Infection risk and role of antibiotic prophylaxis in acute myeloid leukemia patients receiving lower intensity chemotherapy: A literature review

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Abstract

Patients with acute myeloid leukemia (AML) are at high risk for infections due to chemotherapy-induced neutropenia. AML patients who receive lower dose chemotherapy are typically elderly patients who have comorbid conditions or have failed initial therapy. Antibiotic prophylaxis use is not clearly understood in this patient population, but early studies were conducted to study the incidence of infections and the use of antibiotic prophylaxis to reduce the risk of infections. The purpose of this literature review was to determine the incidence of infections in patients with AML, if antibiotic use leads to reduced incidence of infections and the role of antibiotic prophylaxis in patients with AML who received lower intensity chemotherapy. This review searched the PubMed database for relevant papers that addressed the research question using the following search terms: leukemia, infections, febrile neutropenia and chemotherapy. Four retrospective studies were identified using this approach and are included in this review. Comparing the four retrospective studies, there was a significant number of patients infected with Gram negative bacteria and the most common pathogens were *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Increased incidence of infections were observed during cycles 1 and 2 of chemotherapy. In one of the studies, despite use of antibiotic prophylaxis, infections occurred and induced the growth of antibiotic resistant bacteria. In another study, the use of antibiotic prophylaxis significantly decreased the incidence of infections in patients with severe neutropenia. Due to the increased incidence of infections in the early chemotherapy cycles, antibiotic prophylaxis has a potential role during this time period especially for severely neutropenic patients. Febrile neutropenia could be the only sign of infection for AML patients so close monitoring during this time period would allow for early detection of infections and prompt treatment with antibiotics. Further studies are required in order to clarify the role of antibiotic prophylaxis, its indication and duration of use in this patient population.

Introduction

Acute Myeloid Leukemia (AML) is a type of blood cancer which results from malignant transformation and proliferation of hematopoietic stem cells from the bone marrow (1). It is the most common type of acute leukemia seen in adults. According to Canadian Cancer Statistics (2023), an estimated 6,300 Canadians will be diagnosed with leukemia in 2023 and 3,100 Canadians will die from leukemia (2). Between the different types of leukemia, AML is the type of leukemia that has the poorest 5-year overall survival at 23% (2). The median overall survival for older patients who received intensive chemotherapy and hypomethylating agents were 11.5 months and 16.2 months respectively in comparison to patients who received supportive care in which median survival was 1.3 months (3). Patients' prognosis varied depending on patient comorbidities, genetic characteristics of the disease and the type of treatment they received.

Treatment for younger patients with AML typically involved intensive induction chemotherapy with the goal to induce remission (4). Fitness for induction chemotherapy considered patient's age, performance status and comorbidities. Patients who were elderly, frail or have comorbidities were unfit for intensive induction chemotherapy as it was too toxic and led to increased mortality (5).

The standard of care for patients determined to be unfit for intensive chemotherapy included azacitidine and venetoclax. Venetoclax, a B-cell lymphoma 2 (BCL-2) inhibitor, was used in combination with a hypomethylating agent such as azacitidine and this regimen was recommended as a safe and efficacious treatment alternative to intensive chemotherapy (6). Recent advances suggested that azacitidine improved overall survival compared to supportive care despite not achieving complete remission (7). When compared to azacitidine only, the combination of azacitidine and venetoclax increased the incidence of complete remission and

overall survival (8). For patients with an FMS-like tyrosine kinase 3 (FLT3) mutation, the most commonly mutated gene in AML patients, they were resistant to the Azacitidine/Venetoclax regimen (9). The addition of gilteritinib, an FLT3 inhibitor, decreased resistance for patients with an FLT3 mutation such that there were higher rates of complete remission and 72% of patients had an 18-month survival rate. Other medications that were considered as lower dose chemotherapy included low dose cytarabine, cytarabine and venetoclax, enasidenib and ivosidenib. Low dose cytarabine and venetoclax were approved for use in Canada in 2020 for patients >75 years old with newly diagnosed AML (10). This regimen suggested favorable efficacy and tolerable safety profile (11). Enasidenib, on the other hand, was initially used in Canada for relapsed/refractory AML patients with an IDH2 enzyme mutation, however it failed to demonstrate improved overall survival so the drug was withdrawn from the market (12).

Febrile neutropenia has been a common complication of chemotherapy, due to patients immunocompromised state (13). According to the criteria defined by Infectious Diseases Society of America, febrile neutropenia was defined as having a fever of a single oral temperature ≥38.3°C or temperature of ≥ 38.0 °C for more than one hour and neutropenia was defined as neutrophil count of $<0.5 \times 10^9$ or $<1 \times 10^9$ with a predicted decrease to $< 0.5 \times 10^9$ (14). High rates of infections were reported by many studies, however most studies were based on patients who received intensive chemotherapy. Studies suggested that administration of antibiotic prophylaxis reduced Gram-negative bloodstream infections and reduced infectious complications (15, 16). There were limited studies that evaluated infection risk and infectious complications in patients who received lower intensity chemotherapy. In patients with acute myeloid leukemia who were treated with venetoclax and hypomethylating agent, researchers found that 74% of patients experienced infections of varying grades, with pneumonia being the most prevalent type

(17). Studies like this demonstrated that infection rates were high, but due to the limited literature on this topic and lack of randomized control trials, it was unknown whether antibiotic prophylaxis would be beneficial for this patient population.

A retrospective study on antibiotic prophylaxis use in patients who received lower-intensity chemotherapy associated a significant decrease in infections in AML patients who received lower intensity therapeutic regimens as a first line treatment (18). Retrospective studies were limited by their small sample size and retrospective nature. Further research within this topic was needed in order to assess infection risk and assess the role of antibiotic prophylaxis in patients with AML who received lower intensity chemotherapy. Since infection risk was high in this patient population, guidelines on who would benefit from antibiotic prophylaxis is vital for these patients.

This literature review aimed to understand the infection risk of patients with AML who received lower intensity chemotherapy. Studies within this patient population were limited but the hope was to understand infection risk and the role of antibiotic prophylaxis in reducing the incidence of infections. The main objectives of the study focused on: *1)* the role of antibiotic prophylaxis in AML patients who received lower intensity chemotherapy, *2)* the incidence of infections and *3)* if antibiotic use leads to reduced incidence of infections.

Purpose of study

Research question:

What is the role of antibiotic prophylaxis in patients with acute myeloid leukemia who received lower intensity chemotherapy?

Objectives:

To better understand if there is a role for antibiotic prophylaxis use in patients with acute myeloid leukemia receiving lower intensity chemotherapy.

To understand incidence of infections in patients receiving lower intensity chemotherapy.

To understand if antibiotic use leads to reduced incidence of infections.

Methods

a) Study inclusion criteria and characteristics

Inclusion criteria included primary research with records published in English and full-text access to articles. Research articles which investigated outcomes such as incidence of bacterial infections, infection risk, infectious complications and antibiotic prophylaxis use were included in the literature review. Participant size included >5 participants and adult oncology patients with acute myeloid leukemia. Participants received lower intensity chemotherapy which may include any of the following: azacitidine and venetoclax, azacitidine (single agent), cytarabine and venetoclax, low dose cytarabine, gliteritinib, enasidenib and ivosidenib. Studies were excluded if they were not conducted within the past 10 years.

b) Search strategy and study selection

A literature review was conducted using the PubMed database. The key search terms used were: leukemia, infections, febrile neutropenia and chemotherapy. The searches were designed and built as follows: ("Leukemia"[Mesh] OR “acute leukemia” OR “acute myeloid leukemia”) AND (“Infections”[Mesh] OR “infection*” OR “infectious complication*” OR “infection risk”) AND (“Febrile neutropenia”[Mesh] OR “febrile neutropenia) AND (“Drug Therapy”[Mesh] OR “low intensity therapy” OR “low intensity chemotherapy” OR “less intensive chemotherapy” OR

"azacitidine"[MeSH Terms] OR Azacitidine[Text Word] OR "Cytarabine"[Mesh] OR "venetoclax"[All Fields] OR venetoclax[Text Word] OR "gilteritinib"[All Fields] OR gilteritinib[Text Word] OR "enasidenib"[All Fields] OR enasidenib[Text Word] OR "ivosidenib"[All Fields] OR ivosidenib[Text Word]). This search strategy generated 260 studies in PubMed. When articles were narrowed down to articles published in the past 10 years, this generated 158 studies. Due to the paucity of research within this area of literature, the study included systematic reviews, meta-analysis, clinical trials and randomized control trials. After a thorough review of the titles and abstracts of 158 studies, 6 studies were identified. The full texts of the 6 articles were assessed. Out of the 6 articles, 4 articles were included in the review. Flow diagram of study selection can be found in Figure 1 in the Appendix.

Results

a) Study populations included and excluded from the studies

Study characteristics can be found in Table 1 in the Appendix. Patients in the On et al. study (19) and Arora et al. study (20) included patients aged >18 years old who were diagnosed with AML or Relapse/Refractory (R/R) AML and received their first dose of Venetoclax/hypomethylating agent. As for the Trubiano et al. study (21), the sample population included patients who were diagnosed with Myelodysplastic Syndrome (MDS) or AML and received one dose of Azacitidine. Lastly, for the Lorenzana et al. study (22), patients included in the study were patients who received Azacitidine and diagnosed with either high risk MDS, low/intermediate MDS with neutropenia and thrombocytopenia or AML.

Only the On study specified specific exclusion criteria. Patients were excluded if they have a history of prior Venetoclax therapy, previous use of Venetoclax/hypomethylating agent for a

non-AML indication, use of Venetoclax/hypomethylating agent for consolidation therapy and history of previous invasive fungal infections.

b) Study design

The On study was a retrospective cohort study on patients who either had a new diagnosis of AML or R/R AML treated with Venetoclax and a Hypomethylating Agent (HMA) which was either Azacitidine or Decitabine. Patients included in the study received treatment between the period of January 2016 and August 2020. Patients' outcomes were studied during the whole duration of treatment and 30 days after treatment for patients with a shorter treatment duration than what was expected. 235 patients were included for the study. 128 patients had newly diagnosed AML while 107 patients had R/R AML. The chemotherapy regimen for the patients included 52% of patients who received Venetoclax 400 mg daily and the HMA was decitabine for 63% of patients while the rest received azacitidine. Other patients who were not on this regimen received Venetoclax at different doses for a variety of reasons which may include infections (either active or suspected), myelosuppressive state or drug interactions.

The Trubiano study was a retrospective study of patients who have Myelodysplastic Syndrome or AML and received Azacitidine as a single agent. Initially, patients received 75mg/m^2 for 5-7 days and dosing was adjusted according to the treating clinician's guidance. Treatment duration was 5-7 days and given at monthly intervals. 68 patients were eligible to be included in the study. 72% of patients had a diagnosis of MDS while 28% of patients were diagnosed with AML. Patients received antibiotic prophylaxis at the discretion of the clinician.

The Arora study was a retrospective study of patients with either a new diagnosis of AML or R/R AML treated with HMA/Venetoclax. Patients included in the study received treatment between Feb 2017 and May 2021. 106 patients were included in the study. 68% of patients have

de novo AML, 20.8% have secondary AML and 11.3% therapy-related AML. When patients were started on their HMA/Venetoclax treatment, most patients were admitted to hospital for induction. Patients were closely monitored for their WBC count. When WBC count was > 25 $x10^9$/L, patients were started on HMA/Venetoclax treatment and depending on the HMA they received, they were discharged on either the 5^{th} day (Decitabine) or 7^{th} day (Azacitidine). Patients received outpatient follow up thereafter until cycle 1 of chemotherapy is done.

The Lorenzana study was a retrospective study of patients with higher risk MDS or AML and received Azacitidine for treatment. For patients with AML, the study required that they must have >30% blasts in bone marrow aspirates and that they cannot be candidates for a transplant. 60% of patients have MDS, 37% of patients have AML and 4% of patients have Chronic Myelomonocytic Leukemia. Patients were treated with Azacitidine in the outpatient setting. Azacitidine was dosed at 75 mg/m^2 for 7 days. Weekly follow up was done for each patient. Initially, patients received antimicrobial prophylaxis on the first day of treatment until neutrophil count was > 0.5 x 10^9 /L. The antibiotic used was ciprofloxacin and the antifungal was an extended spectrum -azole. However, prophylaxis was discontinued in 2013 when reports stated that there was low infection risk and low infection related mortality associated with azacitidine treatment.

c) Objectives of the study

The main objectives of the Trubiano study (2017) were to assess the incidence of all types of infections, at what stage of treatment the infections occured and the risks of infection. For the Arora study (2022), the primary objectives were to identify the incidence of tumor lysis syndrome and infectious complications specifically for the first cycle of HMA/Venetoclax therapy. The latter study focused on the first cycle as it was learned that the early cycles were

attributed to higher risk of neutropenia and infections as compared to the later cycles of chemotherapy. The On study (2022) primarily assessed for incidence of invasive fungal infections and their secondary outcomes included incidence of bacterial infections. Lastly, as for the Lorenzana study (2017), the primary objectives were to assess the incidence of infections as well as morbidity and mortality. This was the only study among the four studies in this literature review that also assessed antibiotic prophylaxis in this specific population.

d) Incidence of bacterial infections, causative pathogens and infection types

The incidence of bacterial infections in the On study comprised of 110 documented bacterial infections and affected 33.6% of their patient population. As for the Arora study, 39% of the patient population had known infection prior to the beginning of chemotherapy and 24.5% developed a new infection during the first cycle of chemotherapy. For this study, new infections were defined as either an infection which started after chemotherapy initiation or a different type of infection for patients with a pre-existing infection. The Trubiano study quantified incidence of infections within the total number of chemotherapy cycles where 14% of azacitidine cycles had at least one episode of infection. There were 49 confirmed bacterial infections within the 884 cycles of azacitidine therapy in the Trubiano study. Similarly, the Lorenzana study quantified incidence of infections in terms of the total number of treatment cycles. According to the Lorenzana study, 21% of treatment cycles were complicated with infectious events and affected 43% of the patient population.

The major bacterial causative pathogen found in the Trubiano study were Gram-negative pathogens. According to the On study, 47.7% of bacterial infections originated from *Enterobacteriaceae*, 4.7% originated from *Pseudomonas aeruginosa* and 1.2% were Methicillin

resistant *Staphylococcus aureus*. Similarly, the Lorenzana study found that two of the most common bacterial pathogens were *Pseudomonas aeruginosa* and *Escherichia coli*.

The most common type of infection seen in the Trubiano study and Arora study was pneumonia. Other types of infection observed in the Trubiano study included upper respiratory tract infections in 2.9% of the patients, skin and soft tissue infections in 2.4% of patients, urinary tract infections in 1.6% of patients and intraabdominal infections in 1.6% of patients. The patient population in the Arora study were infected with cellulitis, urinary tract infections, colitis and bacteremia. The On study found that bacteremia was the most common infection type seen in 41% of the patient population and pneumonia was the second most common type of infection observed in 23% of the patients. Similar to the Trubiano study, the On study also found 20% of patients were infected with urogenital infections (20%) and intrabdominal abscesses (4.6%). The On study also had a small number of patients infected with extra abdominal abscesses as seen in 12% of patients. As for the Lorenzana study, the two most common types of infection included respiratory infections in which majority of patients (10 out of 18 cases of respiratory infections) had pneumonia and the second infection type was urinary tract infections.

e) Timing of infections

As stated in the Arora study, there was a high incidence of infections during the first cycle of chemotherapy and patients were admitted to hospital during this time period. The study focused on the incidence of infectious complications during the first cycle of chemotherapy. In the Lorenzana study, they provided a brief timeline that the first four treatment cycles of chemotherapy posed as a high risk period for bacterial infections. The On study observed that majority of the infections occurred during the first two cycles of Venetoclax/HMA therapy. Similarly, the Trubiano study suggested similar results where there was an increased number of

bacterial infections in the first two cycles of Azacitidine therapy. In cycle 1, it was observed that there was 23.1 bacterial infections in the patient population followed by 25 bacterial infections in cycle 2. There were 14.1 bacterial infections in cycle 3 and decreased bacterial infections in subsequent cycles.

f) Febrile neutropenia and infection

Neutropenia was common and as much as 94% of the patients in the On study became neutropenic throughout the duration of chemotherapy. 54% of patients required hospitalization for febrile neutropenia. In the Arora study, patients most often developed an infection during neutropenic periods and this was observed in 81% of the patient population. The Lorenzana study described that two factors related to infectious events: low neutrophil counts at the beginning of the cycle and longer duration of neutropenia. Febrile neutropenia episodes commonly occurred during the first five cycles of chemotherapy and observed in 69% of patients in the Trubiano study.

g) Antibiotic prophylaxis use or role?

In the Trubiano study, 31% of patients received antimicrobial prophylaxis in the form of antibiotic, antiviral and antifungal prophylaxis. For antibiotic prophylaxis, 2.1% of patients received trimethoprim/sulfamethoxazole and there was an increase in use of trimethoprim/sulfamethoxazole in patients that had prior chemotherapy. In the On study, a number of patients received antibiotic prophylaxis and despite that, there were 35 infections that occurred. A total of 30 patients received antibiotic prophylaxis and within this group, 3 patients were infected with bacteria that was resistant to the antibiotic that they received as prophylaxis. Similarly, in the Lorenzana study, 41% of patients received antimicrobial prophylaxis and patients who received prophylaxis developed severe disease characteristics and were more

neutropenic. However, when the effect of prophylaxis was restricted to patients with low neutrophil counts (< $0.5x10^9$ /L), administration of antimicrobial prophylaxis was associated with decreased incidence of infections.

Discussion

a) Differences between patient populations (newly diagnosed AML vs high risk MDS vs R/R)

Due to the paucity of data within the topic of infection risk in patients who received lower dose chemotherapy, there was a variety in terms of the diagnosis for the sample of patients included in the four studies. All four of the studies included patients with newly diagnosed AML. However, the Arora and On study also included patients with R/R AML that received Venetoclax/HMA as second line therapy. The Trubiano and Lorenzana study included patients with myelodysplastic syndrome. These differences in patient population led to differences in infection risk. In the On study, 54.4% of patients with R/R AML had bacterial infections while 45.6% of patients with newly diagnosed AML had bacterial infections. It was interesting to note that patients with R/R AML display increased incidence of infections. The On study did not describe differences in age and comorbid conditions between patients with R/R AML and newly diagnosed AML. However, studies have shown that R/R AML patients tend to be younger in age and have less comorbid conditions compared to elderly patients with newly diagnosed AML (20, 23). The increase in infections could be attributed to the prolonged disease course of patients with relapsed/refractory AML and prolonged immunosuppressed state compared to those with newly diagnosed AML.

In the Trubiano study, 36.8% of patients received chemotherapy prior to Azacitidine treatment and there was an observed increase in infectious episodes in this subset of patients. In cycle 3, 33.3% of patients had at least one infectious episode compared to 16% in patients

without prior chemotherapy. Similar to the R/R AML patients, patients who received previous chemotherapy had a prolonged chemotherapy-induced neutropenia which placed them at a prolonged immunosuppressed status and increased their risk for infections. When comparing the patients between these four studies, it was important to consider these differences in their diagnoses as it allowed us to interpret differences in their infection risk.

b) Timing of infections and possible role of antibiotic prophylaxis

Between the four studies, there was a higher incidence of infections during the first cycles of chemotherapy. Majority of infections occurred during the first two cycles of chemotherapy (19) and observed a decrease in infections in chemotherapy cycles 4 and 5 (21). These findings highlighted that the early cycles of lower intensity chemotherapy was a high risk period and displayed the importance of increased monitoring of patients for infections during the first three cycles. Without prior studies in this topic, it is difficult to elucidate if there could be a role for antibiotic prophylaxis during this time period. In the On study, despite receiving antibiotic prophylaxis, infections were observed and induced the growth of antibiotic resistant pathogens. Out of 235 patients included in the On study, 30 patients received antibiotic prophylaxis so the growth of antibiotic resistant pathogens was observed in 3 patients (10%) only. This was a very small sample size and thus, further studies were required in order to fully explain if antibiotic resistance could be considered as a major deterrent to antibiotic prophylaxis use in this patient population.

More studies on antibiotic prophylaxis use were conducted in patients who received high intensity chemotherapy. Antibiotic prophylaxis was studied in patients who received intermediate and high dose cytarabine and the antibiotic prophylaxis group was associated with higher rates of bacteremia in cycle 1 and required hospitalization for infections due to resistant

pathogens (24). Similarly, out of all hematological malignancies, acute myeloid leukemia was the type of blood cancer with the highest number of infections due to carbapenem resistant bacteria (21). Increased growth of resistant bacteria was attributed to factors such as altered immune status of patients and neutropenic state. Patients with malignancies often had altered immune status and for patients with AML, chemotherapy induced neutropenia. Thus, it was difficult to use these two factors alone to assess the growth of resistant bacteria. However, these two factors could help identify patients who were more at risk for infections. When this information was coupled with the information that infections were more prevalent in early chemotherapy cycles, frequent assessments for neutropenia could be done during the first three cycles of chemotherapy. Assessment of neutropenia could occur in the form of frequent outpatient follow-ups or admission to hospital for high risk patients.

c) Neutropenic state, infection and antibiotic prophylaxis

Neutropenia was common during chemotherapy with up to 94% of patients developed neutropenia during chemotherapy (19). Neutropenia predisposed patients to the development of infection and 69% of patients developed an episode of neutropenia during the first five cycles of chemotherapy (17). In patients who received high dose chemotherapy, antibiotic prophylaxis was recommended for patients who were expected to have prolonged (>7 days) and profound neutropenia (ANC $\leq$ 100 cells/mm^3) (14). For patients who received high dose chemotherapy, a number of studies described that there was benefit to receiving antibiotic prophylaxis when patients become neutropenic (14, 26). For patients who received lower dose chemotherapy, there were no studies to date which described the role of antibiotic prophylaxis for neutropenic patients receiving lower dose chemotherapy. Patients who received lower dose chemotherapy were fragile patients based either on their age and/or comorbid conditions and administration of

antibiotic prophylaxis when a patient became neutropenic posed as a good strategy to combat infections. Patients who received lower dose chemotherapy and antibiotic prophylaxis was associated with a significant decrease in the incidence of infections in severe neutropenic patients (22). This described a potential role for use of antibiotic prophylaxis in reducing infections for patients who were severely neutropenic. This was similar to the guideline proposed for patients receiving high dose chemotherapy (14). However, although antibiotic prophylaxis use is significantly associated with decreased infections in neutropenic patients, the Lorenzana study was a retrospective study and had a small sample size of 76 patients. This begs the question whether this has the potential to be generalized to a larger population and whether similar results could be obtained in prospective studies.

Antibiotic prophylaxis comes with its own risks as it may induce growth of resistant bacteria, promote *Clostridium difficile* infections and medication toxicities (24). These factors are required to be seriously considered especially for this patient population because such infections and medication toxicities have the potential to lead to hospitalizations. This could translate to exposure to hospital-acquired infections, delay in chemotherapy, and poor quality of life.

d) Clinical practice implications

Based on the four studies in this literature review, there was a consensus that the early cycles of chemotherapy was a high risk period for infections. No clear guidelines were present as to the proper protocol in terms of reducing the incidence of infections during this time period. However, as proposed in the Arora study and Trubiano study, some patients could benefit from hospital admissions to allow for closer observations in order to detect infections early. Through early detection of infections, prompt empiric antibiotic treatment could be started and possibly, shorter duration of hospital admission, reduced need for interventions such as blood transfusions

and decreased delay in chemotherapy. All these factors could contribute to better quality of life for patients.

However, if patients were required to be admitted to hospital for closer observation of possible infections, this could lead to increased costs to healthcare facilities, hospital-acquired infections and medication toxicities from antibiotic prophylaxis. In this patient population, these drawbacks could be sufficient to consider not admitting patients to hospital simply for close observation. It was unclear whether antibiotic prophylaxis would be appropriate within this patient population. The risk of infection was high, especially in patients who were neutropenic, and infectious complications such as sepsis were associated with high risk of mortality (17). Antibiotic prophylaxis had the potential to decrease infections, but the indication and duration of antibiotic prophylaxis for this specific patient population was yet to be studied. When compared to the guidelines for patients receiving high dose chemotherapy, the indication to start antibiotic prophylaxis included prolonged and profound neutropenia (14). It would be reasonable to apply this to patients receiving lower dose chemotherapy as we have seen in the Lorenzana study where administration of antibiotic prophylaxis has led to significant decrease in infections for patients with low neutrophil count below 0.5×10^9 /L. In patients who were already neutropenic, infections could be decreased by using antibiotic prophylaxis which allowed for decreased need for hospitalizations and allowed for continuation of chemotherapy. By cycles 4 and 5 of chemotherapy, there was an observed decrease in infections (21). In the later cycles of chemotherapy, it was expected that there would be a decreased requirement for antibiotic prophylaxis and decreased monitoring of patients for neutropenia.

Limitations

All studies included in this literature review were retrospective studies. No randomized controlled trials have been conducted to assess the role of antibiotic prophylaxis in patients receiving lower dose chemotherapy. The small sample sizes for the studies made it difficult to have significant associations between the different outcomes studied. Another factor that was a limitation of the review was that there was no consistency in terms of patient population between the four studies included which made direct comparison of infection risk between the patient populations difficult. Lastly, there were differences in institution specific practices including follow-up and administration of antibiotic prophylaxis.

Conclusion

Infections continued to be a major concern for patients with acute myeloid leukemia due to the high risk of mortality in patients who acquired infections (17). Infection prevention through antibiotic prophylaxis in this patient population remained to be a topic that was not well studied in the literature. In this literature review, infection prevention for patients who received lower dose chemotherapy was crucial during the early cycles of chemotherapy where infection risk was high. In the first three cycles of chemotherapy, frequent follow up appointments and closer monitoring were beneficial for patients in order to detect infections early and to begin prompt treatment. In patients with acute myeloid leukemia, febrile neutropenia was the only sign of infection which makes close monitoring of fever and white blood cell count imperative for this patient population.

Antibiotic prophylaxis may be beneficial for this patient population given that they tend to be frail patients with comorbidities or have failed initial therapy. Similar to patients receiving high dose chemotherapy, antibiotic prophylaxis could be considered in patients expected to have

prolonged or profound neutropenia. However, without randomized controlled trials and further studies in this topic, there were no clear guidelines on the indication and duration of antibiotic prophylaxis for this patient population. The retrospective studies in this literature review provide guidance for future research studies in order to better understand the role of antibiotic prophylaxis in AML patients who received lower dose chemotherapy.

Appendix

Figure 1. Study selection.

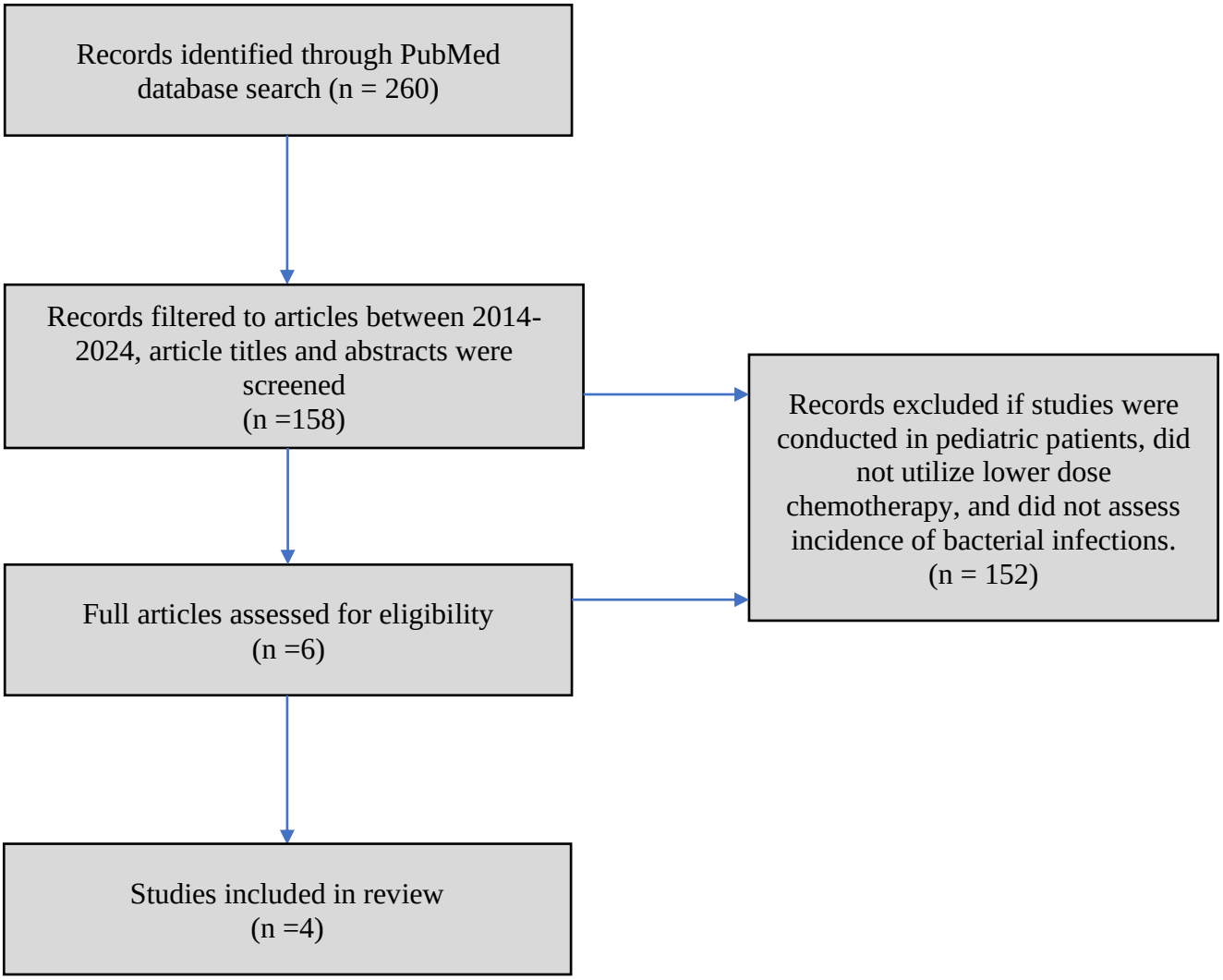

Table 1. Study characteristics of the articles used in the literature review including study type, sample population, sample size, study duration, chemotherapy used, primary objective and secondary objective.

Study and year	Lorenzana 2017	Trubiano 2017	On 2022	Arora 2022
Study type	Retrospective	Retrospective	Retrospective	Retrospective
Sample population	Myelodysplastic Syndrome and Acute Myeloid Leukemia patients	Myelodysplastic Syndrome and Acute Myeloid Leukemia patients	Newly diagnosed Acute Myeloid Leukemia and Relapsed/Refractory Acute Myeloid Leukemia	Newly diagnosed Acute Myeloid Leukemia and Relapsed/Refractory Acute Myeloid Leukemia
Sample size	76	68	235	106
Study duration	December 2007 to October 2016	March 2002 to July 2013	January 2016 to August 2020	February 2017 to May 2021
Chemotherapy	Azacitidine	Azacitidine	Venetoclax/Hypomethylating agent	Venetoclax/Hypomethylating agent
Primary objective	incidence, morbidity and mortality of inefectious events	frequency of infection types, infections per cycle, timing of infections and risk factors and outcomes associated with infection episodes	incidence and characterisation of invasive fungal infections	Incidence of tumor lysis syndrome and infectious complications during first cycle of chemotherapy
Secondary objective	-	-	incidence of bacterial infections, disease response to chemotherapy, incidence of neutropenia and febrile neutropenia, and hospitalisations related to neutropenic fever	role of Venetoclax ramp-up in reducing the risk of TLS

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