

# The burden and outcomes of neutropenic fever following current-era treatment regimens for acute leukaemia and allogeneic haematopoietic cell transplant

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## Introduction

With increased use of alternative donors and evolving antimicrobial resistance, periodic review of the epidemiology of neutropenic fever (NF) in high risk patients is required.

## Aim

We sought to determine the frequency, duration and outcomes of NF in those receiving current-era conditioning regimens for alloHCT or induction and consolidation chemotherapy (CTx) for acute leukaemia (AL).

## Methods

- The PIPPIN study is a prospective, multicentre, randomised trial of conventional CT versus FDG-PET/CT for persistent or recurrent NF in adults with AL receiving CTx or conditioning for alloHCT or autoHCT
- Blood cultures were collected:
  - At NF onset (temp  $\geq 38.0^{\circ}\text{C}$ , neutrophils  $\leq 0.5$  cells/L),
  - If persisting fever  $>72$  h
  - If recurrent fever (new NF  $>72$ h after initial onset of NF)
- True positive BCs were defined by CDC National Healthcare Safety Network 2019 criteria
- Empiric sepsis management included early recognition, fluid resuscitation, empiric therapy with piperacillin-tazobactam, or cefepime +/- metronidazole, or ciprofloxacin + vancomycin
- Fluoroquinolone prophylaxis was not used

## Results

Between Jan 2018 and July 2020, 271 AL and alloHCT participants had 426 treatment cycles (192 alloHCT conditioning, 234 induction/consolidation/re-induction CTx).

49% of cycles were for acute myeloid leukaemia (AML).

**Median duration of neutropenia was:**

- 17 days for alloHCT (range 3-40)
- 19 days of AML induction (range 10-99)
- 11 days of AML consolidation (range 2-39).

**Neutropenic fever** occurred in 79.8% of cycles, including:

- **98.4% of AML induction**
- **90.6% of alloHCT**

Leukaemia chemotherapy	No. of cycles
<b>Induction (n=93)</b>	
7+3	41
HyperCVAD	15
HIDAC +3	8
5+2	8
FLAG	6
Paediatric-inspired ALL protocol	4
Paediatric-inspired ALL ext. induction	3
Other	8
<b>Reinduction (n=20)</b>	
FLAG	11
7+3	3
HIDAC +3	3
Other	3
<b>Consolidation (n=121)</b>	
HyperCVAD	46
HiDAC	32
FLAG	10
Paediatric-inspired ALL consolidation	9
5+2	7
HIDAC+2	6
Other	9
<b>AlloHCT conditioning</b>	
<b>Matched-unrelated (n=92)</b>	
Flu/Mel/Thymo	49
Bu/Cy/Thymo	12
Flu/Cy	11
Etop/TBI/Thymo	5
Flu/Mel	15
<b>Sibling (n=66)</b>	
Flu/Mel	27
Flu/Cy	12
Bu/Cy	10
Cy/TBI	7
Other	10
<b>Haploidentical (n=31)</b>	
Flu/Cy/TBI	17
Flu/Bu	8
Other	6
<b>Cord (n=1)</b>	
Flu/Bu/Mel	1

**Table 1: Treatment cycles for leukaemia induction/consolidation and alloHCT conditioning**

From first to last fever during neutropenia, **median duration of neutropenic fever** was:

- **12 days in AML induction** (IQR 1-25)
- 5 days in alloHCT (IQR 2-12)

**Persistent and/or recurrent NF** occurred in **52.6% of cycles**

- **93.7% of AML induction cycles** had persistent and/or recurrent NF

**41.2%** of NF episodes had  $\geq 1$  **positive BC**. Of 206 unique isolates:

- 32.0% were gram positive
- **61.7% gram negative**
- 5.3% fungal

ICU admission was required for:

- 15.1% of alloHCT conditioning
- 13.5% AML induction/reinduction
- 8.6% AML consolidation

All cause 30-day mortality was:

- 5.2% following alloHCT conditioning
- 1.6% AML induction
- 5.9% AML reinduction
- 1.6% AML consolidation cycles

## Conclusions

NF and persistent and/or recurrent NF are frequent in high-risk patients, especially those receiving AML induction.

ICU admission and all-cause mortality rates were lower than expected, which may in part be due to early recognition and management of sepsis.

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