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ORIGINAL ARTICLE

Exploring the association between alpha hemolytic streptococcal infection and intensive treatment outcomes in acute myeloid leukemia.

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ABSTRACT… Objective: To assess the prevalence of alpha hemolytic streptococcal (AHS) infections and related risk factors in patients with newly diagnosed acute myeloid leukemia (AML) undergoing consistent treatment. **Study Design:** Prospective study. **Setting:** Jinnah Teaching Hospital and DHQ Charsadda undergoing treatment from Hayatabad Medical Complex Peshawar. **Period:** June 2022 to February 2023. **Material & Methods:** AML patients were recruited and algorithmically followed for AHS infections. Core symptoms, diagnostic workups, differential diagnoses, and relevant treatments were assessed in this manner. **Results:** AHS caused 22% of bacteremic infections in 22% of patients, mostly by blood transmission (87%). After treatment, 32% recurred. AHS had a 60% mortality rate ($P < 0.002$). Age, precise induction timing, and high-dose cytarabine significantly enhanced AHS incidence (OR 2.0, 1.8–1.9, and 3.8, respectively). AHS infections increased hospital stays ($P < 0.0002$) and decreased long-term survival (OR 2.8; $P < 0.001$) and disease-free survival (OR 2.1; P 0.008) in bone marrow transplant patients. **Conclusion:** The first prospective study investigating AHS frequency in consistently treated individuals revealed increased rates with intensified AML therapy. AHS bacteremia is particularly likely in adults with prior cases and high-dose cytarabine usage.

Key words: Alpha Hemolytic Streptococcal Infection, Acute Myeloid Leukemia (AML), Cytarabin, Intensive Treatment Outcomes, Therapy.

INTRODUCTION

The cancellation initiation and over time cure rates for AML have improved. Thanks to recent therapeutic intensification, serious negative side effects have increased as a result of this success. It's not uncommon for patients to have severe mucositis and prolonged neutropenia despite treatment with growth factors. Therefore, infections are becoming a leading cause of morbidity and death in this group. The possibility of improvement in these people's rate of full remission has been impeded to some degree as a result of this. However, there still exist critical gaps in our knowledge regarding the prevalence and impact of alpha-hemolytic streptococcal (AHS) infections in this context.[1,2]

One of the most dangerous forms of septicemia is that produced by alpha-hemolytic streptococcal (AHS) infections. During an epidemic of AHS illnesses within the institution in the years 1985-1987, Sotiropoulos et al. examined a group of AML patients. A considerably increased incidence of AHS septicemia was documented after switching to a high-dose cytarabine treatment. 14 out of 15 cases (93%) of AHS septicemia in this multi-agent chemotherapy regimen had been treated with AraC beforehand. Despite such evidence, the overall prevalence of AHS infections and the specific risk factors associated with their occurrence in AML patients undergoing consistent treatment remain unclear. This knowledge gap is significant as addressing these uncertainties can lead to better management and prevention strategies for AHS infections, ultimately improving patient outcomes.[3,4]

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The primary component of therapy in this experiment was cytarabine. Data were collected as part of this experiment to assess the frequency and types of illnesses acquired while receiving this treatment. Among the most common causes of bacterial infections in this population was found to be septicemia caused by AHS. Therefore, the main objective of this study is to prospectively investigate the frequency and risk factors associated with alpha-hemolytic streptococcal (AHS) infections in individuals receiving consistent treatment for acute myeloid leukemia (AML). By filling the knowledge gap regarding the prevalence and impact of AHS infections in this specific patient group, we aim to enhance our understanding of the disease's dynamics and provide valuable insights into preventive measures and targeted interventions for improved patient care and outcomes.

MATERIAL & METHODS

In this prospective study, data were collected from adult participants between the ages of 20 and 30 with Acute Myeloid Leukemia (AML) from June 2022 to February 2023 (after the approval of IRB). AML patients were presented at Jinnah Teaching Hospital and DHQ Charsadda undergoing treatment from Hayatabad Medical Complex Peshawar.

The study aimed to explore the association between Alpha Hemolytic Streptococcal (AHS) infection and intensive treatment outcomes in these patients.[5,6] The therapy administered involved Activation and Boosting Courses. The researchers adopted random allocation for regular and rapid induction timings in Sessions 1, 2, 3, and 4. Intensification Courses, either Capizzi II chemotherapy or autologous BMT, were administered if no HLA-matched related donor was found. Consolidation was employed following Capizzi II treatment[7,8,9], involving three months of low-dose chemotherapy. Patients were categorized into three groups based on modifications during induction and intensification methods.

Patients were prospectively followed, and data were collected throughout the induction process, with each cycle comprising two chemotherapy sessions. Hematologic improvement determined the initiation of cycles 2 and 4 in the traditional timing arm, while the intensive timing arm incorporated granulocyte colony-stimulating factor (G-CSF) beginning on the sixth day of each induction phase.[10,11,12,13] After hematologic recovery from induction cycle 4, the intensifying phase began, and patients were randomly assigned to receive either an autologous 4-hydroxycyclophosphamide-purged BMT or an HDAraC regimen. Throughout the study, safety measures were implemented, including prophylactic antibiotics, systemic antibiotics, and infection-related categorization based on GI toxicity.[14,15,16]

The presence of AHS infections was evaluated based on etiologic agents reported in available categories, and infections were categorized by severity. Analyses assessed various aspects, including the incidence, sites, and severity of AHS infections, as well as mortality rates, recurrent infections, hospitalization duration, overall survival, disease-free survival, and the impact of AHS on hospitalization and course days. The data were analyzed statistically, and subgroup analyses were conducted based on treatment type and experiment year.[17]

To determine the significance of incidence differences, an x2 contrast between proportions was employed, and Cox regression was used to assess overall and disease-free survival rates. The Mann-Whitney U test compared median values in analyzing the effect of AHS on hospitalization and course days.

Ethical approval was obtained with ethical approval letter number 234-22.

Inclusion Criteria

- Adults aged between 20 and 30 years who had been newly diagnosed with Acute Myeloid Leukemia (AML).
- Proper consent of the patients for following specific treatment protocol and follow-up assessments as required by the study.

Exclusion Criteria

- Patients falling outside the specified age range were not included in the study.
- Individuals with pre-existing medical conditions or diseases that could potentially interfere with the study's objectives or treatment outcomes were excluded from participation.
- Patients with a history of previous treatment for AML were not considered.
- Moreover, individuals who were either unwilling or unable to provide informed consent for their involvement were excluded.
- Participants with known allergies or sensitivities to the therapeutic agents used in the study were also not eligible for inclusion to prevent any adverse reactions.
- Pregnant or breastfeeding individuals were excluded from the study to ensure their safety and that of the fetus or child.
- Furthermore, patients with severe immunosuppression or compromised immune function were not included due to potential complications ensure data integrity and study validity.

RESULTS

AHS Infection Frequency and Infection Intensity

Twenty percent of all patients (36 out of 200, or 20%) possessed one or more bouts of AHS bacterial infections during initiation or intensification.

In this study, all infections were found in patients, and AHS contributed to 17% (45 of 189) of those infections (Table-I), with minimal variance in induction (16%; 68 of 170) and amplification (19%; 32 of 180). 21% of the reported bacterial diseases were caused by AHS. Approximately eighty-seven percent (190 of 200) of AHS infections (representing bacteremia/septicemia) were brought on by blood or central venous catheters. At these two locations, AHS was responsible for 28% and 20%, respectively, of all illnesses. AHS was responsible for 26% of all bacteremic events among the study's subjects. 55% of the Gram-positive bacteremias were caused by AHS. AHS bacteremias were more severe than the other illnesses observed in this treatment. The reporting institution rated 60% of AHS bacteremia as life-threatening. This study removes infections undergoing BMT, most of which were deemed to be life-threatening, and found that just 42% of the other infections (from all locations) were deemed to be such (P 6.002). AHS was responsible for 21% and thirteen percent of infections that were deadly and life-threatening. Yet, the death rate directly linked to AHS was no higher than that brought on by other illnesses. Comparatively to 4% of all infections, 3% of AHS illnesses (all of those with bacteremias) were explicitly recognized as the cause of death.

AHS Development Risk Factors

Table-I show the baseline demographics for individuals who have enrolled. Then, these totals are separated into groups according to the likelihood that the individual in question had an AHS illness at the time of induction. Among the five examined baseline factors, only age was shown to be related to AHS bacteremia. The prevalence was higher among the younger patients (20–22 years old) than among the 23–25 year olds (16%) or the 26–30 year olds (12%) (P 6.058).

When infection rates per day of risk were taken into account (Table-II), the variation was quite substantial. Using this strategy, AHS infection rates were considerably greater in individuals under 23 than in those over 23 (for age, twenty-three years, OR, 2.1; P 6.008).

(*The FAB classification recognizes eight subtypes of AML: M0 minimal myeloid differentiation (3%), M1 poorly differentiated myeloblasts (15–20%), M2 myeloblastic with differentiation (25–30%), M3 promyelocytic (5–10%), M4 myelo-monoblastic (20%), M5 monoblastic (2–9%), M6 erythroblastic (3–5%), and M7 megakaryoblastic).

Body Site	Total Number of Infections	% of Infections Attributable to AHS	% of Inductions with AHS	% of Intensification Caused by AHS
Blood	190	28	27	30
Pulmonary	82	2	3	-
Upper GI	113	8	9	-
Lower GI	125	3	3	-
Skin	111	3	3	-
CNS	4	-	-	-
Urinary	123	4	-	12
CVC‡	196	20	21	18
Liver	19	7	7	-
Upper Resp	51	9	11	-
Other	159	11	13	7

Table-I. Shows the percentages of AHS infection at different locations on the body throughout initiation and escalation.

	No. AHS	Rate*	OR	P
AHS induction speed	157	0.181818		
Age range				.008
20-22 years	41	0.23524	1.0	—
23-25 years	73	0.20656	0.8	.50
26-30 years	45	0.23208	0.6	.006
Gender				.85
Male	79	0.28508	1.0	—
Female	77	0.27980	1.0	.85
FAB*				.38
M0	9	0.42992	1.0	—
M1	18	0.27061	0.5	.08
M2	47	0.27037	0.5	.07
M3	11	034446	0.8	.50
M4	33	0.26954	0.6	.07
M5	28	0.30369	0.7	.25
M6	1	0.0795	0.3	.13
M7	6	0.22504	0.5	.06
WBC at diagnosis				.85
0-20 3 10^3	73	0.16333	1.0	—
20-100 3 10^3	56	0.17764	1.1	.64
10013 10^3	27	0.18242	1.1	.62
time of year of diagnosis				.89
Spring	39	0.17343	1.0	—
Summer	35	0.15463	0.8	.62
Fall	37	0.17069	1.0	.94
Winter	45	0.18577	1.1	.75

Table-II. Taking into account the duration of risk, the prevalence of AHS bacteremia during induction and characteristics of patients at the time of AML confirmation

The probability of AHS was 21% among those who had gastrointestinal (GI) toxicity of grade 3 or 4 after inductive methods, compared to 12% in individuals who did not experience gastrointestinal (GI) toxicity during initiation (P.01).

The days with the greatest incidence were tallied for each therapeutic cycle. Patients with intense initiation course 1 (i.e. rounds 1, 2) saw the greatest incidence between days 11 and 15. There were four percent of AHS infections on day zero, 20 percent on day five, 37 percent on day

eleven, 21 percent on day fifteen, and 23 percent on day twenty-one. The peak incidence of AHS infection occurred between days 16 and 20 of the second intensive induction regimen (i.e., cycles 3 and 4). Percentages of AHS infections were 0% through day 5, 8% through day 25, 50% through day 16, and 21% through day 21, respectively. The peak was reached when cycle 4 of chemotherapy was finally administered. In the chemo arm of the intensification phase, the peak incidence occurred between days 16 and 20; this was especially true for the first course, which included the intensively planned HDAraC. After finishing the treatment on days 7 and 8, the proportion of AHS infections on days 0 through 5, 6 through 10, 11 through 15, and 16 through 20 and 21 were 0%, 3%, 21%, 67%, and 13%, accordingly.

Influence of Time and Therapy Group on the Spread of AHS Bacteremia

Patient-by-patient rates of AHS bacteremia in the three induction groups are shown in Table. Fifteen percent of the individuals tested developed AHS bacteremia during induction (including courses 1 and possibly 2). Those who underwent intensive timed induction had a significantly higher chance of AHS bacteremia ($P = 0.008$), independent of G-CSF use. Early cycle 2 commencement was associated with a greater risk of AHS bacteremia (9%) compared to delaying cycle 2 until hematological recovery (6%). The incidence of AHS bacteremia was nearly 2-fold greater for individuals on aggressive arms during induction ($P = 0.03$). Severe cases of AHS sepsis were more common in critical care units ($P = 0.003$). G-CSF did not significantly mitigate AHS sepsis in the intensive timing arms.

Implications for Patient Progression and Outcome Due to AHS Bacteremia

The impact of AHS bacteremia on hospitalization time and course duration was analyzed. Patients with AHS bacteremia during all courses experienced significantly longer hospital stays (11 to 12 days). Course duration was also increased, particularly in the intensive timing arm. AHS bacteremia was used as a time-dependent covariate in Cox regression to assess its impact on survival rates, event-free survival, and overall survival after induction. Disease-free survival was examined to see if AHS infections affected treatment outcomes and recurrence. Among patients who developed AHS during BMT, both autologous and allogeneic, decreased overall survival and disease-free survival were observed compared to those who did not develop AHS (OR, 2.9; $P < 0.002$).

DISCUSSION

Patients with AML have a significant risk of AHS. According to previous studies conducted at a single institution2-10, the present research aimed to answer the following questions about these rates: (1) Were they also seen in a multi-institutional environment; (2) What risk factors were involved; and (3) How did these variables affect the treatment and outcome of the patients. One therapeutic worry was whether or not ramping up initiation and condensation might result in more toxicity, including infections, without improving disease-free lifespan. Increased dose-intensity with closely scheduled chemotherapy has been demonstrated to enhance disease-free survival; however, doing so has a higher risk of harm.[5]

This study gives the first comprehensive population-based examination of AHS infection rates and outcomes. The results of this research show that the probability of getting AHS infection among those having standard AML treatment remains significant (22%). These results also show that AHS incidence is significantly boosted by the intensive timing method. Seventeen percent of all infections, and twenty-two percent of all bacteremic events, in the present study were attributable to AHS. The results also demonstrate that blood transmission is responsible for the vast majority of AHS infections (87%).[6-8]

Several studies have examined the incidence of AHS in bacterial epidemics, finding rates between 14 and 28 percent. Few population-based research have 3,5 attempted to quantify incidence among patients managed in this way. Organizations that were carried out so often

had substantially smaller sample sizes and were conducted at a single institution. Patients with neutropenia who were feverish (10 out of 72) were either receiving treatment for myeloid leukemia or were recipients of allogeneic bone marrow transplants.[9-12]

The incidence of AHS amongst BMT participants has been estimated to range from 10% to 16% in three separate studies.[13,14,15]

Researchers were able to examine the impact of dose-intensity on infections occurrence by analyzing AHS infection rates among individuals receiving this particular randomized treatment regimen for AML. This result suggests that the greater dose-intensity administered in the rigorous time induction arms contributed to a higher occurrence of sickness. The risk was still considerably larger (OR, 1.9–2.0; P 6.03) than using simple temporal induction, even after accounting for the duration of risk using rate analysis.

This research also shows that HDAraC users are twice as likely to get AHS bacteremia. While prior studies have shown a range of AHS risks after HDAraC, these analyses have focused on subsets of the treated population (e.g., those with febrile neutropenia) rather than the overall incidence or rate. This finding is consistent with previous studies that found an increased risk during the HDAraC phase of AML treatment compared to the standard induction (OR, 3.8). In a study with a limited sample size, HDAraC was used as part of a multi-agent regimen to treat 93% of AHS septicemias. Moreover, the results of this research show that GI toxicity is a significant risk factor for the occurrence of AHS bacteremia (22% v 13%, P.02). These results, together with those of other research, suggest that measures taken to lessen GI toxicity could also have a beneficial effect on bacterial infections.[19,20] Autologous BMT recipients had a higher risk of AHS infection than allogeneic BMT recipients (OR, 4.4; P.002), despite both groups using identical pre-transplantation preparation protocols. There was no clear reason for this effect, albeit these people could have been given more antibiotics throughout the transplant period. The use of preventative medications during BMT was not included in the data forms; hence, the reason for the decreased prevalence remains a mystery.[16,17,18]

AHS prophylaxis wouldn't be considered frequently utilized throughout the autologous BMT phase, although the frequency was comparable to that of the intense timing induction periods. There is mounting evidence that TMP-SMX usage contributes to an elevated risk of AHS bacteremia. TMP-SMX prophylaxis was associated with a 50.3-fold increased odds of AHS in one research. Pediatric cancer patients, and AML patients in particular, have been advised to take TMP-SMX as a preventative measure. Compliance was not examined, despite the fact that the authors of the current research strongly suggested doing so as a way to reduce the risk of AHS.

Several pre-existing risk variables for AHS after induction that were present at the time of AML diagnostic were not previously investigated. The patient's age was shown to be linked with likelihood of AHS bacteremia during induction, among the investigated factors present at diagnosis. AHS was more common in children less than 3 years old (18%, P .06) than in those between the ages of 3 and 10 (15%) or in those older than 10 (11%). Looking at infection rates, we found that those in patients younger than 10 years old had a significantly higher rate than those older than 10 years old (OR, 1.6 to 1.9; P .007). Since this organism makes up the vast majority of the normal oral flora, tooth exfoliation and the eruption of new teeth, both of which are prevalent at these ages, may contribute to the increased risk; however, no one has yet investigated this link.

Furthermore, the current research showed that AHS often returned after several rounds of myelosuppressive treatment. There was a 31% chance of a second episode of AHS in individuals who had further treatment after their first infection. The significant recurrence chances seen by Weisman et al.[3] and Sotiropoulos et al.[2] among their respective groups of pediatric patients (46 and 71%, respectively) are consistent with

one another. Therefore, prevention or careful monitoring of individuals with a history of AHS bacteremia should be highly considered.

CONCLUSION

To determine whether or if people with AML had an increased risk of AHS, this research used a carefully selected sample. HDAraC users younger than 23 are more vulnerable. The increased likelihood of AHS infection due to the more aggressive dosing schedules currently in use. AHS infections are notoriously difficult to cure, and even after several rounds of chemotherapy, they often return. Oral penicillin prophylaxis in these high-risk patients: a randomized controlled trial, shows significant decreases in cases of AHS have been seen after the use of this strategy. The doctors treating these patients need to be on high alert for signs of AHS bacteremia and ready to start their patients on empiric antibiotics right away in many instances.

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3	Uzma Ali	Data collection and data analysis.	
4	Amna Khalid	Practical work, Data collection and wirting.	
5	Namra Yunus	Practical work, Data analysis and writing.	
6	Saadia Anwar	Practical work, Data collection, Proof reading.	