Infections in Pediatric AML: What Have We Learned

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Why Study Infections in AML?

- Infections:
  - Contribute to morbidity and mortality, particularly for those receiving intensive therapy
  - Costly
  - Affects quality of life
- AML:
  - High prevalence and incidence of infections
  - Infection-related mortality
  - Newer drugs such as anti-fungals – costly
  - Mandatory hospitalization
    - Resource intensive, parent/child quality of life

How Will We Learn about Infections in AML?

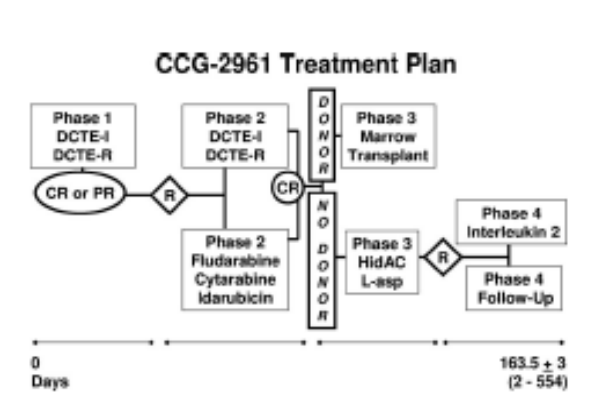
- Retrospective studies
  - Toxicity reporting of co-operative group trials
- Prospective observational trials
- RCTs

Retrospective Evaluation of Toxicity Reporting from Co-operative Group AML Trials

- Children's Oncology Group
  - CCG 2961
  - CCG 2891
- BFM
  - BFM-93

CCG-2961

- Children with AML between 1 month and 21 years of age



Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia

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- Infections on patients accrued between 1996 and 1999
- Infections collected using an infection report form by data managers
- 492 children included

Sung Blood 2007;110:3532-9

Number of Children with Microbiologically Documented Infections on CCG-2961

Table 3. Percentage of patients with at least one microorganism during each phase of therapy

	Phase 1, N = 492		Phase 2						Phase 3, N = 248	
			Total, N = 407		IdaDCTER, N = 205		Fludarabine, N = 202			
Microorganism characteristic	No.	%	No.	%	No.	%	No.	%	No.	%
At least 1 organism	297	60	300	74	157	77	143	71	176	71
1 organism	158	32	150	37	79	39	71	35	98	40
2 organisms	80	16	73	18	41	20	32	16	46	19
3 organisms	30	6	53	13	28	14	25	12	24	10
4 organisms	11	2	16	4	3	1	13	6	6	2
5 or more organisms	9	1	8	1	6	2	2	1	2	0

Sung Blood 2007

Microbiology of Infections

	Phase 1		Phase 2		Phase 3	
	N = 492	%	N = 407	%	N = 248	%
Gram Positive Bacteria	191	39	205	50	111	45
Gram Negative Bacteria	87	18	106	26	69	28
Fungus	88	18	86	21	34	14
Candida albicans	21	4	5	1	2	1
Other *Candida* species	30	6	20	5	7	3
Aspergillus species	20	4	42	10	7	3
Fusarium	2	0	3	1	2	1
Mucor	1	0	1	0	2	1

Infection-Related Mortality on CCG-2961

- Cumulative incidence infection-related mortality 11 ± 2% during chemotherapy (not SCT)
- 58 infection-related deaths:
  - Aspergillus species - 18 (31.0%)
  - Candida species – 15 (25.9%)
  - Coagulase negative staphylococci - 14 (24.1%)
  - Alpha hemolytic streptococci - 9 (15.5%)

Sung Blood 2007

Predictors of Infection-Related Mortality on CCG-2961

Table 6. Potential predictors of infection-related mortality

Characteristic	Hazard ratio (95% CI)	P
Age, y		
0 younger than 2	0.81 (0.37-1.76)	.597
2 to 16	Ref	NA
Older than 16	3.32 (1.87-5.89)	<.001
Ethnicity		
White	Ref	NA
Not white	1.85 (1.10-3.09)	.020
BMI percentile at diagnosis*		
Underweight	3.06 (1.51-6.22)	.002
Normal weight	Ref	NA
Overweight	1.58 (0.76-3.30)	.224
Cytogenetics		
Favorable	Ref	NA
Intermediate	0.95 (0.43-2.08)	.889
Unfavorable	2.32 (0.70-7.64)	.168
Institution size†		
6 or fewer	Ref	NA
More than 6	0.84 (0.45-1.55)	.571

AML-BFM93

- Children with AML between 0 and 17 years of age

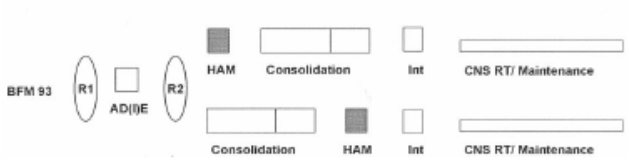

Fig 1. Treatment schedules of studies AML-BFM 87 and 93. CNS, central nervous system; Int, intensification; R1, randomization 1; R2, randomization 2; RT, radiotherapy.

Leukemia (2004) 18, 72–77

www.nature.com/leu

Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93

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[1]*Department of Pediatric Hematology and Oncology, Children's Hospital of the University of Frankfurt/Main, Germany; and* [2]*Department of Pediatric Hematology and Oncology, Children's Hospital of the University of Münster, Germany*

- Infections retrospectively abstracted
- 304 patients including 28 with Down syndrome

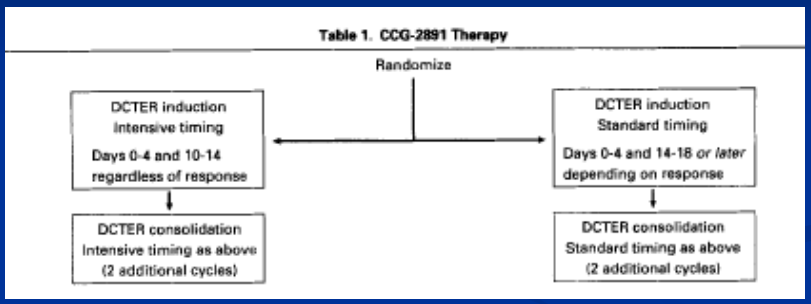
Lehrnbecher Leukemia 2004

Comparison of Infections on CCG-2961 and BFM-93

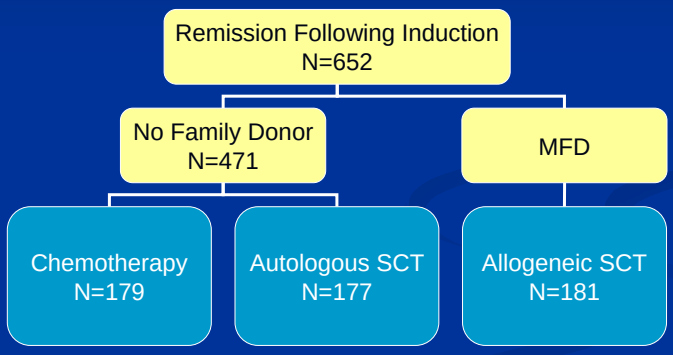
	CCG-2961	BFM-93
N	492	304
Induction Regimen	AraC 200 mg/ m^2/d x 8d Dauno 20 mg/ m^2/d x 4d Ida 5 mg/ m^2/d x 4d VP16 100 mg/ m^2/d x 8d 6TG 100 mg/ m^2/d x 8d Dex 6 mg/ m^2/d x 8d	AraC 100 mg/m^2/d x 8d Dauno 60 mg/m^2/d x 3d OR Ida 12 mg/ m^2x 3d VP16 150 mg/ m^2/day x 3d
Median age (years)	9.6	5.8
At least 1 microbiologically documented infection	60%	Approx 30%
Bacterial infections* Gram positive Gram negative	 69% 31%	 81% 19%
Most common isolates*	CoNS 18% VGS 10% *Candida* spp. 10%	CoNS 32% VGS 22%
Most common sites Blood Lung	 56% 13%	 83% 11%
Infection-related mortality	11%	6.6%
Most common causes of infectious mortality Aspergillus spp. Candida spp. CoNS VGS	 31% 26% 24% 16%	 20% 20%

* All sites on CCG-2961 and bloodstream on BFM-93

CCG-2891 Phase 1



CCG-2891 Phase 2



Viridans Group Streptococci (VGS) on CCG-2891

- Viridans group streptococcal bacteremia - most common cause bacteremia
- 18/887 (21%) of patients at least one episode
- Accounted for 25% of all bacteremia
- 59% “life-threatening”

Gamis JCO 2000

Risk Factors for VGS Bacteremia

Table 5. Patient Characteristics at AML Diagnosis and Rate of AHS Bacteremia During Induction Based on Days of Risk

	No. AHS	Patient-Days	Rate*	OR	P†
AHS rate in induction	156	90,852	0.17171		
Age					.007‡
0-2 years	40	17,847	0.22413	1.0	—
3-10 years	72	36,838	0.19545	0.9	.49§
11+ years	44	36,336	0.12109	0.5	.005
Sex					.84
Male	79	45,378	0.17409	1.0	—
Female	77	45,643	0.16870	1.0	.84
Race					.38
White	110	61,198	0.17974	1.0	—
Nonwhite	46	29,823	0.15424	0.9	.38
FAB					.37
M0	9	2,823	0.31881	1.0	—
M1	18	11,207	0.16061	0.5	.09
M2	47	29,145	0.16126	0.5	.06
M3	11	4,714	0.23335	0.7	.49
M4	33	20,815	0.15854	0.5	.06
M5	28	13,834	0.20240	0.6	.24
M6	1	1,602	0.06242	0.2	.12
M7	6	5,262	0.11403	0.4	.05
WBC at diagnosis					.84
0-20 × 10^3	73	44,695	0.16333	1.0	—
20-100 × 10^3	56	31,525	0.17764	1.1	.64
100+ × 10^3	27	14,801	0.18242	1.1	.62
Season at diagnosis					.88
Spring	39	22,487	0.17343	1.0	—
Summer	35	22,634	0.15463	0.9	.62
Fall	37	21,677	0.17069	1.0	.94
Winter	45	24,223	0.18577	1.1	.75

*Rate = number of AHS bacteremias per 100 patient-days of induction.
†Poisson regression models.
‡P values for test for homogeneity of the OR mean in each baseline risk factor.
§P values for that stratification level relative to baseline level identified by an OR of 1.

Additional Insights

More Risk Factors for VGS

- Asians had no reported episodes (P=.04)
- Those with grade 3 or 4 GI toxicity had more VGS (21% vs 12%, P<.01)

Recurrence Risk

- Those with one episode and were exposed to next course of chemotherapy had recurrence risk 31%
- Those with an episode during both induction courses had 44% risk of third episode

Other Lessons from CCG-2891 Infections by Intensity of Chemotherapy

- Phase 1 (induction), randomized to intensive or standard timing
- Phase 2 (consolidation), those with a family donor were allocated allogeneic stem cell transplantation (SCT); remainder were randomized to autologous SCT or chemotherapy
- Opportunity to compare infections between different treatments on an intent-to-treat basis

Sung et al. Cancer 2009; 115:1100-8

Infections in Induction by Intensive vs Standard Timing

	Standard Timing	Intensive Timing	P value
Number of Patients	335	343	
Bacteria	132 (39.4%)	198 (57.7%)	<0.001
All Gram positive bacteria	107 (31.9%)	159 (46.4%)	<0.001
Coagulase negative staphylococci	41 (12.2%)	53 (15.5%)	0.266
Viridans group *Streptococcus*	28 (8.4%)	53 (15.5%)	0.005
Enterococcus species	15 (4.5%)	24 (7.0%)	0.188
Staphylococcus aureus	14 (4.2%)	17 (5.0%)	0.714
All Gram negative bacteria	46 (13.7%)	91 (26.5%)	<0.001
Pseudomonas species	13 (3.9%)	32 (9.3%)	0.005
Klebsiella species	12 (3.6%)	21 (6.1%)	0.153
Escherichiae coli	11 (3.3%)	16 (4.7%)	0.434
Enterobacter species	5 (1.5%)	13 (3.8%)	0.092
Fungi	33 (9.9%)	94 (27.4%)	<0.001
Yeasts	28 (8.4%)	65 (19.0%)	<0.001
Molds	5 (1.5%)	40 (11.7%)	<0.001
Viruses	13 (3.9%)	48 (14.0%)	<0.001

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Infections by Consolidation

	Chemo	Auto SCT	P val	Allo SCT	P val
Number of Patients	168	137		147	
Bacteria	95 (56.5%)	69 (50.4%)	0.300	59 (40.1%)	0.005
All Gram positive bacteria	63 (37.5%)	47 (34.3%)	0.632	40 (27.2%)	0.055
CoNS	18 (10.7)%	17 (12.4%)	0.719	18 (12.2%)	0.724
Viridans group *Streptococcus*	27 (16.1%)	19 (13.4%)	0.632	4 (2.7%)	<0.001
Enterococcus species	3 (1.8%)	6 (4.4%)	0.308	5 (3.4%)	0.480
Staphylococcus aureus	3 (1.8%)	3 (2.2%)	1.000	3 (2.0%)	1.000
All Gram negative bacteria	48 (28.6%)	34 (24.8%)	0.517	32 (21.8%)	0.195
Pseudomonas species	11 (6.5%)	12 (8.8%)	0.517	10 (6.8%)	1.000
Klebsiella species	9 (5.4%)	7 (5.1%)	1.000	4 (2.7%)	0.271
Escherichiae coli	12 (7.1%)	7 (5.1%)	0.635	9 (6.1%)	0.822
Enterobacter species	4 (2.4%)	3 (2.2%)	1.000	3 (2.0%)	1.000
Fungi	16 (9.5%)	11(8.0%)	0.690	9 (6.1%)	1.000
Yeasts	12 (7.1%)	9 (6.6%)	1.000	6 (4.1%)	0.301
Molds	5 (3.0%)	2(1.5%)	0.465	3 (2.0%)	0.332
Viruses	7 (4.2%)	12(8.8%)	0.151	19 (12.9%)	0.728

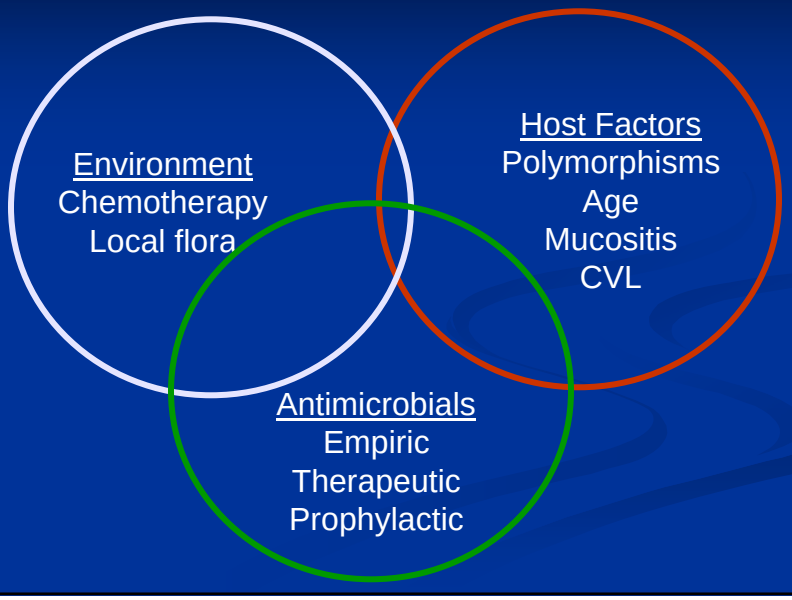
So Where do We Go From Here?

1. Improving risk stratification
2. Improving outcomes related to invasive fungal infections
3. Improving outcomes related to bacterial infections

Improving Risk Stratification

- Risk stratification for cancer therapy:
  - ALL
  - AML
  - Neuroblastoma
- ? Similar approach for infection
  - Tailored therapy
  - Intensity of infection prophylaxis, pre-emptive therapy, empiric therapy or treatment

Contributing Factors to Infection Risk and Outcome



Genetic Component to Susceptibility and Outcome of Infection

- Danish adoption registry
- Premature death from infection much more heritable compared to premature death from cancer or cardiovascular disease

BIOLOGICAL PARENT DIED OF INFECTION:

Child increased risk of premature infectious death

RR 5.8; 95% CI 2.5, 13.7

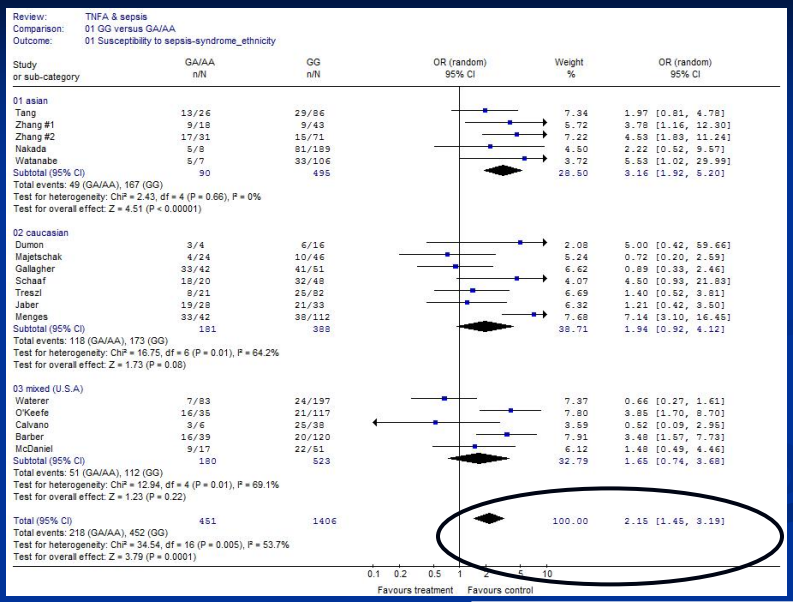
ADOPTIVE PARENT DIED OF INFECTION:

No increased risk of premature infectious death in child

Potential Effect of SNPs on Risk of Infection

- Genetic variation – single nucleotide polymorphsims (SNP)
- Growing evidence that SNPs involved in infection risk or outcome in immunocompetent and immunocompromised populations

Example TNFα-308



Teuffel et al. Crit Care Med in press

Prospective Study to Predict Infections in Children with AML

Primary Aim: To determine the relationship between the rate of invasive bacterial infection and SNPs in genes involved in immunity for children primary AML.

Methods

- Prospective, population based cohort study
- All children with primary AML in Canada and two centres in US
- Somatic DNA within 30 days diagnosis
  - Blood – isolate T lymphocytes
  - Buccal swab
- Candidate gene SNP analysis

Outcomes

Primary

- Number of invasive bacterial infections during time period at risk

Secondary

- Occurrence Gram positive/negative infections
- Occurrence invasive fungal infection
- Number of clinically documented infections

Progress to Date

- Year 3 of patient accrual
- Centres:
  - 15 Canadian
  - 2 US
- 142/300 subjects
  - Median age 9 years (range 0.2 to 17 years)
  - Adequate DNA from all

Studies in Development at COG

Improving Outcomes Related to Invasive Fungal Infections

- CCG-2961 – 14 to 21% of children experienced at least one invasive fungal infection
- Responsible for more than half infection-related deaths
- Primarily *Candida* and *Aspergillus*

Strategies to Improve Fungal Outcomes

- Prophylaxis
- Pre-emptive
- Empiric therapy
- Treatment
- Earlier diagnosis

A Randomized Double Blind Trial of Caspofungin vs Fluconazole to Prevent Invasive Fungal Infections in Children Undergoing Chemotherapy for AML

Study Chair:

Theo Zaoutis MD, MSc

Caspofungin Prophylaxis Studies

- Children undergoing chemotherapy according to the next AML phase 3 trial (AAML0931)
- DBRCT – IV fluconazole vs caspofungin during periods of neutropenia
- Primary outcome – proven or probable invasive fungal infections according to modified EORTC/MSG criteria
- Approximately 550 children

Other Concepts in Development at COG

- Antibiotic prophylaxis in children at higher risk of invasive bacterial infection
  - AML, relapsed ALL, SCT
  - Levofloxacin vs placebo
- Prevention of catheter-related infections
  - SCT
  - Chlorhexidine wipes vs placebo

Conclusions

- Infections continue to contribute substantial morbidity and mortality in paediatric AML
- Co-operative group trials and observational studies:
  - Provide insight into pathogenesis of infection
  - Provide understanding that allows design of future interventional trials
- Need for RCTs to improve infection outcomes

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