

## Incidence and Risk Factors of Infections among Acute Myeloid Leukemia Adult Patients pre and post COVID 19 Pandemic Era: A Tertiary Care Center Experience in Saudi Arabia

Farjah Hassan AlGahtani<sup>1\*</sup>, Aamer Aleem<sup>1</sup>, Razan Abdullah Alzohaifi<sup>2</sup>, Shahad Fahad Althagb<sup>2</sup>, Elaf Abdulaziz Almusahel<sup>2</sup>, Renad Abdulaziz Almutawa<sup>2</sup>, Rema Abdulaziz Almutawa<sup>2</sup>, Lina Musleh Alosaimi<sup>2</sup>, Ahmed Y Gamal<sup>1</sup> and Ghada Metwally ELGohary<sup>1,3</sup>

<sup>1</sup>Department of Medicine, Hematology/Oncology Division, College of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia

<sup>2</sup>King Saud University, Medical Student, Riyadh, Kingdom of Saudi Arabia

<sup>3</sup>Professor of Adult Hematology /Stem CeLL Transplant, Ain Shams University Hospitals, Cairo, Egypt

**\*Corresponding Author:** Farjah Hassan AlGahtani, King Saud University College of Medicine, King Saud Medical City, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

**Received:** January 24, 2022; **Published:** February 26, 2022

### Abstract

**Objectives:** This study aimed to estimate the incidence of infections among adult patients on chemotherapy for acute myeloid leukemia (AML) and determine the most common type of organisms and site of infection(s). Furthermore, we aimed to determine the possible risk factors that enhance the chances of developing infections.

**Methods:** An observational, retrospective, cohort study conducted at King Khalid university hospital (KKUH) in Riyadh, Saudi Arabia. The study reviewed the electronic medical records of 18 adult patients who were diagnosed with AML between January 2015 and January 2021, and treated with chemotherapy. The data were collected and managed by using Google sheets application and analyzed with statistical software package SPSS, version 22.0.

**Results:** Fourteen (77.8%) patients developed infection(s), with a total of 26 episodes of infections. All the 26 episodes were accompanied with neutropenia. Ten (38.5%) of the infectious episodes occurred in blood and 9 (34.6%) in the lungs. Microbiologically, bacteria were the most commonly isolated causative agents (73.1%), mostly gram negative, and E. coli (15.4%) was the most frequent organism. Out of 14 patients who developed infections, these infections were associated with variable complications. Five (35.71%) patients died, although not all deaths were attributed to infections. HIDAC and 3+7 were the most commonly used chemotherapy regimens (38.5% and 26.9%, respectively). Majority of the infectious episodes occurred during the induction phase of chemotherapy (46.2%) and most of the infections (61.54%) occurred during severe neutropenia (<500) phase. Only one case was diagnosed to have Covid19 infection and the patient recovered with the usual Covid19 management protocol.

**Conclusion:** Infections are prevalent among patients with AML, commonly blood and lung infections. Infections are more common during induction phase and most likely related to disease and chemotherapy induced severe neutropenia. The most frequent isolated organisms are gram negative bacteria, commonly E. coli. The Covid19 pandemic had no serious clinical impact on our patients.

**Keywords:** Acute Myeloid Leukaemia; Chemotherapy; Neutropenia; Infections; Bacteria

## Abbreviation

AML: Acute Myeloid Leukaemia; KKHU: King Khalid University Hospital

## Introduction

Acute myeloid leukaemia (AML) is a cancer of blood and bone marrow [1]. It is the second most common type of leukaemia diagnosed in adults among Saudis as reported in Saudi Cancer Registry in 2015. Unfortunately, the prognosis of people with AML remains poor [2] with only 25% overall 5 years survival rates according to the National Cancer Institute (NCI). This is mostly attributed to the high rates of relapses and resistance to therapy [2]. In addition, the median age of a person diagnosed with AML is 68 years with many patients unable to tolerate intensive chemotherapy [3].

In AML, there is accumulation of immature cells in the bone marrow called myeloblasts or blast cells. That leads to a reduction in the number of normal blood cells and people with AML are likely to have anemia, easy bruising, bleeding, and infections [4]. Therefore, AML results in neutropenia, which makes them highly susceptible to infections, which may have a serious impact on outcome.

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1000 cells/mL [5]. And it is inversely related to the incidence and severity of infections [6]. Besides neutropenia, the use of cytotoxic anti-cancer chemotherapy increases the risk of acquiring infections [7] by suppressing the immune system [8], damaging the mucosal lining of gastrointestinal tract [9], and causing prolonged neutropenia [8]. Also, there are other risk factors which may further increase the risk for developing infections. These include, the presence of central venous lines [11], urinary catheters [12], and the use of some drugs such as corticosteroids [11].

The most common type of organism responsible for infections are bacteria but the pattern of bacterial infections has been fluctuating over the past decades [13]. Knowing the type of infections that AML patients are susceptible to, and identifying the contributing risk factors, will help in providing appropriate treatment tailored to the locally prevalent pathogens, as well as preventing complications. In this retrospective study we reported the incidence of infections among adult patients who received chemotherapy for AML between Jan 2015 – Jan 2020 at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. In addition, we also determined the characteristics of these infections and the risk factors associated with infections among this population.

## Methods

This is an analytical, observational, retrospective, cohort study, that was conducted in the oncology and haematology department in KKHU, Riyadh, Saudi Arabia. Data collection was carried out from September 2020 to February 2021. The study enrolled all patients who were diagnosed to have AML between January 2015 to January 2021 and treated with chemotherapy. There were a total of 18 patients which included 9 male and 9 females, above the age of 15 years (mean 51). Patients with incomplete medical records or who had a condition that might interfere with the study's results, were excluded.

Ethical approval for the study was granted by the institutional review board (IRB) of the KKHU. (No. E-20-5453). The participant's anonymity was assured and maintained. Moreover, only the information related to the study was obtained and used.

Patients' information was collected from their electronic medical records. With the use of Google sheets application, the collected data were entered and organized. Data about demographic information, year of diagnosis, type of AML, chemotherapy protocol, phase of treatment and factors thought to contribute to acquiring infections, were recorded. For each phase of chemotherapy, the incidence of fever and infection(s) was documented. For every episode of infection, information about the symptoms, site of infection, causative organism(s), treatment used, presence of complications, and outcome was also obtained.

The data were analyzed by using statistical software package SPSS, version 22.0. Descriptive analysis that were conducted on quantitative variables are the mean ± standard deviation, while frequencies and percentages were used to describe the categorical variables. The statistical significance and the precision of results were not calculated since the obtained sample size (n=18) was small.

**Results**

Eighteen adult patients on chemotherapy for AML were included in this study. Table 1 presents the baseline characteristics of the participants, the mean age was 51 years and 50% of them were male, 72.2% were married, and 66.7% were nonsmokers.

Characteristics		N = 18
Age [mean ± std]		51 ± 17.14
Gender [n, (%)]	Male	9 (50)
	Female	9 (50)
Nationality [n, (%)]	Saudi	13 (72.2)
	Non-Saudi	5 (27.2)
Marital status [n, (%)]	Single	4 (22.2)
	Married	13 (72.2)
	Other	1 (5.6)
Smoking [n, (%)]	Yes	6 (33.3)
	No	12 (66.7)

**Table 1:** Sociodemographic Characteristics of study subjects (n = 18).

Table 2 shows the distribution of incidence of infections among the patients. Fourteen of them developed infections (77.8%), with a total of 26 episodes of infections. Eight patients (44.44 %) had an infection once, while 6 patients (33.34 %) developed multiple infections at different times.

Item	No (%)
No infection	4 (22.22)
Infected once	8 (44.44)
Infected twice	1 (5.56)
Infected 3 times	4 (22.22)
Infected 4 times	1 (5.56)

**Table 2:** Distribution of incidence of Infection (n = 18).

Table 3 shows the comparison of characteristics between patients who developed an infection with the patients who didn't get an infection. Patients with and without an infection were similar in that most of them did not have a chronic disease (50%, 50%), were non-smoker (64.3%, 75%), had a PICC line (42.9%, 50%), and did not have a urinary catheter (64.3%, 75%), respectively. Furthermore, the mean age of patients with infections was 51 and for patients without infections was 52, which was similar. Some of the patients who developed an infection were diagnosed with AML with myelodysplasia-related changes (21.4%) while majority of patients who didn't get

an infection were diagnosed with AML type M2 (50%). Also, there were differences in the type of transfusion they received, 50% of those with infections had PRBC, FFP and platelet transfusions, while 50% of those without infection only received FFP. Furthermore, 5 patients died and deaths occurred only among patients who developed infections (35.7%), although not all the deaths were caused by infections.

Characteristics		Who developed infection (n=14)	Who did not develop infection (n=4)
Age [mean ± std]		51 ± 17.5	52 ± 18.2
Gender [n, (%)]	Male	7 (50)	2 (50)
	Female	7 (50)	2 (50)
Marital status [n, (%)]	Single	4 (28.6)	0 (0)
	Married	10 (71.4)	3 (75)
	Other	0 (0)	1 (25)
Nationality [n, (%)]	Non-Saudi	4 (28.6)	1 (25)
	Saudi	10 (71.4)	3 (75)
AML [n, (%)]	M0	1 (7.14)	0 (0)
	M1	2 (14.3)	0 (0)
	M2	2 (14.3)	2 (50)
	M3	1 (7.14)	0 (0)
	M4	1 (7.14)	0 (0)
	M5	2 (14.3)	0 (0)
	Acute monocytic leukemia	0 (0)	1 (25)
	(Post Hodgkin lymphoma ) therapy related AML	1 (7.14)	0 (0)
	AML+MRC (Myelodysplastic related changes)	3 (21.4)	0 (0)
	Others	1 (7.14)	1 (25)
Chronic diseases [n, (%)]	None	7 (50)	2 (50)
	HTN	1 (7.14)	0 (0)
	DM	0 (0)	1 (25)
	DLP	1 (7.14)	0 (0)
	CKD	2 (14.29)	0 (0)
	More than one disease (HTN, DM, DLP or CKD)	3 (21.43)	1 (25)
Smoking [n, (%)]	No	9 (64.29)	3 (75)
	Yes	5 (35.71)	1 (25)
Central venous line [n, (%)]	None	1 (7.14)	1 (25)
	Hickman line	5 (35.71)	1 (25)
	Picc line	6 (42.86)	2 (50)
	Tunneled double subclavian	1 (7.14)	0 (0)
	Hickman+ Picc line	1 (7.14)	0 (0)

<b>Blood products</b>  <b>[n, (%)]</b>	Not known	4 (28.57)	1 (25)
	FFP	1 (7.14)	2 (50)
	PLT	0 (0)	0 (0)
	PRBCs	2 (14.29)	1 (25)
	More than one type include (FFP, PLT, PRBCs)	7 (50)	0 (0)
<b>Urinary catheter</b>  <b>[n, (%)]</b>	No	9 (64.29)	3 (75)
	Yes	5 (35.71)	1 (25)
<b>Death [n, (%)]</b>	No	9 (64.3)	4 (100)
	Yes	5 (35.71)	0 (0)

**Table 3:** Comparison of characteristics between patients who developed an infection (n = 14) and those who didn't get an infection (n = 4).

Table 4 shows the clinical profile of the infections among adult patients on chemotherapy for AML. The most common observed affected site for infections was blood (38.5%), followed by lungs (34.6%). The most common cause of infections were bacteria (73.1%), and E-coli was the most frequent organism (15.4%). The patients were receiving different chemotherapeutic protocols and HIDAC (38.5%) and 3+7 (26.9) were the most commonly used regimens. It was very notable that the majority of the infectious episodes occurred during the induction phase of chemotherapy (46.2%). Nineteen of the infectious episodes were accompanied by fever (73.1%). All the infectious episodes were associated with some degree of neutropenia; while most of the infections occurred (61.54%) during severe neutropenia of less than 500 cell/mL. Out of the 26 infectious episodes, there were 14 cases of complete recovery (53.8%) and eight cases failed to recover (30.8%). In 12 episodes of infection the length of hospitalization was less than 30 days (46.15%). Fifteen episodes were not associated with any complication (42.3%), but in the remaining eight episodes patients developed different complications, including typhlitis (11.5%) and respiratory arrest (11.5%).

	<b>Parameter</b>	<b>Number</b>	<b>%</b>
<b>Site of infection</b>	<b>Lungs</b>	9	34.6
	<b>Blood</b>	10	38.5
	Heart	1	3.8
	Skin	3	11.5
	Eyes	1	3.8
	GI - stool	1	3.8
	Blood and skin	1	3.8
<b>Type of infection</b>	unspecified	2	7.69
	Bacterial	19	73.1
	Fungal	5	19.22
<b>Chemotherapeutic protocol</b>	7 +3	7	26.9
	2+5	5	19.2
	FLAG	1	3.8
	VPCY	1	3.8
	Velcade and venetoclax	1	3.8
	azacitidine	4	15.4
	HIDAC	10	38.5
	azacitidine + venetoclax	1	3.8

<b>Phase</b>	Not-specified	5	19.2
	Induction	12	46.2
	consolidation #1	5	19.2
	consolidation #2	2	7.7
	consolidation #3	2	7.7
<b>WBCs</b>	below 1.0 x 10 <sup>9</sup> /L	12	46.2
	1-2.5	3	11.5
	2.5- 4.5	3	11.5
	Over 4.5	8	30.8
<b>RBCs</b>	2-3 X 10 <sup>6</sup> /mcl	14	53.8
	3-4.2	12	46.2
<b>Hb</b>	below 6 g/dL	1	3.8
	6-9	17	65.4
	9-12	8	30.8
<b>Platelets</b>	below 50 X 10 <sup>9</sup> / L	19	73.1
	50-150	5	19.2
	150-250	2	7.7
<b>Neutrophils</b>	below 500 cell/mL	16	61.54
	500 - 1000	7	26.92
	1000 - 1500	3	11.54
	above 1500	0	0
<b>Presence of fever</b>	No	7	26.9
	Yes	19	73.1
<b>Underlying organism</b>	unknown	2	7.7
	E.Coli	4	15.4
	Klebsiella pneumoniae	3	11.54
	Pseudomonas aeruginosa	2	7.7
	Stenotrophomonas maltophilia & Pseudomonas aeruginosa	1	3.8
	H.Influenza	1	3.8
	enterobacter cloacae	1	3.8
	Clostridium difficile	2	7.7
	methicillin-susceptible Staphylococcus aureus	1	3.8
	Streptococcus mitis	1	3.8
	staphylococcus epidermidis	1	3.8
	Streptococcus parasanguinis	1	3.8
	Granulicatella adiacens	1	3.8
	candida species	3	11.54
	aspergillus	2	7.7
<b>Remission</b>	Didn't recover from infection	8	30.8
	Recovered from infection	14	53.8
	Empty cell- file is closed	4	15.4
<b>Complications</b>	None	11	42.3
	GI bleeding	1	3.8
	lip necrosis	1	3.8
	chest wall abscess	1	3.8
	typhlitis	3	11.5
	Respiratory arrest	3	11.5
	unknown - empty	6	23.1

**Table 4:** Clinical profile of patients and details of infections among adult patients with acute myeloid leukemia (n=26 infections).

Only one patient contacted Covid19 infection and the patient recovered with the usual Covid19 management protocol.

## **Discussion**

Patients with AML have a high likelihood of developing infections [14] due to neutropenia and an immunosuppressed state caused by chemotherapy and the disease itself. They have an increased morbidity and mortality due to the neutropenic infectious complications [15]. Therefore, prevention and early management of infections is crucial to improve the patients' outcome.

This retrospective cohort study evaluated the incidence of infections among adult patients who received chemotherapy for AML by studying all infectious episodes in each patient. We found that 14 of our 18 patients (77.8%) had 26 episodes of infections accompanied by neutropenia, and most of these infections were bacterial (73.1%). The infectious episodes were frequent during the induction phase of the therapy (46.2%).

There has been a continuous shift in the most common type of infections in AML patients with neutropenia. In the early 1950s and 1960s, staphylococcus aureus was the most frequently isolated bacterium [16]. With the introduction of beta-lactamase resistant penicillins, gram-negative bacilli became the predominant organisms [13]. Since the 1980s, several studies have demonstrated a shift in the etiology from a predominance of gram-negative bacilli to gram-positive cocci [13]. However, a study done in Saudi Arabia on the epidemiology and source of infections in febrile neutropenia patients, showed an equal ratio of gram positive and gram negative bacteria in the positive blood cultures [17].

We found that the most frequently isolated organisms were gram negative bacteria, in particular E. coli followed by klebsiella pneumoniae and pseudomonas aeruginosa. Our findings were in concordance with many other studies that showed gram negative bacteria, mainly E. coli as one the most commonly isolated organisms in AML patients [18]. And this might confirm the fact that gram negative bacteria are becoming more resistant and prevalent as highlighted in recent studies [19].

Other gram negative bacteria we found include Stenotrophomonas maltophilia, Enterobacter cloacae and Haemophilus influenzae, each one isolated once (3.8%).

Gram positive bacteria, however, were less common in our cohort, which corresponds with the recent papers that showed decline in the rate of gram positive bacterial infections among AML patients. For example, a study conducted in 2015 reported that gram positive bacteria represented 19% of isolated microorganisms versus Gram negative that accounted for 81% of total isolates [18]. Coagulase negative staphylococcus has been documented as the most common gram positive bacteria in the majority of previous studies [20]. However, our study showed Clostridium difficile (7.7%) to be the commonest gram positive bacterium, while all of the remaining bacteria occurred once only and include granulatella adiacens, methicillin-susceptible staphylococcus aureus, staphylococcus epidermidis, streptococcus mitis, and streptococcus parasanguinis.

We also found that candida (11.54%) species were predominantly responsible for fungal infections followed by aspergillus (7.7%). However, fungal infections in general were less frequent among our patients (19.23%) as in some previous studies; for example, 11% of infections were fungal in origin in a study [21], while no fungal infection was found in another study [8]. One investigator noticed that fungal infections occurred in patients with prolonged neutropenia and who received protracted courses of antibiotics [22].

The blood (38.5%) and lungs (34.6%) were the most common sites of infection, which is similar to the observations in other studies [10]. However, some studies found gastrointestinal tract to be the most common sites of infections [23].

It is known that neutropenia [13] and chemotherapy [7], especially the induction phase [24], contribute to severe immune suppression and high rates of infections. And this was also seen in our study. Interestingly, one of our observation was association of infection with the

type of AML. More patients who developed an infection were diagnosed with AML with myelodysplasia-related changes (21.4%), while the patients who didn't get an infection were diagnosed with AML type M2 (50%). This finding is likely by chance and the small sample size does not allow us to associate likelihood of infections with the type of AML.

It is also known that prompt initiation of empirical antibiotics in febrile neutropenia is crucial in the management of AML patients [13]. Nevertheless, infections are still a major cause of poor outcomes in AML patients. In our cohort, 5 deaths occurred, all of them in patients who developed infections, although not all of the deaths were attributed to infections. Similarly, a study found that infections were responsible for 35 (87.5%) out of 40 deaths in 327 AML patients on chemotherapy [18], which highlights the role of infections in AML mortality and outcome.

## **Conclusion**

Infections are prevalent among patients with AML commonly blood and lung infections chemotherapy induced neutropenia and neutrophilic dysfunction . Most frequently isolated organisms are gram negative bacteria, predominantly E. coli. These infections can lead to unfortunate outcomes as expected in many other centers. The Covid19 pandemic had no serious clinical impact on our patients.

## **Strength**

The study targets AML which is an important disease entity, particularly in Saudi Arabia where it is considered a public health problem [25] for the burden it puts on the healthcare system. Besides, our center showed a good control for COVID19 spreading among our patients due to our firm COVID19 protocols and infection control measures implemented since the start of the pandemic.

## **Limitations and Recommendations**

Our study was retrospective in nature and the sample size was small and not enough to draw firm conclusions whether or not the risk of infection varied between different types of AML. As there was only one patient affected with COVID19, it was not possible to study the effect of COVID19.

We recommend doing a multicenter study in Saudi Arabia, with larger numbers of patients to study the impact of infections on the outcome of AML.

## **Acknowledgement**

We extend our sincere appreciation for Researchers supporting Program at King Saud University ,Riyadh,Saudi Arabia.

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**Volume 5 Issue 3 March 2022**

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