Early Antibiotic Discontinuation or De-escalation in High-Risk Patients With AML With Febrile Neutropenia and Prolonged Neutropenia

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ABSTRACT

Background: There is minimal data evaluating the safety of antibiotic de-escalation in patients with acute myeloid leukemia (AML) with fever and ongoing neutropenia. Therefore, this study evaluated antibiotic prescribing, infection-related outcomes, and patient outcomes of an antibiotic de-escalation initiative. Patients and Methods: This pre–post quasiexperimental study included adult patients with AML hospitalized with febrile neutropenia. An antibiotic de-escalation guideline was implemented in January 2017, which promoted de-escalation or discontinuation of intravenous antipseudomonal ß-lactams. The primary outcome assessment was the incidence of bacterial infection in a historical control group before guideline implementation compared with an intervention group after guideline implementation. Results: A total of 93 patients were included. Antibiotic de-escalation occurred more frequently in the intervention group (71.7% vs 7.5%; P < .001), which resulted in fewer days of therapy for intravenous antipseudomonal ß-lactams (14 vs 25 days; P < .001). Thirty-day all-cause mortality and length of hospitalization were not different between groups. However, the intervention group had significantly fewer episodes of Clostridioides difficile colitis (5.7% vs 27.5%; P = .007). Conclusions: Implementation of an antibiotic de-escalation guideline resulted in decreased use of intravenous antipseudomonal ß-lactams and fewer episodes of C difficile colitis, without adversely impacting patient outcomes. Additional studies are needed, preferably in the form of randomized controlled trials, to confirm these results.


Background

The optimal duration of antibiotic therapy for patients with febrile neutropenia (FN) remains unknown. The Infectious Diseases Society of America recommends broad-spectrum intravenous antibiotic therapy until neutrophil count recovery for high-risk patients with FN.1 NCCN suggests that de-escalation can be considered in patients without documented infection. In patients with documented infection, de-escalation may be influenced by neutrophil recovery, defervescence, infection site, infecting pathogen, and underlying illness, but specific recommendations based on these factors are not provided.2 Both of these recommendations are based on poor- to moderate-quality evidence derived from either limited clinical data or expert opinion. The European Conference on Infections in Leukemia recommends streamlining of antibiotic therapy based on clinical course, although this is also limited to patients without documented infection and is supported by minimal evidence.3 Patients with acute myeloid leukemia (AML) develop severe, prolonged neutropenia after high-intensity induction chemotherapy.1–3 Based on current practice guidelines, this has the potential to result in intravenous antipseudomonal ß-lactam exposure for weeks, regardless of clinical course or identification of infection. Prolonged antimicrobial therapy is a known risk factor for development of infection with multidrug-resistant (MDR) organisms and Clostridioides difficile (CDI), which is common in hospitalized oncology patients.4–6 In addition, emerging data suggest that disruption of the human microbiome, a known consequence of antimicrobial exposure, is also associated with an increase in infectious complications after reinduction chemotherapy in patients with leukemia.7 There is increased interest in exploring the impact of intravenous antibiotic de-escalation in patients at high risk for FN who have an underlying hematologic malignancy or are receiving allogeneic hematopoietic cell transplants (allo-HCTs).8–10 A recent randomized, open-label, multicenter study in patients with FN without a
documented infectious source showed an overall reduction in empirical antimicrobial therapy (EAT)–free days without adversely affecting clinical outcomes. It is worth noting the inclusion of lower-risk patients with lymphomas or multiple myeloma, and those receiving consolidation chemotherapy in that study. Because high-intensity induction chemotherapy is expected to lead to prolonged periods of severe neutropenia in patients with AML, we aimed to evaluate the impact of an antibiotic de-escalation guideline in this high-risk group.

**Patients and Methods**

**Study Design and Participants**

We conducted a single-center, pre-post, quasi-experimental study at a licensed 1,000-bed tertiary care academic medical center with 120 dedicated oncology beds (Michigan Medicine). Adult patients (age ≥18 years) with FN who underwent high-intensity induction chemotherapy for either newly diagnosed or relapsed/refractory AML were included. The primary outcome of the study was to evaluate the incidence of infection after implementation of a de-escalation guideline compared with a historical cohort before guideline implementation. The study period included patients hospitalized between September 2015 and February 2018. The historical and intervention groups consisted of patients admitted to Michigan Medicine before and after implementation of the guideline. Subjects were identified using the University of Michigan Leukemia and Bone Marrow Transplant Database, which includes every patient diagnosed with acute leukemia. Manual chart review was conducted to collect data for all patients, and data were stored securely within the RedCap data collection tool. Patients receiving nonintensive induction chemotherapy approaches (ie, hypomethylating agent-based therapy) were excluded. Patients were also excluded if they were admitted as a transfer from an outside hospital, died within 5 days of FN onset, or recovered their neutrophil count within 5 days of FN onset.

**Definitions**

The following definitions were used in the present study:

- **Febrile neutropenia**: a single oral temperature ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-hour period in patients with an absolute neutrophil count <500 cells/mm³ or expected to decrease to <500 cells/mm³ within 48 hours.

- **Low suspicion for bacterial infection**: absence of positive bacterial cultures and no evidence of bacterial infection based on imaging or physical examination as documented in the electronic medical record (EMR) by the patient’s treating physician.

- **Suspected bacterial infection**: imaging or physical examination findings suggestive of bacterial infection as documented in the EMR by the patient’s treating physician without positive bacterial cultures.

- **Documented bacterial infection**: positive bacterial cultures plus imaging or physical examination findings consistent with infection as documented in the EMR by the patient’s treating physician.

**Guideline Development**

Michigan Medicine has a guideline for initial treatment of FN that was unchanged during both study periods. For initial workup of FN, the guideline recommends 2 sets of blood cultures (central and peripheral), a chest radiograph, urine culture, and considerations for throat, sputum, stool, and wound cultures, as appropriate.

The preferred intravenous antipseudomonal β-lactam is piperacillin/tazobactam, and cefepime or meropenem are reserved for patients with previous antimicrobial resistance or antimicrobial intolerance. There was no guidance provided for de-escalation of antimicrobial therapy in the guideline during the control period.

An updated guideline, which included recommendations for antibiotic de-escalation, was developed by a multidisciplinary group of hematologists, infectious diseases physicians, and clinical pharmacists. The guideline was approved by the Michigan Medicine Pharmacy and Therapeutics Committee and implemented in January 2017. Prior to the development of the guideline, antibiotic duration of therapy was dictated by the treating physician. Education was provided to hematology/oncology physicians, advanced practice providers, and clinical pharmacists both in person and via email after implementation. The guideline was published and readily accessible to clinicians via the Michigan Medicine Antimicrobial Stewardship Program webpage. Guideline adherence was promoted daily on patient care rounds by inpatient hematology/oncology clinical pharmacist specialists.

The guideline recommended a clinical assessment at day 5 of antibiotic therapy and then stratified de-escalation or discontinuation based on clinical stability, identification of infection/causative pathogen, and resolution of fever (Figure 1). To proceed with antibiotic de-escalation, patients needed to be afebrile for a minimum of 48 hours and clinically stable as determined by the treating physician. Patients meeting criteria for de-escalation were then categorized into 1 of 3 groups: those with (1) low suspicion for bacterial infection, (2) suspected bacterial infection, or (3) documented bacterial infection. These categories applied to patients at the initial onset of FN and after de-escalation of antimicrobial therapy. Patients not meeting criteria for de-escalation at day 5...
were reevaluated daily thereafter. In patients with newly diagnosed AML with a low suspicion for bacterial infection, intravenous antipseudomonal β-lactam therapy was discontinued once clinical criteria were met. In patients with newly diagnosed AML and a suspected bacterial infection, intravenous antibiotic therapy was tailored to target the suspected source of infection and then discontinued after the treatment course was completed. The guideline provided duration of therapy recommendations for several infectious diseases. Lastly, in patients with newly diagnosed AML with documented bacterial infection, antibiotic therapy was tailored to the susceptibility profile of the isolated pathogen and continued for an appropriate duration of therapy as outlined in the guideline. In all 3 groups, patients with relapsed/refractory AML were de-escalated to a fluoroquinolone for prophylaxis after initial presentation of febrile neutropenia in patients with AML following chemotherapy.

Start broad-spectrum intravenous antibiotics per protocol, obtain cultures, and perform appropriate workup for source of infection.

Evaluate for de-escalation at day 5

Low suspicion for bacterial infection
- All bacterial cultures are negative
- No suggestion of bacterial infection on imaging studies or physical examination

Suspected bacterial infection
- All bacterial cultures are negative
- Imaging studies or physical examination suggest possible bacterial infection

Documented bacterial infection
- Positive bacterial cultures, plus imaging or physical examination finding consistent with infection

Treatment recommendations
- Clinically stable and afebrile for 48 hours, then de-escalate therapy as below

- Patients with newly diagnosed AML: discontinue antibiotic therapy, including antipseudomonal β-lactam, with daily assessment for potential infection
- Patients with relapsed/refractory AML: de-escalate to levofloxacin, 500 mg daily

- Clinically stable and afebrile for 48 hours, then tailor therapy to target suspected source of infection
- See below for duration recommendations

- Patients with newly diagnosed AML: discontinue antibiotic therapy according to duration of therapy recommendations with daily assessment for potential infection
- Patients with relapsed/refractory AML: de-escalate to levofloxacin, 500 mg daily

- Patients with newly diagnosed AML: discontinue antibiotic therapy according to duration of therapy recommendations with daily assessment for potential infection
- Patients with relapsed/refractory AML: de-escalate to levofloxacin, 500 mg daily

Daily monitoring for signs and symptoms of infection
Reinitiate intravenous antipseudomonal β-lactam therapy if:
- Fever (temperature ≥38.3°C or ≥38.0°C sustained for 1 hour)
- Positive bacterial cultures, physical examination, or radiographic imaging with probable or documented bacterial infection

Figure 1. Antibiotic de-escalation in clinically stable and afebrile adult patients with AML.
Abbreviation: AML, acute myeloid leukemia.
intravenous antibiotic discontinuation. Monitoring for signs and symptoms of infection after de-escalation was performed daily, and intravenous antipseudomonal β-lactam therapy was restarted in any patient who recovered or in whom infection was suspected, per institutional FN guidelines. In any patient who required readmission, an attending oncologist and the oncology team, and the attending oncologist made the final decision to adhere to or deviate from the guideline.

Outcomes
The primary efficacy endpoint was the incidence of suspected or documented bacterial infection after antibiotic de-escalation. In the historical group, outcomes were assessed no sooner than day 5 of FN onset after patients would have met clinical criteria for de-escalation as described in the intervention group. The primary endpoint was assessed until the time of absolute neutrophil count recovery or hospital discharge. Secondary outcomes included the incidence of CDI within 30 days of resolution of neutropenia, intravenous antipseudomonal antibiotic days of therapy (DoTs), hospital length of stay (LoS), all-cause mortality at 30 days, and incidence of new-onset methicillin-resistant Staphylococcus aureus or vancomycin-resistant Enterococcus faecium colonization at 30 days. Our microbiology laboratory uses a 2-step CDI enzyme immunoassay and toxin test and runs CDI tests only for patients with unformed stools. Methicillin-resistant S. aureus and vancomycin-resistant E. faecium colonization are assessed at baseline and weekly thereafter.

Statistical Analysis
Data were analyzed using SPSS Statistics, version 25 (IBM Corp). Descriptive statistical analysis was performed for patients’ baseline demographic characteristics. Dichotomous variables were compared using a Pearson chi-square test or Fisher exact test when appropriate. Continuous variables with nonparametric distributions were expressed as medians with corresponding interquartile ranges, and categorical variables were expressed as numbers with corresponding percentages. The Mann-Whitney U test was performed to compare differences between groups with nonparametric data. A P value <.05 was considered statistically significant for all comparisons.

Results
Patients hospitalized between September 2015 and February 2018 were assessed for inclusion. A total of 163 patients with an admitting diagnosis of AML were identified, of whom 70 were excluded (Figure 2). The most common reason for exclusion was treatment with a hypomethylating agent (n=36). A total of 93 patients met criteria for inclusion (40 in the historical group and 53 in the intervention group). Baseline characteristics were similar between the groups (Table 1). At the time of antibiotic de-escalation, both groups had a similar number of patients with a low suspicion for bacterial infection and documented bacterial infection, whereas more patients in the historical group had a suspected bacterial infection designation (10% vs 0%; P=.03). The duration of initial fever was also similar between the historical and intervention groups (4 vs 3 days, respectively; P=.15) (Table 2).

The incidence of suspected or documented bacterial infection in the historical and intervention groups was similar (18 [45%] vs 18 [34%]; P=.29). All-cause mortality at 30 days and hospital LoS were also similar between the groups (Table 3). Total antipseudomonal β-lactam DoTs were significantly less in the intervention group than in the historical group (14 vs 25; P<.001), and the incidence of CDI was also significantly lower (3 [5.7%] vs 11 [27.5%], respectively; P=.007). Patients in the intervention group were more likely to have their intravenous antipseudomonal antibiotics de-escalated during their episode of neutropenia (38 [71.7%] vs 3 [7.5%]; P<.001). In the intervention group, 27 patients had intravenous antipseudomonal antibiotics restarted after initial de-escalation or discontinuation. A total of 28 pathogens were identified (15 in the historic group vs 13 in the intervention group), and the pathogen distribution is reported in Table 4.
Discussion
The use of broad-spectrum antibiotics has significantly reduced mortality rates in patients with FN. Despite this, there remain limited data to help guide appropriate duration of antimicrobial prescribing. The Infectious Diseases Society of America recommendation to continue broad-spectrum intravenous antibiotic therapy until neutrophil count recovery is supported by the assertion that “years of experience have proven this approach to be safe and effective.” In recent years, clinical data in several other infectious diseases have shown that shorter courses of antibiotic therapy are just as effective as longer courses and may be associated with fewer adverse effects or the development of resistance. Because patients with hematologic malignancies rely on effective antimicrobial therapy for prevention and management of infectious complications, there remains an ongoing need for antimicrobial stewardship interventions to minimize unnecessary antimicrobial exposure and potentially slow the development of resistance.

To our knowledge, this is the first study to assess the impact of an antibiotic de-escalation algorithm in high-risk patients with AML and FN. Five days was chosen in our intervention as the assessment point for de-escalation because 5 to 7 days is the median time to defervescence described in the literature and because all culture results and imaging studies are generally completed within 5 days. In addition, shorter antibiotic courses of 5 to 7 days have been shown to be noninferior to longer treatment durations for several infectious disease states.

Kroll et al previously evaluated the safety of antibiotic de-escalation in high-risk patients with FN after receipt of EAT for 14 days and did not observe a difference in the rate of re-fever or need for escalation of antibiotic therapy.
Similarly, a study in allo-HCT recipients with FN without a documented or clinically diagnosed source of infection who were de-escalated to fluoroquinolone prophylaxis at day 5 did not have a higher rate of recurrent fever (15% vs 19%; \( P = .026 \)). A more recent multicenter study randomized patients with FN undergoing allo-HCT or receiving treatment for a hematologic malignancy with no etiologic diagnosis to either stop antibiotic therapy after 72 hours of apyrexia and clinical recovery or continue until neutrophil count recovery. The authors observed a decrease in EAT-free days (13.6 vs 16.1, respectively; absolute difference, \(-2.4 [95\% \text{ CI}, -4.6 \text{ to } -0.3]; P = .026\)) without an impact on total days of fever or all-cause mortality.

Our study has several notable differences from these publications that are worth noting. Patients were candidates for antibiotic de-escalation or discontinuation as early as day 5 of FN onset. In addition, fluoroquinolone prophylaxis was only routinely recommended for patients with relapsed/refractory AML after completion of empirical or definitive therapy. Patients with de novo AML without...

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### Table 3. Infection- and Treatment-Related Endpoints After De-escalation Intervention

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Historical Group ( n \ (% ) )</th>
<th>Intervention Group ( n \ (% ) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of suspected or documented infection after antibiotic de-escalation*</td>
<td>18 (45.0)</td>
<td>18 (34.0)</td>
<td>.29</td>
</tr>
<tr>
<td>All-cause mortality at 30 d</td>
<td>6 (15.0)</td>
<td>6 (11.3)</td>
<td>.76</td>
</tr>
<tr>
<td>Hospital LoS, median (IQR), d</td>
<td>29 (24–37)</td>
<td>27 (24–39)</td>
<td>.47</td>
</tr>
<tr>
<td>Incidence of CDI</td>
<td>11 (27.5%)</td>
<td>3 (5.7%)</td>
<td>.007</td>
</tr>
<tr>
<td>De-escalation of IV antipseudomonal therapy</td>
<td>3 (7.5%)</td>
<td>38 (71.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IV antipseudomonal DoT, median</td>
<td>25</td>
<td>14</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridioides difficile infection; DoT, days of therapy; IQR, interquartile range; IV, intravenous; LoS, length of stay.

*Patients in both groups were counted as having developed infection after meeting criteria for de-escalation (clinical stability between days 5 and 7), regardless of whether IV antipseudomonal antibiotics were continued or de-escalated.

### Table 4. Pathogens Retrieved From Patients With Documented Bacterial Infection After Antibiotic De-escalation

<table>
<thead>
<tr>
<th>Organism</th>
<th>Historical Group ( n \ (% ) )</th>
<th>Intervention Group ( n \ (% ) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achromobacter spp</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4 (26.6)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>—</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2 (13.3)</td>
<td>—</td>
</tr>
<tr>
<td>Leptotrichia spp</td>
<td>—</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 (13.3)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulicatella adiacens</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Streptococcus salivarius</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methicillin-susceptible Staphylococcus aureus</td>
<td>1 (6.7)</td>
<td>—</td>
</tr>
<tr>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>—</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Vancomycin-susceptible Enterococcus faecalis</td>
<td>—</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus faecium</td>
<td>—</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td>—</td>
<td>1 (7.7)</td>
</tr>
</tbody>
</table>
an identified infectious source were de-escalated off antibiotics entirely, and no fluoroquinolone prophylaxis was provided. Levofoxacin was used in patients with relapsed/refractory AML, primarily based on data showing a significant reduction in the rate of gram-negative bacteremia in that specific population.\(^15\)\(^16\) Our study also addressed antibiotic de-escalation in patients with suspected or microbiologically confirmed bacterial infection, a group that has not been evaluated in previous publications. In contrast with other studies that evaluate a heterogeneous group of patients with both low- and high-risk hematologic malignancies, we evaluated the impact of antibiotic de-escalation in one of the highest-risk leukemia groups. Lastly, although the data that are currently available suggest that antibiotic de-escalation may be safe, the primary focus has been on surrogate (eg, recurrence of fever) or antimicrobial-related endpoints (eg, DoTs). Our primary endpoint was development of infection after de-escalation of broad-spectrum antimicrobial therapy during an episode of FN, an endpoint more relevant to clinicians.

With respect to the primary outcome of rate of infection after antibiotic de-escalation, it is reassuring that no trend toward worse outcomes was identified. In fact, the rates of infection after antibiotic de-escalation and all-cause mortality were numerically lower in the intervention group. However, this study is limited by the relatively small number of patients, and future larger studies are needed to accurately quantify the impact of de-escalation on clinical outcomes. In addition, this pre-post study design evaluated prescribing after guideline implementation, but adherence to the guideline was based on clinical judgment and may lead to interprescriber bias in antibiotic choice and duration.

Mortality rates of up to 18% have been described in the literature for high-risk patients with FN and gram-negative bacteremia.\(^17\) The observed mortality rates of 15% and 11% in the historical and intervention groups, respectively, are in line with this figure. Given the known differences in observed mortality rates between gram-positive and gram-negative bacteremia in this high-risk group (18% vs 5%, respectively), the etiologic shift from mostly gram-negative cases in the historical group to mostly gram-positive cases in the intervention group is worth exploring further in future studies.\(^17\)

Antibiotic exposure has been strongly associated with the development of CDI and in many instances is a modifiable risk factor.\(^18\) Patients in the intervention group in our study had a significant reduction in intravenous antipseudomonal β-lactam DoTs with a corresponding nearly 5-fold reduction in rates of CDI (27.5% vs 5.7%; \(P=.007\)). To our knowledge, this is the first study to show a significant reduction in rates of CDI in this population after implementation of a de-escalation effort. Given the known morbidity and attributable mortality associated with CDI, efforts should be made to mitigate its negative effects. It is worth noting that the overall reduction in total antipseudomonal antibiotic DoTs was noted despite a high rate of reinitiation after initial de-escalation. This may be explained by the fact that all patients in the intervention group were candidates for subsequent de-escalation once clinical criteria were met.

Additional limitations of this study include its retrospective study design, which may not account for all possible confounders between the study arms. De-escalation recommendations were provided by pharmacists in the intervention group but were ultimately at the discretion of the treating physician in both groups. Although patients were de-escalated more often in the postintervention group, roughly 30% remained on intravenous broad-spectrum antibiotic therapy throughout their period of neutropenia. Although the rationale for continuation of antibiotic therapy is hard to fully characterize due to the retrospective nature of this study, a 70% rate of compliance is higher than what has been reported previously for guideline-based management of FN.\(^19\) This is likely a result of a multidisciplinary intervention that provided daily reinforcement by hematology/oncology-trained clinical pharmacist specialists. This underscores the important role that multidisciplinary teams play in promoting antimicrobial stewardship efforts in oncology patients. Moreover, although we assessed for de-escalation from intravenous antipseudomonal therapy during the period of neutropenia, we did not assess for compliance with all aspects of the guideline. In addition, the findings of this study are limited to a single center, rely extensively on documentation available in EMRs, and may not be generalizable to other facilities. Finally, because of the low rate of MDR infections in our AML population, we were not able to capture the impact of antibiotic de-escalation on the incidence of MDR organisms in patients undergoing AML induction or in those proceeding to allo-HCT. Our study was limited in the duration of follow-up, and our inability to follow patients for months or years also limits our ability to characterize the impact of this intervention on future infections with MDR organisms. However, it is possible the significant reduction in antipseudomonal DoTs (11 days) in this setting will have a positive long-term impact on resistance patterns in these high-risk patient populations.

Conclusions

An antibiotic de-escalation guideline in clinically stable, febrile patients with AML and FN did not affect the rate of bacterial infection after antibiotic de-escalation, all cause-mortality, or hospital LoS. Although additional studies are needed, preferably in the form of blinded, randomized controlled trials, this study adds to the
increasing body of literature suggesting that antibiotic de-escalation in this population is safe and can result in a significant reduction in antipseudomonal DoT and CDI incidence.

References


Author contributions: All authors helped develop the project, implement the intervention, analyze the results, and develop the manuscript.

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