

Practicing Antimicrobial Stewardship: De-Escalating Antibiotics in Patients With Acute Myeloid Leukemia and Neutropenic Fever

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We compared risk of recurrent fever in patients with acute myeloid leukemia undergoing induction chemotherapy with febrile neutropenia without an infectious source in which antibacterials were de-escalated before neutrophil recovery versus continued. There was less recurrent fever when antibacterials were de-escalated early with no increased adverse events.

Keywords: acute myeloid leukemia, antimicrobial stewardship, neutropenic fever.

In the era of increased antibiotic resistance, minimizing the use of broad-spectrum antibiotics is essential. Prolonged use of broad-spectrum antibiotics is associated with increased risk of multidrug-resistant organisms, *Clostridioides difficile* infection (CDI), and invasive fungal infection [1]. Antimicrobial stewardship is underutilized in patients with febrile neutropenia (FN). In FN, a pathogen is only identified 20%–30% of the time, leaving most patients without an identifiable infectious source of fever [2]. Optimal antibiotic duration in these patients is unknown. Infectious Diseases Society of America guidelines that drive US practice state that in neutropenic patients with unexplained fever, the initial antibiotic regimen should continue until the absolute neutrophil count (ANC) is greater than 500 cells/ μ L [3]. European Conference on Infections in Leukemia guidelines differ and state that empiric antibiotics can be discontinued after 72 hours in patients who have been

hemodynamically stable since presentation and afebrile for at least 48 hours, irrespective of ANC [4]. We sought to determine whether there was a difference in risk of recurrent fever in patients with acute myeloid leukemia (AML) undergoing induction chemotherapy who developed FN without an identifiable infectious source in which antibacterials were de-escalated before neutrophil recovery compared with those in which antibacterials were continued until neutrophil recovery.

METHODS

We conducted a retrospective chart review of adult patients with AML who underwent induction chemotherapy with “7 + 3” (cytarabine and an anthracycline) at the Mount Sinai Hospital in New York, NY from 2009 to 2017. Patients were included if they developed FN, defined as a temperature of 100.4°F for 1 hour or a single temperature of 101°F in patients with an ANC less than 500 cells/ μ L. Escalation of antibiotics was defined as changing from either no antibiotic or prophylactic levofloxacin to broad-spectrum, antipseudomonal intravenous therapy with either piperacillin-tazobactam, cefepime, carbapenems, or aztreonam. De-escalation was defined as changing from broad-spectrum intravenous therapy to either prophylactic levofloxacin or cessation of antibiotics. Patients were excluded if they had an identifiable infectious source, either microbiologically (positive culture from a sterile site) or clinically (based on physical exam and radiographic findings). To compare baseline characteristics, we classified patients as belonging to the short-duration (SD) group that had antibiotics de-escalated before achieving ANC recovery (ANC of \geq 500 cells/ μ L) or the long-duration (LD) group that had escalated antibiotics continued until ANC recovery. The primary outcome was risk of recurrent FN. Secondary outcomes were adverse events related to antibiotics, intensive care unit (ICU) transfer, and all-cause in-hospital mortality.

Because the patients in the SD group switched from receiving escalated antibiotics to de-escalated antibiotics at variable times before ANC recovery, the model needed to account for the time-varying nature of the data and multiple recurrent FN episodes. The Anderson-Gill [5] (AG) model with a time-varying covariate for de-escalation was used to estimate the hazard ratio (HR) for risk of recurrent FN associated with de-escalation of antibiotics. The AG model used a counting style process in which a subject with multiple FNs was considered as multiple subjects for analytic purposes. The Lin and Wei robust sandwich variance estimator was used to account for multiple FN events per subject. De-escalation of antibiotics was treated as a time-varying covariate in which any patient that had antibiotics de-escalated was represented in both the escalation and de-escalation groups, whereas a patient that never had antibiotics

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de-escalated was only represented in the escalation group. In addition to presenting the HR, we report the rates of recurrent FN in each group as the number of total recurrent FN episodes divided by the number of days at risk for recurrent FN, defined as total days of ANC <500 cells/ μ L in which the patient was free of FN after resolution of first fever. An FN episode was counted as recurrent if it occurred at least 48 hours after apyrexia. The study period only included the current admission. Patients were censored at the time of discharge or ANC recovery. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Three hundred ninety patients with AML underwent induction chemotherapy with 7 + 3 from 2009 to 2017, and 135 had documented FN (35%). Of those 135, 77 (57%) patients had no identifiable infectious source. All patients had antibiotics escalated at the onset of FN. Thirty-eight (49%) patients comprised the SD group and 39 (51%) patients comprised the LD group. The groups were similar in terms of median age, gender, comorbid conditions, and, when available, Eastern Cooperative Oncology Group performance status. There was no difference in use of antimicrobial prophylaxis before FN ($P = .58$) or clinical remission of AML at 30 days ($P = 1.00$). There appeared to be a longer duration of neutropenia in the SD group; however, 37% of patients in the SD group were discharged before ANC recovery, compared with only 3% of patients in the LD group, and were censored from this part of the statistical analysis. The escalated antibiotic was primarily cefepime (92% [SD] vs 90% [LD]), and most patients also received vancomycin (79% [SD] vs 87% [LD], $P = .34$). The median number of antibiotic days for first episode of FN was 9 in the SD group and 15 in the LD group ($P < .01$). There was no difference in rates of adverse antibiotic events including drug rash (5% [SD] vs 13% [LD] $P = .43$) and CDI within 90 days of induction chemotherapy (5% [SD] vs 5% [LD], $P = 1.00$), ICU transfers (3% [SD] vs 15% [LD], $P = .11$), and all-cause in-hospital mortality (3% [SD] vs 10% [LD], $P = .40$).

The number of recurrent fevers ranged from 0 to 8 per patient, with most patients experiencing 1 recurrent fever. In the de-escalation group, there were 38 recurrent fevers during a total of 754 patient-days at risk, a rate of 0.05. In the escalation group, there were 38 recurrent fevers during a total of 508 patient-days at risk, a rate of 0.07. We found a 46% reduction in risk of recurrent fever in the de-escalation group compared with the escalation group (HR, 0.54; 95% confidence interval, 0.34–0.88; $P = .01$).

Although there was recurrent fever in the de-escalation group, only 2 patients had a new microbiologically documented infection, whereas all other patients had no identifiable infectious source of fever. Both patients had vancomycin-resistant *Enterococcus* bacteremia.

DISCUSSION

Our results suggest that the risk of recurrent fever is reduced in AML patients with FN without an infectious source when antibiotics are de-escalated before ANC recovery compared with continuation of antibiotics until ANC recovery. Other studies have addressed this, although no published studies focus on a patient population with AML undergoing induction chemotherapy [2, 6–10]. A retrospective study in allogeneic hematopoietic stem cell transplant recipients found that early antimicrobial de-escalation was noninferior to continued antibiotic administration for the primary end point of recurrent fever [2]. Studies have also examined complete antibiotic discontinuation, as opposed to de-escalation. The How Long study is a prospective, randomized, controlled phase 4 trial in patients with hematologic malignancy and FN in which empiric antimicrobial therapy (EAT) was withdrawn in patients who were afebrile for 72 hours, irrespective of ANC [6]. In the control group, EAT was continued until ANC recovery [6]. The experimental group had significantly fewer antibiotic days with no significant difference in adverse events [6]. The ANTIBIOSTOP study prospectively compared antibiotic cessation after 48 hours of apyrexia to antibiotic cessation by day 5, regardless of ANC or body temperature, and found no difference in recurrent fever, in-hospital mortality, ICU transfer, or recurrent infection within 48 hours of cessation [7]. These studies show that early de-escalation or cessation of antibiotics is associated with fewer days of antibiotics without causing harm.

We originally hypothesized that there would be no difference in the rate of recurrent fever between the 2 groups, but instead we found a decreased risk in the de-escalation group. Given the limitations of our study, which was based on a retrospective study design and a small cohort, it is unclear why there was less fever in the de-escalation group, although this has also been described in other studies [2]. It is likely that there were uncontrolled differences between the 2 groups. Although there were no differences in comorbidities, perhaps less antibiotic use in the SD group reflects a perception of providers that these patients were “less sick,” representing a selection bias. Furthermore, more patients in the SD group were discharged before ANC recovery, and thus they had a shorter duration of follow-up for the primary outcome. An additional limitation of our study is that patients were only followed for the current admission, so it is not known whether early antibiotic de-escalation contributes to future adverse events.

CONCLUSIONS

In conclusion, our study suggests that antibiotic de-escalation before ANC recovery in patients with AML and FN with no identifiable infectious source is associated with a lower risk of recurrent fever and has no impact on adverse events such as adverse drug events, ICU transfer, and in-hospital mortality. Physicians should consider de-escalation before ANC recovery

in the appropriate setting. Future research should focus on prospective randomized controlled trials to better illustrate the safety of antibiotic de-escalation in this vulnerable population and inform future guidelines.

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