linearly interpolating between these values based on the percentile. As such, reported quartile values may be reported as rounded to the nearest tenth.

1. **Appendix Figures**

**![Diagram

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**eFigure 1. Study Flow Diagram**

All potentially eligible patients discharged between 5/2018 and 9/2019 received a random number 1-276 and were reviewed in order of randomization until our target of 100 total patients were included for final analysis. Abbreviations: MSSU = Medical Short Stay Unit; UTI = urinary tract infection; SSTI = skin and soft tissue infection.

Table

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**eFigure 2. Institutional Guidelines Pocket-Card**

Appropriate treatment duration for SSTIs was considered to be 7 days for this study, rather than 5 days as shown in this card. These guidelines in full detail, including for other infection types, can be found online at: <https://www.med.umich.edu/asp/adult.html>

1. **Appendix Tables**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **eTable 1. Common Factors Influencing Antibiotic Use, Overall and by Disease State** | | | | | | |
|  |  |  | | | |  |
| **INFLUENCING FACTORS** | **ALL** | **DISEASE STATE** | | | | **EXAMPLE OF FACTOR INFLUENCING OVERUSE** |
|  |  |  | | | |  |
|  |  | **Pneumonia** | **UTI** | **SSTI** | **Other** |  |
|  | **(N = 100)** | **(N = 22)** | **(N = 21)** | **(N = 47)** | **(N = 10)** |  |
| Consultant involved, n (%) | 33 (33%) | 3 (14%) | 1 (5%) | 21 (45%) | 8 (80%) | Despite institutional guidelines recommending 5 days, an ID consultant recommended 14 days of cefazolin for improving non-purulent cellulitis due to patient's history of prior cellulitis. |
| & Had antibiotic overuse, n (%) | 27 (27%) | 1 (5%) | 1 (5%) | 19 (40%) | 6 (60%) |
|  |  |  |  |  |  |
| Source control procedure, n (%) | 21 (21%) | 0 | 0 | 20 (43%) | 1 (10%) | Patient with dental abscess failed to improve on ampicillin-sulbactam prior to source control and was changed to levofloxacin and metronidazole. Patient rapidly improved after source control but was still discharged on levofloxacin and metronidazole. |
| & Had antibiotic overuse, n (%) | 16 (16%) | 0 (X%) | 0 (X%) | 16 (34%) | 0 (X%) |
|  |  |  |  |  |  |
| Slow to respond a, n (%) | 9 (9%) | 1 (5%) | 0 | 8 (17%) | 0 | Patient remained febrile for 24 hours following initiation of appropriate antibiotics (vancomycin for cellulitis) but then improved. Despite this patient was described as “slow to respond” and prescribed an excess duration at discharge. |
| & Had antibiotic overuse, n (%) | 8 (8%) | 0 (X%) | 0 (X%) | 8 (17%) | 0 (X%) |
|  |  |  |  |  |  |
| Failed outpatient therapy b, n (%) | 21 (21%) | 1 (5%) | 1 (5%) | 16 (34%) | 3 (30%) | Patient admitted due to worsening non-purulent cellulitis despite 72 hours of doxycycline as outpatient. Patient then improved on vancomycin and transitioned to and discharged on prolonged course of trimethoprim-sulfamethoxazole. |
| & Had antibiotic overuse, n (%) | 14 (14%) | 1 (5%) | 1 (5%) | 10 (21%) | 2 (20%) |
|  |  |  |  |  |  |
| Miscalculation of duration c, n (%) | 20 (20%) | 3 (14%) | 7 (33%) | 8 (17%) | 2 (20%) | Discharge summary intended planned 14 days of therapy for pyelonephritis, but patient received 11 outpatient days plus 4.5 days of inpatient therapy for excess total duration. |
| & Had antibiotic overuse, n (%) | 18 (18%) | 2 (9%) | 7 (33%) | 7 (15%) | 2 (20%)X%) |
|  |  |  |  |  |  |
| Positive culture data present, n (%) | 45 (45%) | 7 (32%) | 21 (100%) | 16 (34%) | 1 (10%) | Patient discharged on cephalexin for UTI. This choice was not changed despite *Enterococcus* growing in urine culture. |
| & Had antibiotic overuse (due to failure to adjust based on culture data d, n (%) | 7 (7%) | 1 (5%) | 3 (14%) | 2 (4%) | 1 (10%) |
|  |  |  |  |  |
| See appendix for definition of disease states. Percentages listed for disease states included all patients with that disease state. Abbreviations: UTI = urinary tract infection; SSTI = skin and soft tissue infection; ID = Infectious Disease. | | | | | | |
| a Slow to respond was defined as documentation by providers of delayed clinical improvement despite a patient having received less than 48-72 hours of appropriate therapy | | | | | | |
| b Failure of outpatient therapy was defined as documentation by providers of a patient not clinically improving on preceding outpatient antibiotics despite the patient having previously received an inappropriate regimen or less than 72 hours of an appropriate regimen. | | | | | | |
| c Miscalculation of duration was defined as stating a total duration in the discharge summary that did not match actual duration of prescribed antibiotics or prescribing guideline-recommended days of outpatient therapy but not including inpatient days of therapy already received. | | | | | | |
| d For culture data, antibiotic overuse row only includes instances where antibiotics were not appropriately changed as a result of culture data. | | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 2. Comparing Characteristics of Discharge Antibiotic Cases by Appropriateness Category, Bivariable Analyses** | | | | | | | |
|  | |  | | |  | | |
| **CHARACTERISTIC** | | **OVERALL APPROPRIATENESS** | | | **DURATION a** | | |
|  | |  | | |  | | |
|  |  | **Appropriate** | **Antibiotic Overuse** | **P-value** | **Appropriate Duration** | **Excess Duration** | **P-value** |
|
| Demographics | n | 22 | 78 | N/A | 44 | 54 | N/A |
| Age, mean years (SD) | 53.1 (17.0) | 61.5 (18.8) | 0.063 | 57.3 (19.7) | 61.4 (17.9) | 0.283 |
| Gender, # Female (%) | 16 (73%) | 41 (53%) | 0.092 | 29 (66%) | 28 (52%) | 0.161 |
| Race, # White (%) | 12 (55%) | 68 (87%) | 0.001 | 32 (73%) | 46 (85%) | 0.128 |
| Median Charlson score (IQR) | 2 (1, 4) | 3 (1, 8) | 0.058 | 3 (1, 8) | 3 (1, 7) | 0.939 |
| Disease State | Pneumonia (n = 22), n (%) | 8 (36%) | 14 (18%) | 0.066 | 14 (32%) | 8 (15%) | 0.045 |
| UTI (n = 21), n (%) | 4 (18%) | 17 (22%) | 0.713 | 12 (27%) | 9 (17%) | 0.203 |
| SSTI (n = 47), n (%) | 8 (36%) | 39 (50%) | 0.258 | 15 (34%) | 32 (59%) | 0.013 |
| Other (n = 10), n (%) | 2 (9%) | 8 (10%) | 0.872 | 3 (7%) | 5 (9%) | 0.661 |
| Clinical Data & Admission Details | Length of stay, median days (IQR) | 2.3 (1.5, 4.0) | 3.0 (1.9, 4.2) | 0.341 | 2.2 (1.7, 4.1) | 3.0 (2.6, 4.6) | 0.423 |
| Culture data available, n (%) | 10 (46%) | 35 (45%) | 0.961 | 24 (55%) | 21 (39%) | 0.122 |
| ID consultant involved, n (%) | 2 (9%) | 16 (21%) | 0.218 | 3 (7%) | 15 (28%) | 0.008 |
| Any consultant involved, n (%) | 6 (27%) | 27 (35%) | 0.518 | 9 (21%) | 22 (41%) | 0.032 |
| Source control procedure, n (%) | 5 (23%) | 16 (21%) | 0.822 | 7 (16%) | 14 (26%) | 0.229 |
| "Slow to respond" b, n (%) | 1 (5%) | 8 (10%) | 0.408 | 2 (5%) | 7 (13%) | 0.151 |
| "Failed outpatient therapy" c, n (%) | 4 (18%) | 8 (10%) | 0.312 | 5 (11%) | 6 (11%) | 0.969 |
| Flouroquinolone use, n (%) | 0 (0%) | 9 (12%) | 0.095 | 5 (11%) | 4 (7%) | 0.500 |
| Beta-lactam use, n (%) | 15 (68%) | 43 (55%) | 0.273 | 24 (55%) | 33 (61%) | 0.512 |
| P-values calculated using Chi-squared, Fisher exact, or two-sided t-tests, as appropriate. \* next to p-value indicates p < 0.05, which was considered significant. Percentages listed are using N of that appropriateness category. Abbreviations**:** SD = standard deviation; IQR = interquartile range; PCP = primary care physician; UTI = urinary tract infection; SSTI = skin and soft tissue infection; ID = Infectious Disease; ED = emergency department. N/A indicates not applicable because values were 0. | | | | | | | |
| a Total n = 98 for Duration characteristic as 2 cases were characterized as “too short duration” and not shown here. | | | | | | | |
| b “Slow to respond” was defined as the presence of documentation or data reflecting minimal clinical improvement within the first 24 or 48 hours of appropriate therapy. | | | | | | | |
| c “Failure of outpatient therapy” was defined as the lack of clinical improvement despite at least 72 hours of preceding outpatient antibiotics. | | | | | | | |

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