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LIFE-THREATENING AND FATAL INFECTIONS IN CHILDREN WITH ACUTE MYELOID LEUKEMIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Abstract

To determine among children with acute myeloid leukemia (AML), whether the proportions of life-threatening or fatal infections differed according to intensity of induction or type of intensification treatment.

Subjects were children enrolled on Children's Cancer Group (CCG) 2891 with *de novo* AML. In Phase 1 (induction) patients were randomized to four cycles of chemotherapy either administered as intensive or standard timing. In Phase 2 (intensification), those achieving remission were allocated to allogeneic stem cell transplantation (SCT) if a suitable family donor was available while the remainder were randomized to autologous SCT or chemotherapy. Each infection was classified prospectively as non-life threatening, life-threatening or fatal.

The proportion of all infections that were considered life-threatening or fatal was higher with intensive timing compared with standard timing induction (60.3% versus 37.3%, P<.0001). Infections caused by Gram positive and negative bacteria and fungi were significantly more likely to be severe during intensive compared with standard timing induction. Most molds were life-

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SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1: Appendix 1 (Sung et al_AML COG Report_R2_SDC.doc)

Supplemental Digital Content 2: Appendix 2 (Sung et al_AML COG Report_R2_SDC.doc)

Supplemental Digital Content 3: Appendix 3 (Sung et al_AML COG Report_R2_SDC.doc)

threatening or fatal. Chemotherapy intensification was not associated with less severe infections compared to SCT.

Intensive timing was associated with more severe infections compared to standard timing induction. Prophylactic strategies are likely more important with intensive induction regimens.

Keywords

infections; children; acute myeloid leukemia

INTRODUCTION

Infections are an important cause of morbidity and mortality for children with acute myeloid leukemia (AML) (1). Children with AML are particularly susceptible to severe infections, likely related to the intensity of therapy resulting in repeated episodes of prolonged and profound neutropenia. Infectious deaths are relatively common in this population, with an infection-related mortality rate between 5.4% and 7.3% during chemotherapy (2–5). Furthermore, life-threatening but non-fatal infections are frequent, result in morbidity, and may limit the ability to deliver chemotherapy.

One strategy to optimize survival for children with AML would be to focus on the prevention of the most severe infections, in other words, those that are life-threatening or fatal. In order to accomplish this goal, the initial steps would be to understand the demographics of life-threatening and fatal infections by causative organism and to understand how this distribution differs according to different intensity and types of therapy. These types of data may be helpful for improving patient care and guiding choices for empiric and possibly prophylactic regimens.

CCG 2891 was a Children's Cancer Group Phase III trial in which therapy was divided into two phases (6, 7). Phase 1 (induction) consisted of four cycles of induction chemotherapy; children were randomized to receive therapy administered as intensive or standard timing. During phase 2 (intensification), those with a suitable family donor were allocated to allogeneic stem cell transplantation (SCT), whereas those without a donor were randomized to autologous SCT or chemotherapy. Consequently, this trial design allowed us to examine whether the proportion of life-threatening or fatal infections differed according to intensity of therapy (intensive versus standard timing induction) or type of intensification (chemotherapy, autologous SCT, or allogeneic SCT) among comparable groups of patients.

A systematic evaluation of infections in AML patients would first include an understanding of the spectrum of all infections followed by a description of which infections are considered severe (life-threatening or fatal). We previously accomplished the former goal and described the prevalence of organisms that caused microbiologically documented infections for children treated on CCG 2891 by type of therapy received (8). The focus of this subsequent report is to describe which organisms were more likely to be considered life-threatening or fatal and to determine whether intensity of induction or type of intensification therapy impacts on the proportion of life-threatening or fatal infections.

Therefore, the primary objective was to describe whether the proportions of life-threatening or fatal infections differed according to intensity of induction or type of intensification therapy. The secondary objectives were (a) to describe the proportion of infections during induction that were life-threatening or fatal by infection site and (b) to describe risk factors for life-threatening or fatal infections during induction.

MATERIALS AND METHODS

Patients

The patients included in this report were those enrolled on CCG 2891 (6, 7). Children less than 21 years of age with newly diagnosed AML, and acute undifferentiated or biphenotypic leukemia with evidence of myeloid differentiation, were eligible. Patients with acute promyelocytic leukemia became ineligible in April 1992. For this analysis, patients with Down's syndrome, AML as a second malignancy, myelodysplastic syndrome or isolated chloroma were excluded. We also excluded 15 patients who started with standard timing and whose protocol was changed to intensive timing when an analysis revealed the superiority of intensive timing. Institutional research ethics approval was obtained from each of the participating centers and written informed consent was obtained from all participants.

CCG 2891 Characteristics

This trial was open to patient accrual from October 1989 to May 1995. The specific therapy of this trial consisted of two phases of therapy. Phase 1 induction contained four cycles of chemotherapy. Initial treatment consisted of two cycles of a five-drug regimen of chemotherapy administered over four days: dexamethasone, cytarabine, 6-thioganine, etoposide, and rubidomycin (DCTER). Patients were randomized to receive the second cycle of DCTER either with intensive timing after a 6 day rest period irrespective of bone marrow status or hematological recovery, or to standard timing in which bone marrow was examined on day 14. Those in whom the day 14 marrow demonstrated good leukemia response had their second DCTER administered when the blood counts recovered whereas those with > 40% blasts on their day 14 bone marrow proceeded to the second DCTER immediately. The next two cycles of DCTER were then given either as intensive or standard timing according to the initial randomization. All patients in both arms received identical cumulative doses of induction chemotherapy. Those in remission after four DCTER cycles with an appropriate family donor were allocated to allogeneic SCT. All others were randomized to autologous SCT or intensive chemotherapy. Intensive chemotherapy consisted of four courses of three chemotherapy regimens. Course 1 consisted of high dose, intensively-timed cytarabine, and L-asparaginase, courses 2 and 3 consisted of 6-thioguanine, vincristine, cytarabine, cyclophosphamide, and 5-azacytidine, and course 4 consisted of cytarabine, daunorubicin, etoposide, 6-thioganine, and dexamethasone. Collectively, either SCT or the four courses of chemotherapy were referred to as Phase 2 intensification. For Phase 2 chemotherapy intensification, only course 1 was included in this analysis since only this course consisted of intensive chemotherapy.

Supportive Care Recommendations on CCG 2891

Initially, the use of hematopoietic growth factors was not permitted except for granulocyte-macrophage colony stimulating factor which was allowed for poor engraftment following SCT. However, in an attempt to reduce infection outcomes, prophylactic granulocyte colony stimulating factor was introduced in 1993 in a non-randomized fashion. (9). Since the addition of growth factor did not impact on infection outcomes, we did not examine the impact of its use in this paper.

All children received trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jiroveci*. Either nystatin or clotrimazole troches were recommended for fungal prophylaxis.

In the event of febrile neutropenia defined as an absolute neutrophil counts less than 500/ul and an oral temperature greater than 38°C twice in 12 hours or greater than 38.5°C once, empiric systemic antibiotics were strongly recommended. The suggested regimen was vancomycin and antibiotics with Gram negative coverage appropriate to cover *Pseudomonas* species and *Escherichia coli*. Concomitant with starting antibacterial agents for fever and neutropenia, intravenous miconazole also was strongly suggested. For those with persistent fever during neutropenia in those who had received antibiotic therapy for seven or more days without identification of an infectious agent, empiric administration of amphotericin B was suggested.

Outcomes

Infections were prospectively collected by institutional clinical research associates using a standardized data collection form. A separate infection form was completed for each significant infection with instructions to not submit positive surveillance cultures. For organisms such as coagulase negative staphylococci, there was no effort made to distinguish true infections from likely contaminants. Clinically documented infections were classified based upon physician reports. For each infection, site and organism name were collected. In addition, each infection was graded as non-life threatening, life-threatening, or fatal by the clinical research associates and confirmed by the principal investigators when classification was uncertain.

Statistical Analysis

The primary outcome was expressed as the proportion of patients experiencing a given infection type that was classified as life-threatening or fatal relative to all infections of that type, within a specific phase and type of therapy. The time period at risk was during study chemotherapy administration or SCT and did not include time after removal from study for any reason, or relapse. For most children, the time period at risk began on the day chemotherapy was initiated and extended until the day before initiation of the next course of chemotherapy except for SCT. The follow-up period for SCT was 100 days after transplantation. Finally, as an exploratory analysis, we also examined the association between having a life-threatening infection versus not having a life-threatening infection during induction and influence on event-free and overall survival using infection status as a time-dependent covariate in a Cox proportional hazards model. The analyses were all

conducted as intent-to-treat; in other words children were analyzed in the group to which they were randomized (or allocated in the case of allogeneic SCT).

The primary objective was to compare the proportion of infections that were classified as life-threatening or fatal by intensity of induction or type of intensification treatment. This analysis was conducted using the Fisher's exact test. Because those who experience infections during Phase 2 are a selected group of children who survived Phase 1 and remained on study, we chose to focus the secondary objectives solely during Phase 1. The proportion of patients with life-threatening or fatal infections by site was described using proportions. For the secondary analysis describing predictors of any life-threatening or fatal infection, this aim was accomplished using univariate, and if appropriate, multivariate logistic regression. Statistical analyses were performed using SAS/STAT software, Version 9.2 of the SAS System, copyright SAS Institute Inc., Cary, NC, USA.) All tests of significance were 2-sided, and statistical significance was defined as $P < .05$.

RESULTS

A total of 872 patients were enrolled on CCG 2891. Details of the demographics have previously been published (6) but in short, 422/872 (48%) were female, 176/872 (20%) were less two years of age, and 345/872 (40%) were between two and ten years of age. Of these 872 patients, 678 were randomized to intensive (n=343) versus standard (n=335) timing induction and 452 were allocated or randomized to chemotherapy (n=168), autologous SCT (n=137), or allogeneic SCT (n=147) in Phase 2. For the induction question, 194 non-randomized patients were allocated to intensive timing when an analysis revealed better disease outcome with intensive timing. The non-randomized patients are not included in the following analyses. Among the randomized patients, the most common FAB type was M2 (216/678, 32%) followed by M4 (149/678, 22%); there were 50 children with M3 AML.

Table I illustrates that the proportion of all infections that were life-threatening or fatal was significantly greater for intensive compared with standard timing (60.3% versus 37.3%, P<. 0001) during Phase 1 induction. Infections caused by Gram positive bacteria, Gram negative bacteria and fungi were significantly more likely to be classified as life-threatening or fatal when occurring during intensive timing. More specifically, infections caused by viridans group streptococci, *Pseudomonas* species and *Escherichia coli* were more likely to be life-threatening or fatal when occurring during intensive timing versus standard timing. Most molds were considered life-threatening or fatal and this proportion was not influenced by whether it occurred during standard or intensive timing induction. Appendices 1 and 2 separate out life-threatening and fatal infection by induction type; similar findings were found in the stratified analysis as compared to the overall analysis (see Table, Supplemental Digital Content 1 and 2). More specifically, the proportion of infections that were fatal was significantly greater for intensive compared with standard timing for all infections and bacterial infections.

Table II illustrates that infections occurring during chemotherapy and autologous SCT were similar in terms of the proportion that were life-threatening or fatal. While infections occurring during chemotherapy were more likely to be life-threatening or fatal compared

with allogeneic SCT (58.8% versus 42.7%, P=.043), this difference was not obviously associated with a particular type of infection. Appendix 3 separates out life-threatening infection by consolidation type; these results are similar to the analysis when life-threatening and fatal infections were combined (see Table, Supplemental Digital Content 3). There was insufficient number of fatal events to examine infection type by consolidation therapy type.

In terms of different sites of infection, Table III demonstrates that infections involving the blood, lung, liver, and central nervous system were associated with a high (>60%) proportion of infections that were life-threatening or fatal. Conversely, infections involving the upper gastrointestinal system, skin, and urinary tract were rarely (<32%) considered severe.

Table IV illustrates the univariate logistic regression analyses that examine factors associated with all, bacterial and fungal life-threatening or fatal infections. Older age was significantly associated with increased infections overall. Otherwise, in general, age, initial white blood cell count, gender, and ethnicity did not impact on the proportion of infections that were considered life-threatening or fatal. FAB type M3 had borderline significant association with increased bacterial infection. Conversely, intensive timing was significantly associated with life-threatening or fatal infections with all infection outcomes. We conducted a multiple regression analysis with all infections as the outcome and examined the contribution of intensive timing and age group. In this model, intensive timing (odds ratio (OR) 2.51, 95% confidence interval (CI) 1.65 to 3.82, P<0.0001) remained significantly associated with infection while age > 10 did not remain significant (OR 1.67, 95% CI 0.96 to 2.92, P=0.071).

In the exploratory analysis, those who experienced a life-threatening infection (excluding fatal infections) did not have a significantly different event-free survival (hazard ratio 0.92; P=0.507) or overall survival (hazard ratio 0.84; P=0.155) compared to children who did not experience a life-threatening infection, accounting for induction therapy

DISCUSSION

We found that the proportion of infections that were classified as life-threatening or fatal was high among pediatric patients with AML receiving induction or intensification treatment. We also found that intensive timing of chemotherapy is the most important determinant of life-threatening or fatal infection during induction and that chemotherapy intensification was not associated with less severe infections compared to autologous or allogeneic SCT. Our report is important because previously, we knew that intensive timing was an important determinant of the prevalence of infection in pediatric AML. The current report now provides evidence that intensive timing not only increases the prevalence of infection but among those infections, intensive timing is associated with more severe infection. Our report also is important as it quantifies the degree to which these patients are at risk for life-threatening or fatal infections. There are probably at least two considerations when planning infection management strategies within a given patient population – the prevalence of infections and their severity. This report addresses the latter consideration.

While several reports have described the rate of infection-related mortality in AML patients (10, 11), our report is unique in the examination of life-threatening infections.

We found that irrespective of treatment intensity (during Phase 1) or type (during Phase 2), molds were most likely to be life-threatening or fatal. This prominence of mold infections as an important cause of infection and infectious mortality in pediatric AML has previously been described (4, 11). Our findings add additional weight to the argument that prevention of molds is an important consideration during AML therapy.

Viridans group streptococci is known to be an important cause of infection in pediatric AML (12, 13) and a report from CCG 2891 previously showed that that viridians group streptococci was more likely life-threatening compared to other organisms (14). Conversely, an adult study that retrospectively reviewed AML patients receiving induction or consolidation therapy found that severe sepsis was associated with Gram negative but not Gram positive organisms isolated from blood culture (15). While our report did not formally compare which organisms were more likely to be associated with life-threatening or fatal infection, viridians group streptococci and molds were prominent causes of severe infection. The difference in our CCG reports and the adult report may be related to differences in supportive care practices between different countries or between adult and pediatric centers or to differences in AML chemotherapy.

Our secondary analysis of describing the proportion of severe infection by site and predicting those infections most likely to be life-threatening or fatal focused on Phase 1 induction and did not include Phase 2 intensification. We rationalized this analysis on the basis of two factors. First, those in Phase 2 are a select subset of those who survive and are in remission by the end of Phase 1. Second, Creutzig and colleagues demonstrated that the incidence of lethal infections was highest during induction (10), thus making this period the most relevant for our purposes.

Our report is limited as rigid definitions for “life-threatening” was not used in this study and therefore, it is possible that there was variability in how life-threatening was classified within and between different centers. However, our approach may also be advantageous as it may encompass the gestault of clinicians, which is likely an important predictor of patient outcome. Another limitation of our report is that we could not separate out possible contaminants from true infections for organisms such as coagulase negative staphylococci. Finally, rigid definitions of pneumonia, liver infections and urinary tract infections also were not used and thus, there may have been some variability in classification.

In conclusion, about 60% of infections occurring during intensive timing induction were considered life-threatening or fatal and severe infections were more common with intensive as compared to standard timing induction. Chemotherapy intensification was not associated with less severe infections compared to autologous or allogeneic SCT. Molds were usually life-threatening or fatal. These data suggest that prophylaxis strategies should be considered during intensive induction regimens and that prophylaxis for molds may be an important future strategy in pediatric AML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I

PROPORTION OF PATIENTS EXPERIENCING INFECTIONS THAT WERE LIFE-THREATENING OR FATAL DURING INDUCTION BY MICROORGANISM*

	Standard N=335	Intensive N=343	P Value
All Infections	56/150 (37.3%)	147/244 (60.3%)	<0.0001
Bacteria	48/132 (36.4%)	118/198 (59.6%)	<0.0001
Gram positive bacteria	40/107 (37.4%)	89/159 (56.0)	0.004
CoNS	14/41 (34.2%)	29/53 (54.7%)	0.061
Viridans group *Streptococcus*	12/28 (42.9%)	38/53 (71.7%)	0.016
Enterococcus species	5/15 (33.3%)	8/24 (33.3%)	1.000
Staphylococcus aureus	5/14 (35.7%)	5/17 (29.4%)	1.000
Pneumococcus	0	1/3 (33.3%)	NA
Other Gram positives	9/43 (20.9%)	43/78 (55.1%)	0.0003
Gram negative bacteria	10/46 (21.7%)	52/91 (57.1%)	0.0001
Pseudomonas species	3/13 (23.1%)	19/32 (59.4%)	0.047
Klebsiella species	4/12 (33.3%)	11/21 (52.4%)	0.469
Escherichiae coli	1/11 (9.1%)	8/16 (50.0%)	0.042
Enterobacter species	2/5 (40.0%)	6/13 (46.2%)	1.000
Citrobacter species	0	1/2 (50.0%)	NA
Other Gram negatives	1/15 (6.7%)	18/25 (72.0%)	<0.0001
Fungi	12/33 (36.4%)	59/94 (62.8%)	0.014
Yeasts	8/28 (28.6%)	32/65 (49.2%)	0.073
Candida species	7/25 (28.0%)	30/60 (50.0%)	0.092
Non-*Candida* yeasts	1/4 (25.0%)	3/12 (25.0%)	1.000
Molds	4/5 (80.0%)	34/40 (85.0%)	1.000
Aspergillus species	1/2 (50.5%)	26/30 (86.7%)	0.292
Non-*Aspergillus* molds	3/3 (100.0%)	9/11 (81.8%)	1.000
Viruses	2/13 (15.4%)	17/48 (35.4%)	0.311

Abbreviations: CoNS – coagulase negative *Staphylococcus*

*This table illustrates the proportion of infections during induction which were classified as life-threatening or fatal

Note: The sub-categories do not necessarily total the higher level of categories since patients may have more than one type of infection

TABLE II

PROPORTION OF PATIENTS EXPERIENCING INFECTIONS THAT WERE LIFE-THREATENING OR FATAL DURING INTENSIFICATION BY MICROORGANISM*

	Chemo N=168	AutoSCT N=137	P Value**	Allo SCT N=147	P Value***
All Infections	60/102 (58.8%)	34/72 (47.2%)	0.165	29/68 (42.7%)	0.043
Bacteria	52/95 (54.7%)	32/69 (46.4%)	0.343	26/59 (44.1%)	0.246
Gram positive bacteria	32/63 (50.8%)	22/47 (46.8%)	0.704	19/40 (47.5%)	0.840
Coagulase negative Staphylococci	8/18 (44.4%)	8/17 (47.1%)	1.000	11/18 (61.1%)	0.505
Viridans group streptococci	14//27 (51.9%)	9/19 (47.4%)	1.000	4/4 (100.0%)	0.120
Enterococcus species	0/3 (0%)	3/6 (50.0%)	0.464	3/5 (60.0%)	0.196
Staphylococcus aureus	1/3 (33.3%)	1/3 (33.3%)	1.000	1/3 (33.3%)	1.000
Pneumococcus	0	0	NA	0/1 (0%)	NA
Other Gram positives	12/23 (52.2%)	4/13 (30.8%)	0.301	5/19 (26.3%)	0.120
Gram negative bacteria	26/48 (54.2%)	15/34 (44.1%)	0.502	11/32 (34.4%)	0.110
Pseudomonas species	5/11 (45.5%)	3/12 (25.0%)	0.400	3/10 (30.0%)	0.659
Klebsiella species	5/9 (55.6%)	2/7 (28.6%)	0.358	1 /4 (25.0%)	0.559
Escherichiae coli	7/12 (58.3%)	2/7 (28.6%)	0.350	4/9 (44.4%)	0.670
Enterobacter species	2/4 (50.0%)	1/3 (33.3%)	1.000	1/3 (33.3%)	1.000
Citrobacter species	2/3 (66.7%)	1/1 (100.0%)	1.000	3/5 (60.0%)	1.000
Other Gram negatives	7/14 (50.0%)	6/14 (42.9%)	1.000	3/11 (27.3%)	0.414

	Chemo N=168	AutoSCT N=137	P Value**	Allo SCT N=147	P Value***
Fungi	11/16 (68.8%)	4/11 (36.4%)	0.130	6/9 (66.7%)	1.000
Yeasts	6/12 (50.5%)	2/9 (22.2)	0.367	3/6 (50.0%)	1.000
Candida species	5/11 (45.5%)	1/7 (14.3%)	0.316	3/5 (60.0%)	1.000
Non-*Candida* yeasts	1/1 (100.0%)	1 /2 (50.0%)	1.000	0/1 (0%)	1.000
Molds	5/5 (100.0%)	2/2 (100.0%)	NA	3/3 (100.0%)	NA
Aspergillus species	3/3 (100.0%)	0	NA	3/3 (100.0%)	NA
Non-*Aspergillus* Molds	3/3 (100.0%)	2/2 (100.0%)	NA	0	NA
Viruses	4/7 (57.1%)	4/12 (33.3%)	0.377	4/19 (21.1%)	0.149

* This table illustrates the proportion of infections during induction which were classified as life-threatening or fatal

** P value is for comparison between autologous stem cell transplantation versus chemotherapy

*** P value is for comparison between allogeneic stem cell transplantation versus chemotherapy

Note: The sub-categories do not necessarily total the higher level of categories since patients may have more than one type of infection

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TABLE III

PROPORTION OF INFECTIONS THAT WERE LIFE-THREATENING OR FATAL DURING INDUCTION BY SITE

	All organisms	Bacteria	Gram Positive	Gram Negative	All Fungi	Yeasts	Molds	Viruses
Blood	137/227 (60.4%)	131/218 (60.1%)	97/170 (57.1%)	51/80 (63.8%)	13/18 (72.2%)	11/15 (73.3%)	2/3 (66.7%)	3 /4 (75.0%)
Pulmonary	25/31 (80.7%)	6/9 (66.7%)	4/4 (100%)	0/1 (0%)	23/24 (95.8%)	5/6 (83.3%)	20/20 (100.0%)	1/3 (33.3%)
Upper GI	17/53 (32.1%)	6/16 (37.5%)	5/14 (35.7%)	2/5 (40%)	5/21 (23.8%)	4/20 (20.0%)	2/2 (100.0%)	8/20 (40.0%)
Lower GI	23/58 (39.7%)	16/35 (45.7%)	13/29 (44.8%)	3/7 (42.9%)	6/15 (40.0%)	5/14 (35.7%)	1/1 (100.0%)	1/6 (16.7%)
Skin and Subcutaneous	10/48 (20.8%)	7/31 (22.6%)	5/25 (20%)	2/7 (28.6%)	2/8 (25.0%)	0/4 (0%)	2/4 (50.0%	1/10 (10.0%)
CNS	1/1 (100.0%)	0	0	0	1/1 (100.0%)	0	1/1 (100.0%)	0
Urinary Tract	8/47 (17.0%)	1/29 (3.5%)	1/17 (5.9%)	0/14 (0%)	6/20 (30.0%)	6/20 (30.0%)	0	1/2 (50.0%)
CVC	25/58 (43.1%)	20/54 (37.0%)	7/14 (50.0%)	6/24 (25.0%)	5/7 (71.4%)	4/6 (66.7%)	2/2 (100.0%)	0
Liver	5/8 (62.5%)	3/4 (75.0%)	3/4 (75.0%)	0	2/4 (50.0%)	1/3 (33.3%)	1/1 (100.0%)	0
Upper Respiratory	10/23 (43.5%)	2/6 (33.3%)	2/5 (40.0%)	0/2 (0%)	4/7 (57.1%)	2/3 (66.7%)	2/4 (50.0%)	4/10 (40.0%)

Abbreviations: CNS – central nervous system; CVC – central venous catheter

TABLE IV

PREDICTORS OF LIFE-THREATENING/ FATAL INFECTION IN PHASE 1

Potential Predictor	Odds Ratio (95% CI)	P value
ALL INFECTIONS		
Age		
0 to < 2 Years	Ref	
2 to 10 Years	1.42 (0.83, 2.45)	0.202
> 10 Years	1.75 (1.02, 3.02)	0.044
Initial WBC > 50,000/uL	0.81 (0.52, 1.26)	0.350
FAB Type		
M0	0.83 (0.28, 2.40)	0.724
M1	1.49 (0.77, 2.90)	0.242
M2	Ref	
M3	1.97 (0.89, 4.36)	0.094
M4	0.78 (0.45, 1.34)	0.369
M5	0.81 (0.43, 1.53)	0.520
M7	0.79 (0.32, 1.94)	0.601
Male gender	1.02 (0.69, 1.52)	0.905
Ethnicity		
White	Ref	
Non-white	1.39 (0.91, 2.14)	0.127
Intensive Timing	2.54 (1.67, 3.87)	<0.0001
BACTERIA		
Age		
0 to < 2 Years	Ref	
2 to 10 Years	1.41 (0.79, 2.53)	0.249
> 10 Years	1.62 (0.90, 2.90)	0.106
Initial WBC > 50,000/uL	0.77 (0.47, 1.25)	0.291
FAB Type		
M0	0.68 (0.20, 2.26)	0.527
M1	1.40 (0.68, 2.86)	0.362
M2	Ref	
M3	2.49 (1.02, 6.08)	0.045
M4	0.60 (0.33, 1.11)	0.104
M5	0.80 (0.40, 1.58)	0.517
M7	0.85 (0.32, 2.26)	0.751
Male gender	1.03 (0.67, 1.58)	0.909
Ethnicity		
White	Ref	
Non-white	1.19 (0.75, 1.88)	0.459
Intensive Timing	2.58 (1.64, 4.07)	<0.0001

Potential Predictor	Odds Ratio (95% CI)	P value
FUNGI		
Age		
0 to < 2 Years	Ref	
2 to 10 Years	1.48 (0.51, 4.29)	0.469
> 10 Years	1.51 (0.54, 4.27)	0.436
Initial WBC > 50,000/uL	0.79 (0.36, 1.74)	0.555
FAB Type		
M0	0.44 (0.07, 2.89)	0.389
M1	1.30 (0.44, 3.91)	0.631
M2	Ref	
M3	1.14 (0.29, 4.51)	0.847
M4	0.61 (0.24, 1.58)	0.308
M5	0.44 (0.13, 1.45)	0.175
M7	1.31 (0.11, 15.57)	0.832
Male gender	1.40 (0.69, 2.83)	0.356
Ethnicity		
White	Ref	
Non-white	0.91 (0.44, 1.88)	0.790
Intensive Timing	2.95 (1.30, 6.72)	0.010

Abbreviation: CI – confidence interval; FAB – French American British

*M6 is not shown as there were only 14 observations for this group and none were life-threatening or fatal