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Decreased Induction Morbidity and Mortality Following Modification to Induction Therapy in Infants with Acute Lymphoblastic Leukemia Enrolled on AALL0631: a Report from the Children's Oncology Group

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Abstract

Background—Infants with acute lymphoblastic leukemia (ALL) have a poor prognosis.

Intensification of therapy has resulted in fewer relapses but increased early deaths, resulting in failure to improve survival.

Procedure—AALL0631 is a Phase 3 study for infants (< 366 days of age) with newly diagnosed ALL. Induction initially (Cohort 1) consisted of 3 weeks of therapy based on COG P9407. Due to excessive early mortality, induction was amended to a less intensive 5 weeks of therapy based on

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Interfant-99. Additionally, enhanced supportive care guidelines were incorporated with hospitalization during induction until evidence of marrow recovery and recommendations for prevention/treatment of infections (Cohort 2).

Results—Induction mortality was significantly lower for patients in Cohort 2 (2/123, 1.6%) versus Cohort 1 (4/26, 15.4%; $p=0.009$). All induction deaths were infection related except one due to progressive disease (Cohort 2). Sterile site infections were lower for patients in Cohort 2 (24/123, 19.5%) versus Cohort 1 (15/26, 57.7%; $p=0.0002$), with a significantly lower rate of Gram positive infections during induction for patients in Cohort 2, $p=0.0002$. No clinically significant differences in grades 3–5 non-infectious toxicities were observed between the two cohorts. Higher complete response rates were observed at end induction intensification for Cohort 2 (week 9, 94/100, 94%) versus Cohort 1 (week 7, 17/25, 68%; $p=0.0012$).

Conclusion—De-intensification of induction therapy and enhanced supportive care guidelines significantly decreased induction mortality and sterile site infections, without decreasing complete remission rates.

Keywords

Mortality; Infant Acute Lymphoblastic Leukemia

INTRODUCTION

Event free survival (EFS) of children diagnosed with acute lymphoblastic leukemia (ALL) exceeds 85% with current multi-agent regimens [1–8]. However, outcome for infants with ALL is much worse, with EFS of 23–51% [8–16]. Compared to older children, infants are more likely to have hyperleukocytosis, central nervous system disease, and rearrangement of the 11q23 mixed lineage leukemia (*MLL*) gene [9,11–15]. Clinical trials have established that intensification of therapy results in fewer early relapses, but also results in increased toxic mortality, notably during induction, with no substantial improvement in long-term survival [7–12,16–18].

The Children's Oncology Group (COG) AALL0631 infant ALL study was designed to introduce post-induction targeted therapy (with the FLT3 inhibitor lestaurtinib) built upon the predecessor COG P9407 backbone. This report focuses on the unexpectedly high incidence of treatment-related mortality during induction, and the observed decrease in incidence following adoption of a modified Interfant-99 induction regimen [15].

METHODS

Patients

AALL0631 is a Phase 3 study for infants less than 366 days of age with newly diagnosed ALL or acute undifferentiated leukemia. Patients with T cell ALL are eligible, as are those with bilineage or biphenotypic acute leukemia provided the morphology and immunophenotype are predominately lymphoid. Patients with mature B-cell ALL, acute myelogenous leukemia, Down Syndrome, or who are ≥ 36 weeks gestational age are not eligible.

The study was approved by the National Cancer Institute and by Institutional Review Boards at the individual COG member institutions prior to patient enrollment. Informed consent was obtained from parents or guardians according to Department of Health and Human Services Guidelines.

Treatment

All infants enrolled on AALL0631 receive a common induction therapy (Table I). This therapy was initially based (Cohort 1) upon the 3 week COG P9407 induction [16]. Modifications from the predecessor COG P9407 induction included dose reduction of daunorubicin of approximately 15% and substitution of one dose of PEG-asparaginase for 8 doses of native L-asparaginase. The study opened to accrual in January 2008 and was temporarily closed to accrual in November 2008 due to excessive induction toxicity. The study was amended and re-opened in August 2009 to include a modified 5-week Interfant-99 based induction [15] and enhanced supportive care guidelines (Cohort 2). Induction therapy for Cohort 2 was longer in duration and less intensive. All non-intrathecal agents were dosed per meter squared. Additionally, differences in Cohort 2 versus 1 include: a 7 day prednisone prophase, lower daunorubicin dose, modified intrathecal therapy, modified vincristine dosages, low dose cytarabine, omission of cyclophosphamide and filgrastim, and substitution of native L-asparaginase for PEG-L-asparaginase. Complete remission (< 5% blasts on bone marrow examination) was determined following induction/intensification in Cohort 1 (completion of week 7) and Cohort 2 (completion of week 9). Induction intensification consisted of 2 doses of high dose methotrexate (4 grams/m² over 24 hours) on days 1 and 8 followed by leucovorin rescue and 5 days of cyclophosphamide (300 mg/m²/dose) and etoposide (100 mg/m²/dose) in days 15–19 followed by filgrastim until count recovery parameters were met and remission status was assessed.

Supportive care guidelines were provided for institutional consideration. They were intended to give general direction for optimal patient care but were not protocol mandated as individual patient characteristics and institutional practices were also a consideration. General supportive care guidelines for Cohort 1 included: (1) broad-spectrum intravenous antibiotics for fever and neutropenia to include adequate coverage for viridans group streptococci and double Gram negative coverage, (2) empiric antifungal therapy for persistent or recurrent fever after 3–5 days of broad-spectrum antibiotics, (3) prophylaxis against *Pneumocystis jiroveci*, (4) prophylaxis against respiratory syncytial virus with palivizumab, (5) influenza vaccination for those 6 months of age, and (6) intravenous immunoglobulin (IVIG) therapy for infants with IgG levels < 500 mg/dL. Additional recommendations added for Cohort 2 in the August 2009 amendment included: (1) hospitalization during induction until evidence of marrow recovery and (2) consideration of anti-fungal prophylaxis in addition to empiric antifungal therapy. No specific agent for anti-fungal prophylaxis was recommended, and if anti-fungal prophylaxis was considered consultation with Infectious Disease was strongly recommended.

Toxicities were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. Grade 3 and higher infection data were collected prospectively and monitored centrally in real-time to optimize reporting accuracy. Specific infectious

pathogens assessed included all sterile site infections (such as blood, urine, and cerebrospinal fluid) and clinically significant respiratory non-sterile infections (such as respiratory syncytial virus, influenza and parainfluenza). Infectious complications included in this report were identified during induction and prior to induction intensification (Cohort 1 weeks 1–3; Cohort 2 weeks 1–5).

Statistical Considerations

Data as of 30 September 2012 are included in this report. One hundred forty-nine eligible patients (26 in Cohort 1; 123 in Cohort 2) were included in the analyses. Induction mortality and toxicity rates between Cohorts 1 and 2 were compared using Fisher's exact test. The odds ratio (OR) and its corresponding 95% confidence interval were computed to describe induction deaths between Cohorts 1 and 2. Time to an infectious death was defined as the time from start date of induction therapy to date of death. Statistical significance was defined as a *p*-value less than 0.05. All analyses were performed using SAS® software.

RESULTS

From January 2008 until September 2012, 149 eligible infants were enrolled on AALL0631: 26 into Cohort 1 and 123 into Cohort 2. Induction death occurred in 6 patients, 4/26 (15.4%) in Cohort 1 and 2/123 (1.6%) in Cohort 2 (OR: 11.0; 95% CI: 1.9, 63.8; *p*=0.009). All induction deaths were infection related (Table II) except one due to progressive disease in Cohort 2. Of the 5 infectious deaths, one (Cohort 1) occurred in an infant 1 day of age at diagnosis; all other deaths occurred in infants >90 days of age at diagnosis. Median time to infectious death was 23 days (range 17–39), and etiologies included Gram positive bacteria, Gram negative bacteria, and fungal organisms.

The incidence of microbiologically confirmed sterile site infections during induction were significantly lower in patients in Cohort 2 (24/123, 19.5%) versus Cohort 1 (15/26, 57.7%; *p*=0.0002). The rate of Gram positive infections was significantly lower in Cohort 2 versus 1 (Table III). There was no significant difference in the rate of fungal or Gram negative infections between Cohorts.

Clinically significant non-sterile site respiratory tract pathogens were identified during induction in 2/26 (7.7%) versus 2/123 (1.6%) patients in Cohort 1 versus 2, respectively, *p*=0.1406. Non-sterile respiratory tract infections resulted in 2 of the 5 infectious deaths during induction therapy (Table II), and an additional two non-lethal pulmonary infections were seen in Cohort 2 with methicillin-resistant *Staphylococcus aureus* and influenza B. Significant respiratory tract infections during induction included Gram positive, Gram negative, fungal, and viral etiologies.

There were no clinically significant differences in the rates of Grade 3–5 non-infectious toxicities during induction between Cohorts 1 and 2. Hypertension, mucositis, skin ulceration, diarrhea, and elevated alanine aminotransferase occurred in 17 (11.4%), 12 (8.1%), 9 (6%), 12 (8.1%), and 13 (8.7%) patients, respectively. End of induction/induction intensification complete response rates were higher for Cohort 2 (week 9, 94/100, 94%) versus Cohort 1 (week 7, 17/25, 68%; *p*=0.0012).

DISCUSSION

Infants treated on Cohort 2 versus Cohort 1 of the AALL0631 had a lower induction death rate. Protocol changes for infants treated on Cohort 2 included de-intensification of therapy, along with enhanced supportive care guidelines. It is unknown to what degree each of these changes may have contributed to improved induction survival. It was also possible that investigator awareness of the infectious toxicities may have resulted in earlier intervention and thus improved outcome for ill infants. The improved induction survival on the modified Interfant-99 based induction allowed for advancement to subsequent cycles of therapy where targeted therapy could be introduced.

Treatment of infants with ALL has been a challenge, and, unlike what has occurred for older children with ALL [1,2,4–6], little improvement has been observed in survival over the past twenty years. Studies performed prior to 1995 were associated with a high rate of early relapse [7,9,11,12,19]. Interfant-99, the largest study of infants with ALL, enrolled 474 evaluable subjects from 22 countries through the collaborative efforts of 17 study groups between 1999 and 2005. Complete remission rate at end induction was 94% (445/474) and EFS at 4 years was $47 \pm 2.6\%$. Induction mortality rate was 3.8% (18/474), indicating that intensity of induction was tolerable [15].

The immediate predecessor to COG AALL0631 was COG P9407, which introduced intensified therapy in an effort to decrease early relapse rates and to improve long-term survival. However, the initial treatment regimen was associated with a high induction mortality rate requiring several protocol modifications to de-intensify therapy and enhance supportive care recommendations. The AALL0631 was built upon these protocol modifications. Infants enrolled on the COG P9407 before and after these modifications had induction mortality rates of 25% and 5.7%, respectively [16]. Event-free survival rates for infants treated in COG P9407 and Interfant-99 were both less than 50%, suggesting that the benefit from intensification of standard chemotherapeutic agents has been maximized and innovative treatment strategies are required to improve survival [15,16].

With safety established on the revised COG P9407 induction, it was chosen as the backbone for the AALL0631, and the FLT3 inhibitor lestaurtinib was introduced as post-induction targeted therapy. Despite the established safety of the revised COG P9407 induction [16], excessive induction mortality early in conduct of AALL0631 (Cohort 1) necessitated modification to the initial AALL0631 study design. Differences between the revised COG P9407 induction and the original AALL0631 induction included a decreased daunorubicin dose and substitution of PEG-asparaginase for native L-asparaginase in AALL0631. Thus, while intensity was decreased with the daunorubicin dose change, it may have been increased with the asparaginase substitution due to the longer half-life of PEG-asparaginase versus L-asparaginase in older children and adults and due to the lack of understanding of the pharmacokinetic properties of these preparations in infants. While it is possible that these modifications to the revised COG P9407 induction contributed to the observed increase in mortality on AALL0631, it is also possible that the mortality rate was an artifact of small sample size and/or patient composition. Regardless of the cause of increased mortality, the primary objective of AALL0631 was to test whether addition of a targeted agent to post-

induction therapy would improve outcome. Therefore, changes to induction were made in an effort to maximize the probability that patients would be eligible to participate in the post-induction intervention.

Infection related mortality was further analyzed for AALL0631 Cohort 1 and compared to the COG P9407 (post 2001 amendment) and Interfant-99 clinical trials based on age at diagnosis. Infants < 7 days of age had significant mortality during induction on all studies, albeit patient numbers were small, with induction mortality in 1 of 2 (50%), 2 of 9 (22%) and 1 of 2 (50%) patients on the P9407, Interfant-99 and AALL0631, respectively. Even less data was available for infants 7–29 days of age at diagnosis, with only one death reported among the three trials. For infants ≥ 30 days of age at diagnosis, induction mortality was seen in 5/137 (4%), 18/452 (4%) and 3/24 (13%) of patients on the COG P9407, Interfant-99 and AALL0631, respectively [20]. Given these differences, an Interfant-99 based induction therapy was incorporated into AALL0631. Additional modifications to AALL0631 included enhanced supportive care guidelines, with the specific recommendation that infants be hospitalized until evidence of marrow recovery during induction. Following these changes to induction therapy, infection related induction mortality was similar to other infant ALL protocols [15,16].

The revised AALL0631 induction included low dose cytarabine instead of cyclophosphamide, lower daunorubicin dose, and use of native L-asparaginase instead of PEG-asparaginase. Dexamethasone (4.5 mg/m²/day) was also included in the revised induction, although its use had not been tolerated on the original COG P9407 at higher dosages (10 mg/m²/day). Thus, lower dose of dexamethasone on a different multi-agent induction backbone and/or following a 7 day prednisone prophase, such as Interfant 99, appears to be better tolerated. This is significant, as administration of dexamethasone during induction chemotherapy has been associated with improved long-term outcomes compared to prednisone in various ALL patient subsets [21–25].

Etiologies of infectious complications were similar to prior studies and included bacterial, fungal, and viral causes in Cohorts 1 and 2. Gram positive infections were more common in Cohort 1. Although mortality decreased and rates of infectious complications decreased, there was no significant difference in non-infectious toxicities between Cohorts. The reason for these differences is unknown, but may be the result of small sample size or may be that there are differences in non-infectious toxicities that cannot be ascertained by the current grading system (such as the duration of specific toxicities, for example).

In conclusion, rates of induction deaths decreased in Cohort 2 versus 1 due to de-intensification of induction therapy and enhanced supportive care guidelines. This change in induction therapy did not compromise therapy with increased complete response rates at end induction intensification for Cohort 2 versus Cohort 1. Further follow-up is needed to determine if the changes in induction therapy will impact EFS.

However, maximizing the likelihood that infants with ALL will successfully reach the post-induction phase of therapy will facilitate testing of promising targeted therapies.

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References

1. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*. 2010; 24(2):265–284. [PubMed: 20010625]
2. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009; 360(26):2730–2741. [PubMed: 19553647]
3. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol*. 2012; 30(14):1663–1669. [PubMed: 22412151]
4. Larsen EC, Salzer WL, Devidas M, et al. Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Oncology Group Study AALL0232. *ASCO Meeting Abstracts*. 2011; 29(15_suppl):3.
5. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2008; 111(5):2548–2555. [PubMed: 18039957]
6. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2011; 118(2):243–251. [PubMed: 21562038]
7. Silverman LB, McLean TW, Gelber RD, et al. Intensified therapy for infants with acute lymphoblastic leukemia: results from the Dana-Farber Cancer Institute Consortium. *Cancer*. 1997; 80(12):2285–2295. [PubMed: 9404706]
8. Chessells JM, Eden OB, Bailey CC, et al. Acute lymphoblastic leukaemia in infancy: experience in MRC UKALL trials. Report from the Medical Research Council Working Party on Childhood Leukaemia. *Leukemia*. 1994; 8(8):1275–1279. [PubMed: 8057661]
9. Reaman G, Zeltzer P, Bleyer WA, et al. Acute lymphoblastic leukemia in infants less than one year of age: a cumulative experience of the Children's Cancer Study Group. *J Clin Oncol*. 1985; 3(11):1513–1521. [PubMed: 3863894]
10. Frankel LS, Ochs J, Shuster JJ, et al. Therapeutic trial for infant acute lymphoblastic leukemia: the Pediatric Oncology Group experience (POG 8493). *J Pediatr Hematol Oncol*. 1997; 19(1):35–42. [PubMed: 9065717]
11. Dordelmann M, Reiter A, Borkhardt A, et al. Prednisone response is the strongest predictor of treatment outcome in infant acute lymphoblastic leukemia. *Blood*. 1999; 94(4):1209–1217. [PubMed: 10438708]
12. Reaman GH, Spoto R, Sensel MG, et al. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia treated on two consecutive trials of the Children's Cancer Group. *J Clin Oncol*. 1999; 17(2):445–455. [PubMed: 10080584]
13. Hilden JM, Dinndorf PA, Meerbaum SO, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. *Blood*. 2006; 108(2):441–451. [PubMed: 16556894]
14. Tomizawa D, Koh K, Sato T, et al. Outcome of risk-based therapy for infant acute lymphoblastic leukemia with or without an MLL gene rearrangement, with emphasis on late effects: a final report of two consecutive studies, MLL96 and MLL98, of the Japan Infant Leukemia Study Group. *Leukemia*. 2007; 21(11):2258–2263. [PubMed: 17690691]
15. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *The Lancet*. 2007; 370(9583):240–250.

16. Salzer WL, Jones TL, Devidas M, et al. Modifications to induction therapy decrease risk of early death in infants with acute lymphoblastic leukemia treated on Children's Oncology Group P9407. *Pediatr Blood Cancer*. 2012; 59(5):834–839. [PubMed: 22488662]
17. Salzer W, Dinndorf P, Dreyer Z, et al. Analysis of infectious complications in infants with acute lymphoblastic leukemia treated on the Children's Cancer Group Protocol 1953: a report from the Children's Oncology Group. *J Pediatr Hematol Oncol*. 2009; 31(6):398–405. [PubMed: 19648788]
18. Ferster A, Bertrand Y, Benoit Y, et al. Improved survival for acute lymphoblastic leukaemia in infancy: the experience of EORTC-Childhood Leukaemia Cooperative Group. *Br J Haematol*. 1994; 86(2):284–290. [PubMed: 8199016]
19. Igarashi S, Manabe A, Ohara A, et al. No Advantage of Dexamethasone Over Prednisolone for the Outcome of Standard- and Intermediate-Risk Childhood Acute Lymphoblastic Leukemia in the Tokyo Children's Cancer Study Group L95-14 Protocol. *Journal of Clinical Oncology*. 2005; 23(27):6489–6498. [PubMed: 16170158]
20. van der Linden MH, Valsecchi MG, De Lorenzo P, et al. Outcome of congenital acute lymphoblastic leukemia treated on the Interfant-99 protocol. *Blood*. 2009; 114(18):3764–3768. [PubMed: 19657114]
21. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005; 129(6):734–745. [PubMed: 15952999]
22. Schrappe M, Zimmermann M, Moricke A, et al. Dexamethasone in Induction Can Eliminate One Third of All Relapses in Childhood Acute Lymphoblastic Leukemia (ALL): Results of An International Randomized Trial in 3655 Patients (Trial AIEOP-BFM ALL 2000). *ASH Annual Meeting Abstracts*. 2008; 112(11):7.
23. Winick NJ, Salzer WL, Devidas M, et al. Dexamethasone (DEX) versus prednisone (PRED) during induction for children with high risk acute lymphoblastic leukemia (HR-ALL): a report from the Children's oncology group study AALL0232. *ASCO Meeting Abstracts*. 29(15_suppl): 9504.
24. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003; 101(10):3809–3817. [PubMed: 12531809]
25. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol*. 2013; 31(9):1202–1210. [PubMed: 23358966]

Table I**AALL0631 Induction**

Cohort 1 (2008)	Cohort 2 (2009–2012)[^]
TIT* days 1, 8, 15	IT** MTX day 1 IT HC and Ara-C day 15 IT MTX and HC day 29
VCR 0.05 mg/kg, days 1, 15; VCR 0.03 mg/kg, day 8	VCR 1.125 mg/m ² , days 8, 15, 22, 29
PDN 40 mg/m ² /day div TID, days 1–21	PDN 45 mg/m ² /day div TID, days 1–7 Dex 4.5 mg/m ² /day div TID, days 8–28
Daun IV over 30 min, days 1, 2 < 6 months - 1.7 mg/kg/day 6 – < 9 months - 2.1 mg/kg/day 9 months - 2.6 mg/kg/day	Daun 22.5 mg/m ² /day IV over 30 min, days 8, 9
Cy 250 mg/m ² every 12 hours x 4 doses, days 3, 4 (with MESNA)	Ara-C 56.25 mg/m ² /day days 8–21
PEG-asf 2,500 Units/m ² IM day 4 Filgrastim 5mcg/kg/day, beginning day 5 until ANC 500/μL	L-Asp 7500 Units/m ² IM days 15, 18, 22, 25, 29, 33

MTX – methotrexate, HC – hydrocortisone, Ara-C – cytosine arabinoside, VCR-vincristine, PDN-prednisone, Dex – dexamethasone, Daun-daunorubicin, Cy-cyclophosphamide, PEG-Asp- PEG-asparaginase, L-Asp-native L-asparaginase, IV – intravenous, IM – intramuscular, TID - three times daily.

[^] 7 days < 6 months of age - 11% reduction on all non-IT agents; < 7 days of age - additional 25% reduction on all non-IT agents;

* TIT - < 1 year of age - intrathecal (IT) MTX 7.5 mg, HC 7.5 mg, Ara-C 15 mg; 1 year of age - IT MTX 8 mg, HC 8 mg, Ara-C 16 mg;

** IT - < 1 year of age - IT MTX 6 mg, HC 12 mg, Ara-C 15 mg; 1 year of age - IT MTX 8 mg, HC 16 mg, Ara-C 20 mg;

Table II

Etiology of Infectious Deaths

	Age at Diagnosis	Day of Death	Site	Organism
Cohort 1 (n=26)	1	23	Sinus	<i>Aspergillus fumigatus</i>
	92	32	Blood	<i>Candida tropicalis</i>
	285	17	Lung	<i>Aspergillus fumigatus</i> <i>Pseudomonas aeruginosa</i>
	289	18	Blood	<i>Bacillus cereus</i>
Cohort 2 (n=123)	129	39	Blood	<i>Candida parapsilosis</i> <i>Enterococcus faecium</i>

Table III

Patients with Sterile Site Infections

Infectious Etiology	Cohort 1 (n=26)	Cohort 2 (n=123)	p
Fungal	2 (7.7%)	1 (0.8%)	0.0788
Gram Negative Bacteria	6 (23.1%)	16 (13%)	0.2228
Gram Positive Bacteria	11 (42.3%)	12 (9.8%)	0.0002
Viral	0	0	—