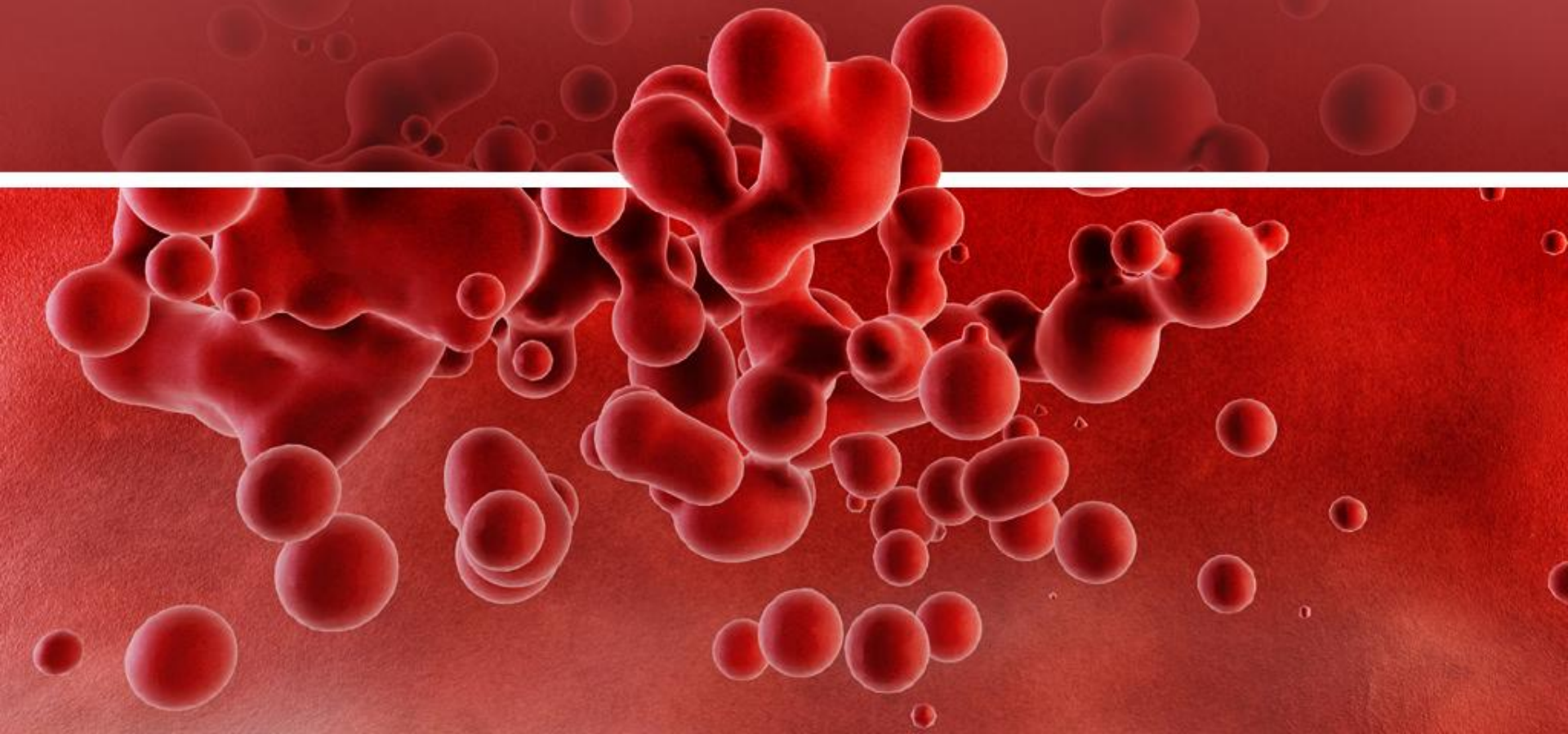
Infection Prophylaxis for AML Patients Treated with Venetoclax plus Azacitidine

Melanie King
MUN PharmD + MSc (Pharm) Student



Objectives

- Describe infection prophylaxis protocols at other institutions
- Appraise infection prophylaxis recommendations based off research studies
- Recognize the impact of New Brunswick Drug Plan Drug Formulary on infection prophylaxis prescribing
- Applying venetoclax dose adjustments when prescribing azole antifungal prophylaxis

Is this a Current Concern in Practice?

Meet Mr. AL

-Mr. AL is a 69 year old male with **AML**

-Completed 4 cycles of **venetoclax with azacitidine** and on preventative valacyclovir

-History of **neutropenia**

-Mr. AL has an appointment to receive a platelet transfusion but has a fall and ends up in the emergency department where it is discovered he is in **rapid atrial fibrillation** and has a low blood pressure

-He is started on **amiodarone** (a p-glycoprotein inhibitor)

-Due to his current condition Mr. AL's **venetoclax is put on hold**

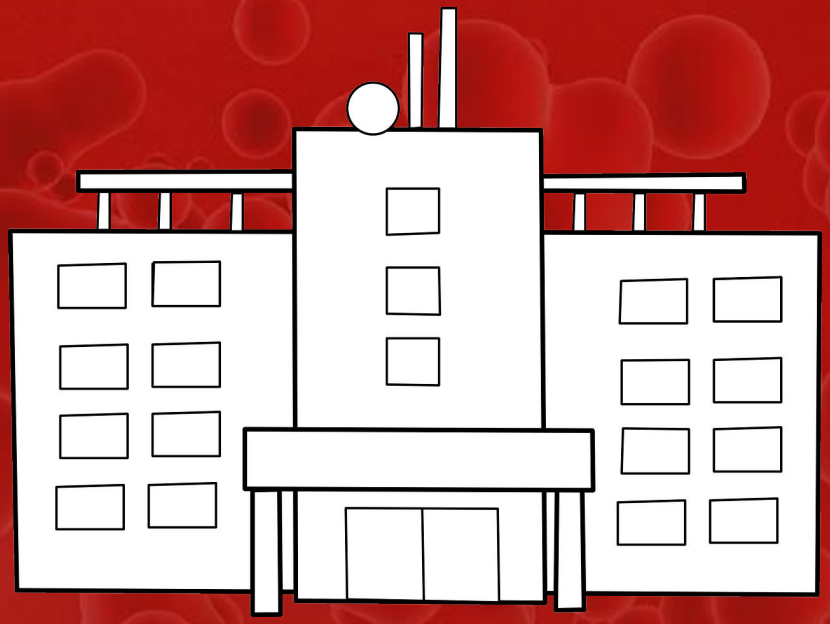
Meet the Mr. AL

- After being admitted, Mr. AL develops signs of pneumonia and is started on broad spectrum antibiotics

- Further laboratory testing indicates **a fungal infection which is confirmed by bronchoscopy to be invasive aspergillosis**

- After consultation with infectious disease, Mr. AL is started on **isavuconazole (moderate CYP 3A4 inhibitor) for 6-12 weeks** as agents such as voriconazole is contraindicated due to an interaction with Mr. AL's amiodarone for his atrial fibrillation

What are other institutions doing?



Antifungal Prophylaxis Continued

Institution	Antifungal(s) Regimen	Criteria
BC Cancer	Fluconazole 400mg po daily	Recommended if ANC less than 0.5 x 10^9/L during cycle 1
Michigan Medicine	Posaconazole 300mg po daily	started when ANC < 500/ microliter and continued until neutropenia resolves
Cancer Care Manitoba	Voriconazole 200 mg po twice a day on an empty stomach	Physician's discretion
Sunnybrook	Voriconazole 200 mg po twice a day	Neutrophils < 0.5 and otherwise on a case by case basis for all azacitidine based therapies
Saskatoon Cancer Centre	Fluconazole 400mg po daily	None specified
The Ottawa Hospital	Fluconazole 400mg daily	All patients

1) BC Cancer Protocol Summary for Therapy of Acute Myeloid Leukemia using azaCITIDine and Venetoclax
2) Michigan Medicine: PROPHYLAXIS GUIDELINES FOR THE ADULT HEMATOLOGY PATIENT
3) Cancer Care Manitoba: Regimen Reference Order – LEUK – azaCITIDine + venetoclax ARIA: LEUK – [azaCITIDine + venetoclax]
4) Sunnybrook Hematology: Acute Myeloid Leukemia (excluding acute promyelocytic leukemia)
5) Venetoclax plus azacitidine Saskatoon Cancer Centre Order Set
6) The Ottawa Hospital Protocol received from hematology pharmacist

Antiviral Prophylaxis Continued

Institution	Antiviral(s) Regimen	Criteria
BC Cancer	Valacyclovir 500 mg PO BID for duration of treatment	HSV or VZV seropositive
Michigan Medicine	Acyclovir 400mg twice a day	For all chemo cycles
Cancer Care Manitoba	Valacyclovir 500mg po twice a day	Recommended Supportive Medications
Sunnybrook	Valacyclovir 500 mg PO daily and continued until end of chemotherapy	For all azacitidine based therapies
Saskatoon Cancer Centre	Valacyclovir 500mg po twice a day	Not Specified
The Ottawa Hospital	Acyclovir 800mg daily	All patients

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Antibiotic Prophylaxis Continued

Institution	Antibiotic(s) Regimen	Criteria
BC Cancer	Levofloxacin 500 mg po daily	Is recommended if ANC less than 0.5 x 10^9/L during cycle 1. At physician discretion other treatments may be considered
Michigan Medicine	Levofloxacin 500 mg po daily	Started when ANC < 500/ microliter and continued until neutropenia resolves
Cancer Care Manitoba	Levofloxacin 500 mg po daily	Recommended supportive medications
Sunnybrook	None	None
Saskatoon Cancer Centre	None	None
The Ottawa Hospital	Septra PJP prophylaxis dosing	All patients

1) BC Cancer Protocol Summary for Therapy of Acute Myeloid Leukemia using azaCITIDine and Venetoclax
2) Michigan Medicine: PROPHYLAXIS GUIDELINES FOR THE ADULT HEMATOLOGY PATIENT
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What does research study data recommend?

Antifungal Prophylaxis Studies

	Outcomes of antifungal prophylaxis for newly diagnosed AML patients treated with hypomethylating agent and venetoclax **Chen et al. - Leukemia & Lymphoma - 2022**	**Incidence of Invasive Fungal Infections in Patients With Previously Untreated Acute Myeloid Leukemia Receiving Venetoclax and Azacitidine** **Zhang et al. - Open Forum Infectious Diseases- 2022**
Study Type	Observational, retrospective, cohort study	Observational, retrospective, cohort study
Primary Outcome	Outcomes of antifungal prophylaxis for newly diagnosed AML patients treated with hypomethylating agent and venetoclax	Invasive fungal infection Incidence during Ven/ Aza therapy
Methods	-Antifungal prophylaxis was **identified by antifungals being given before a documented diagnosis of a fungal infection** -Identified in the DFCI Hematologic Malignancy Data Repository	**-Antifungal prophylaxis was defined as receiving 1 or more days of systemic antifungals** while being treated with Venetoclax + Azacitidine -Invasive fungal infections were classified as proven, probable or possible based on clinical, radiologic and laboratory criteria
Patient Population	**-131 patients** **-17% received antifungal prophylaxis** -Median age was **72 years old** -Most common prophylaxis was **fluconazole followed by isavuconazole and voriconazole/posaconazole**	**–144 patients** -Median age was **72 years old** -Antifungals used were **anidulafungin, fluconazole and isavuconazole**
Results	-The **incidence of invasive fungal infection did not significantly differ between those on antifungal prophylaxis vs not** (14% in no prophylaxis and 9.1% in prophylaxis group) -Poor fitness and TP53 mutation was associated with a larger hazard for invasive fungal infections **-Survival probability showed no significant difference in those who received antifungal prophylaxis vs not**	-Only **10 patients (6.9%) received antifungal prophylaxis** Out of 144 patients there were **25 cases of invasive fungal infection (17%)** **-Nobody on antifungal prophylaxis developed an invasive fungal infection**

Impact of Fluoroquinolone Prophylaxis on Neutropenic Fever, Infections, and Antimicrobial Resistance in Newly Diagnosed AML Patients
Caro et al.-Clinical Lymphoma, Myeloma and Leukemia, 2022

Study Type: Observational, retrospective, cohort study

Primary Outcome: Development of neutropenic fever during frontline therapy

Number of participants: 121 patients

Study duration: Retrospective chart review from 2012-2019

Inclusion Criteria: Newly diagnosed AML patients who had received frontline therapy at Mount Sinai Hospital in New York, NY between 2012- 2019

Exclusion Criteria: Patients who did not become neutropenic during induction therapy, started antibiotic prophylaxis >7 days prior to onset of neutropenia, patients who developed fever the same day as frontline chemo, fever less than or equal to two days after neutropenia

Methods:

- Retrospective chart review
- Examined patients from time of AML diagnosis until 6 months following frontline treatment starting
- As per institution protocol **patients also received prophylactic acyclovir and voriconazole or posaconazole**

Characteristics of patients:

- Median age for no prophylaxis was **62 years old** and **65 years old** for those on prophylaxis

Impact of Fluoroquinolone Prophylaxis on Neutropenic Fever, Infections, and Antimicrobial Resistance in Newly Diagnosed AML Patients
Caro et al.-Clinical Lymphoma, Myeloma and Leukemia, 2022

Results:

- **All but two patients received levofloxacin (1 had ciprofloxacin and 1 had amoxi-clav)**
- **Mean duration of prophylaxis was 10 days**
- In the multivariate analysis the i**ncidence of neutropenic fever was lower HR of 0.73, 95% CI, 0.36-0.97 for those who received antibiotic prophylaxis**
  - **No difference in overall mortality**
  - Median follow up time was 37.8 months from beginning of neutropenia to last follow-up
  - **No difference in groups of length in hospitalization, ICU admission, use of mechanical ventilation or use of vasopressors**
  - During frontline chemo those that got prophylaxis had a 51% lower risk of bloodstream infections

Conclusion: This study stated the use of fluoroquinolone prophylaxis in areas with high resistance reduced the risk of neutropenic fever, systemic bacterial infection and did not increase antimicrobial resistance. The study group recognized the need for prospective randomized trials to verify these findings.

Limitations:

- Not specific to venetoclax + azacitidine
- Retrospective, single centre site
- Short period for mean duration of prophylaxis
- Neutropenic fever does not necessarily mean there is a bacterial infection

Other Considerations

- A retrospective study done by MD Anderson published in 2021 found those on Venetoclax + Azacitidine had found the time to platelet recovery of those treated with azole prophylaxis was longer than those who did not[1]
- Individual risk factors of patients for infection
- Azole drug interactions with venetoclax require dose reduction whereas fluoroquinolones like levofloxacin and antivirals do not
- Pill burden
- Drug coverage

1. Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia Rausch et al.-Cancer, 2021

Drug coverage of Infection Prophylaxis Agents

NBPDP Drug Coverage for Infection Prophylactic agents

Drug	Drug Type	NBPDP Coverage
Fluconazole	Antifungal	Covered
Posaconazole	Antifungal	**Not covered**
Voriconazole	Antifungal	Special Authorization for • For the management of invasive aspergillosis • For culture proven invasive candidiasis with documented resistance to fluconazole. • Must be prescribed by a hematologist, infectious disease specialist or medical microbiologist. • Initial requests will be approved for a maximum of 3 months
Ciprofloxacin	Antibiotic	Special Authorization but not required if submitted by internal med, hematology, infectious disease, medical microbiologists, oncologists, GP in oncology, respirology or urology
Levofloxacin	Antibiotic	Special Authorization but not required if submitted by internal med, hematology, infectious disease, medical microbiologists, oncologists, GP in oncology, respirology or urology
Acyclovir	Antiviral	Covered
Valacyclovir	Antiviral	Covered

NB DRUG Formulary:
https://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf

Venetoclax dose adjustments with CYP3A4 interactions

Anti-Infective prophylaxis recommendations in VIALE-A and VIALE-C protocols are based on institutional infectious organisms, their drug resistance patterns, and local guidance

Recommendations for Anti-Infective Prophylaxis from VIALE-A and VIALE-C Protocols[1,2]

- Anti-infective prophylaxis for bacterial, viral and fungal infections are required for all patients with ANC of <500/µL.
- Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of these agents should be based on regional guidelines or institutional standards.
  - Potential for drug-drug interactions should be considered.

AML=Acute Myeloid Leukemia. ANC=Absolute Neutrophil Count.

1. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29. 2. Wei AH, et al. Blood. 2020;135(24):2137-2145.

Summary of Concomitant CYP3A Inhibitor Use

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Anti-Infective Prophylaxis Use in AML

- Patients with AML are at high risk for febrile neutropenia and life-threatening infections[1]
- CYP3A inhibitors are widely used in AML patients for prophylaxis and treatment of invasive fungal infections[1]
- Co-administration with antifungal agents which are strong or moderate CYP3A inhibitors will increase venetoclax exposures[2]

Dose Modifications for Venetoclax With CYP3A Inhibitors and P-gp Inhibitors

Strong[2]

Reduce VEN to 100 mg

Moderate

Reduce VEN by at least 50%

VEN + AZA:[2] 200 mg | VEN + LDAC:[3] 300 mg

CYP3A inhibitor use in VIALE-A[3]

of VEN+AZA patients received a CYP3Ai in the first two cycles of VIALE-A

Median duration of prophylactic CYP3Ai use

12.5 DAYS (range: 1-614)*

Similar median OS by CYP3Ai Use:

None:	Moderate:	Strong:
15.2	12.3	12.2

AML=Acute Myeloid Leukemia. AZA=Azacitidine.
CR=Complete Remission. CRi=CR with Incomplete Count Recovery.
CYP3A=Cytochrome P450 3A. CYP3Ai=CYP3A Inhibitor.
LDAC=Low-Dose Cytarabine. OS=Overall Survival. VEN=Venetoclax.

*For any end date that was not available, the end date was the date of study cut.

1. Taplitz RA, et al. J Clin Oncol. 2018;36(30):3043-3054.
2. Venclexta Product Monograph, September 27, 2016; Date of Revision: January 21, 2021. Submission Control no:243474 .
3. Jonas BA, et al. Poster #2846. ASH 62nd Annual Meeting; Dec 5-8, 2020; Virtual.

Dose modifications for managing potential interactions[1,3,4]

Coadministered drug	Initiation and ramp-up phase	Steady daily dose after ramp-up phase
Posaconazole	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 70 mg	Reduce the VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitors* Clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, voriconazole	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg	Reduce the VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitors* Aprepitant, ciprofloxacin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil	Reduce the VENCLEXTA dose by at least 50%	
P-gp inhibitors* Amiodarone, cyclosporine, dronedarone, quinidine, ranolazine, verapamil		

Venetoclax Website

Impact of Multiple Concomitant CYP3A Inhibitors on Venetoclax Pharmacokinetics: A PBPK and Population PK-Informed Analysis
Mukherjee et al.-Journal of Clinical Pharmacology, 2023

- Used a PBPK model and popPK model to study drug interaction of venetoclax with CYP3A inhibitors

- Attempted to simulate clinical scenarios like posaconazole with venetoclax and ciprofloxacin with venetoclax

- Appears addition of another competitive CYP3A inhibitor in combination with a strong CYP3A4 inhibitor did not increase venetoclax exposure more than a strong CYP3A4 inhibitor alone

- **Dose adjustment for more than one strong CYP3A inhibitors should be dose reduced the same as just one strong CYP3A inhibitor**

Efficacy with Dose Reduction

CYP3A inhibitors and impact of these agents on outcomes in patients with acute myeloid leukemia treated with venetoclax plus azacitidine on the VIALE-A study

Jonas et al.- Blood, 2020

- Anti-infective prophylaxis was given in those with **neutrophils <500 /microL**
- Venetoclax dose was **reduced from 400mg to 200mg for moderate CYP3A4** inhibitors and to **50mg for those on strong CYP3A4 inhibitors**
- Moderate CYP3A4 inhibitors were given to 41/ 286 on venetoclax plus azacitidine and 18/145 for patients on placebo plus azacitidine
- **Difference in median overall survival was not statistically significant between the groups**
- **Concluded composite remission rates were similar for those treated with CYP3A4 inhibitors and those who were not (1.4 vs 1.2 months respectively)**

What dose of venetoclax should Mr. AL be restarted on if being treated also with isavuconazole and amiodarone?

Back to Mr. AL

- **There is no evidence based answer**
- Currently there are no studies that address co-administration of both a moderate CYP3A4 inhibitor and p-glycoprotein inhibitor with venetoclax

However…

- Mr. AL was taken off amiodarone making restarting venetoclax eventually more straight forward
- As **isavuconazole is a moderate inhibitor of CYP3A4** when he is well enough to restart venetoclax he should receive a **50% dose reduction** while on isavuconazole treatment
- If Mr. AL is switched to **voriconazole** as it is no longer a contraindication due to discontinuation of amiodarone, the venetoclax should be **dose reduced by 75%** as voriconazole is a **strong CYP3A4 inhibitor**

My Conclusions

- The decision to use antimicrobial prophylaxis is multifactorial and there is not a one option fits all

- Antifungals with broader spectrum such as posaconazole is very costly and NBPDP will not cover so the cost burden combined with weak evidence for its use may not be worth the potential benefit

- For levofloxacin the theoretical benefit may not be worth it as there are concerns of antimicrobial resistance, side effects, not great evidence

- Valacyclovir or acyclovir has few drug interactions, covered by NBPDP and generally well tolerated so there is not too many concerns using antiviral prophylaxis

Questions?