

Epidemiology of febrile events (FE) and safety of early antibiotic discontinuation in neutropenic patients (pts) with acute lymphoblastic leukemia (ALL)

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Background

Hematological patients undergoing intensive myelosuppressive treatment are at high risk for severe, life-threatening infectious complications. Epidemiology and incidence of these infections differ depending on the type of underlying malignancy and chemotherapy.

Nowadays the important problem is a growing resistance to antibiotics among the pathogens of infectious complications. One of the major causes of antimicrobial resistance is an increased and prolonged administration of antibiotics. The aim of this study was to evaluate the epidemiology of FE and safety of early antibiotic discontinuation in neutropenic pts with ALL on different chemotherapy phases.

Material/methods

Single-center, prospective observational study in adults with newly diagnosed ALL treated by «ALL - 2009» protocol (NCT01193933) was performed from Jan 2013 till Nov 2015. Pts were followed up for 180 days.

Results

Total of 44 pts were enrolled (22 - male, 22 - female; median age 26 (17 - 61). On admission hyperleukocytosis was in 25% (11/44) of pts, ECOG score ≥ 3 had 61% (27/44). These pts had 165 chemotherapy phases. Neutropenia was in 38% of chemotherapy phases, median duration was 15 (2 - 45) days, more frequent and prolonged in 1st induction then in other CP (68% vs 48% vs 13% vs 21%, $p=0.05$; 23.5 vs 8.5 vs 10 vs 7 days, $p=0.03$) (Fig. 1). FE occurred in 23% (38/165) of chemotherapy phases, predominantly in 1st induction, none FE were in 2nd consolidation. FE reasons were: fever of unknown origin (FUO) in 21%, clinically documented infection (CDI) in 47%, bloodstream infection (BSI) in 32% (Tabl. 1). Among BSI pathogens Gram-negative bacteria were in 66%, Gram-positive bacteria were in 44% (Fig. 2).

Rate of invasive mycoses (IM) was 16% (7/44). Molds were in 9% ($n=4$) pts and yeasts – in 7% ($n=3$). All IM occurred in induction. Nobody had IM in consolidation ($p=0.009$).

Antibiotics were stopped in 45% (17/38) of FE in persistently neutropenic pts (Tabl. 2). Antibiotics were reinstated in 29% (5/17) of pts due to recurrent fever.

None pts with antibiotic discontinuation were admitted to ICU and all of them survived.

Overall 180 days mortality was 7% (3/44), 2 pts died in 1st induction (1 – IA + mucormycosis, 1 – IA + BSI (*B. cereus*) and 1 - after 2nd consolidation in follow-up period (BSI due to *Salmonella* spp.).

Results

Single-center, prospective observational study Jan 2013 – Nov 2015

165 chemotherapy phases in 44 adult patients in with newly diagnosed ALL («ALL - 2009» protocol, NCT01193933)

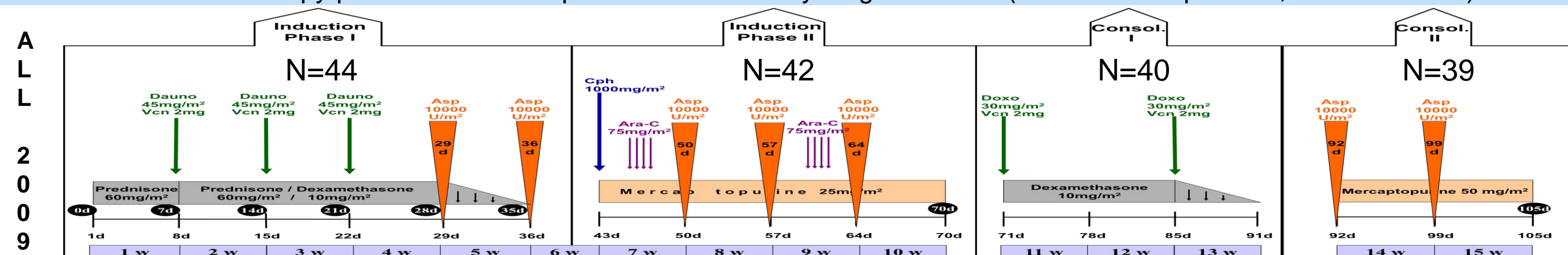
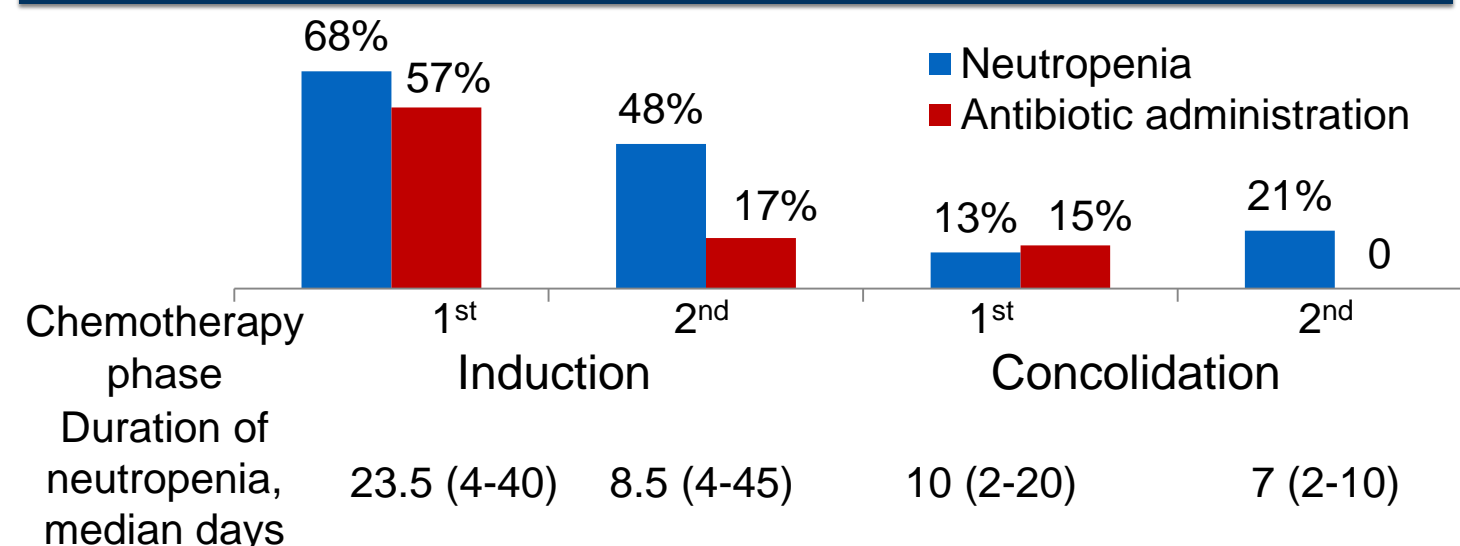


Fig. 1. Antibiotic administration and neutropenia



Tabl. 1. Epidemiology of FE on chemotherapy phases

	Induction		Consolidation
	1 st n=44	2 nd n=42	1 st n=40
Antibiotic administration	25 (57%)	7 (17%)	6 (15%)
FUO	6 (14%)	1 (2%)	1 (2,5%)
CDI	13 (29%)	4 (10%)	1 (2,5%)
Pneumonia	12 (27%)	2 (5%)	1 (2,5%)
Cellulitis	1 (2%)	2 (5%)	-
BSI	6 (14%)	2 (5%)	4 (10%)
Total duration of antibiotics median days	13 (2-70)	26 (7-36)	13 (6-18)

- FE occurred in 23% (38/165) of chemotherapy phases
- FE prevailed in 1st induction (57% vs 17% - 2nd induction vs 15% - 1st consolidation, $p=0.0001$); none FE were in 2nd consolidation
- Most pts (79%) had CMI and BSI

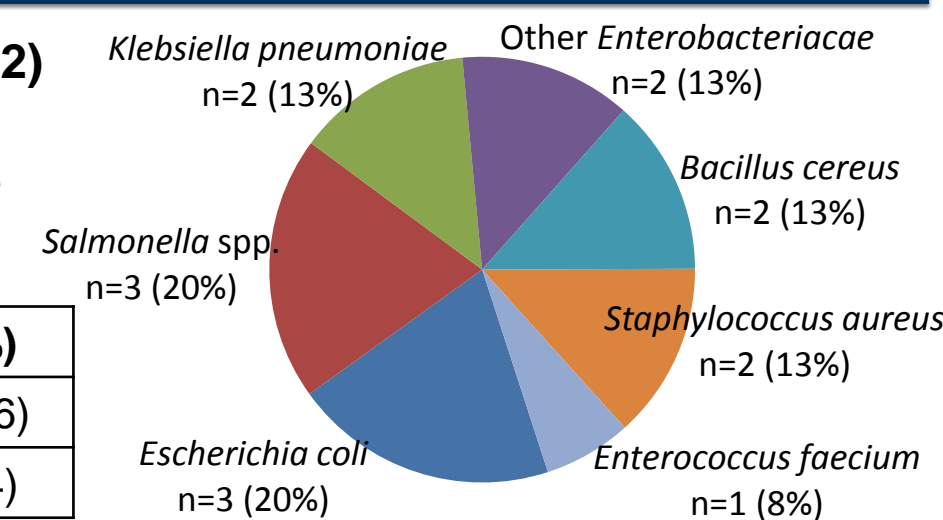
- Rate of IM was 16% (7/44): 7% ($n=3$) – IA (probable), 2% ($n=1$) - mixed IA + mucormycosis (probable), 7% ($n=3$) - hepatosplenic candidiasis
- All IM occurred in induction, nobody had IM in consolidation ($p=0.009$)

Fig. 2. Etiology of blood stream infections

Blood cultures (n=12)

- Monoculture - 9
- Mixed culture - 3

	N (%)
Gram-negative	10 (66)
Gram-positive	5 (34)



Tabl. 2. Antibiotic discontinuation in neutropenic pts

Antibiotic discontinuation	17/38 (45%)
Days from afebrile to antibiotics discontinuation	6 (1-19)
FUO	2,5 (1-3)
CMI and BSI	7 (1-19)
WBC ($10^9/L$) at antibiotic discontinuation, median	$0.7 \times 10^9/L$ (0.2–0.9)
Days from antibiotic stop to neutrophil recovery	8 (4-29)
Antibiotic reinstatement	5/17 (29%)
FUO	1
CDI (cellulitis)	2
BSI (<i>Enterobacter cloacae</i>)	1
IA (probable)	1
Mortality	0

- Antibiotics were stopped in 45% of persistently neutropenic pts
- Fever recurrence was in 29% of these pts
- None pts died in whom the antibiotics were stopped

Conclusions

Our study showed relatively low rate of infections (23%) in ALL pts treated by «ALL-2009» protocol. FE prevailed in 1st induction, nobody had infections in 2nd consolidation. Most pts (79%) had CMI and BSI. Antibiotics were safely stopped in 45% of persistently neutropenic pts. FR was in 29% of them and did not affect mortality.

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