Empirical antimicrobial therapy withdrawal after 72 hours of apyrexia in hematological patients with febrile neutropenia is safe and reduce unnecessary antibotic exposure: final results of randomized clinical trial “How Long”

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Transparency declaration

- JM Cisneros as served as a speaker for Novartis, Astellas, Pfizer, Merck Sharp & Dohme, Janssen and AstraZeneca

Introduction

- The **optimal length** of empirical antibacterial therapy (EAT) in hematological patients with febrile neutropenia is **still a challenge.**

- The **standard approach** is to continue EAT until neutrophils recovery, especially for high-risk patients.

  (Freifeld AG, **IDSA** Clinical Practice Guidelines. *Clin Infect Dis 2*011)

- The **discontinuation of EAT** in these patients after resolution of fever, and despite **persistent neutropenia,** is an increasing approach (Averbuch D, **European guidelines** (4th ECIL). Haematologica 2013)

- But there are **no published trials** to confirm efficacy and safety this recommendation.

Hypothesis

- In hematological high-risk patients with febrile neutropenia, **wait for recovery of neutropenia for EAT discontinuation**, unnecessarily prolong the length of treatment, favours bacterial resistance, and is opposite to the urgent need to optimize antimicrobial therapy.

- Whereas EAT discontinuation driven by a **clinical approach,** irrespectively of neutrophils recovery, would optimize EAT, reducing the potential negative consequences for the patient.

Objectives

- Main objective: to establish whether an **clinical approach** (apyrexia and clinical recovery) **is better** than the **standard approach** (recovery from neutropenia), to decide the suspension of empirical antibacterial therapy.

- Secondary objective: to demonstrate that the clinical approach **is as safe as** the standard.

Material and methods

- Investigator-driven, multicenter, randomized, open-labelled, in a superiority clinical trial (Nº EUDRACT: 2011-005152-34; NCT01581333 in *clinicaltrials.gov)*
- The setting: Six academic hospital in Spain
- Study period: may-12 to may-16

INCLUSION CRITERIA

ADULT PATIENTS (>16) with HEMATOLOGIC MALIGNANCY OR AUTOLOGOUS OR ALLOGENEIC SCT

+

HIGH RISK FEBRILE NEUTROPENIA

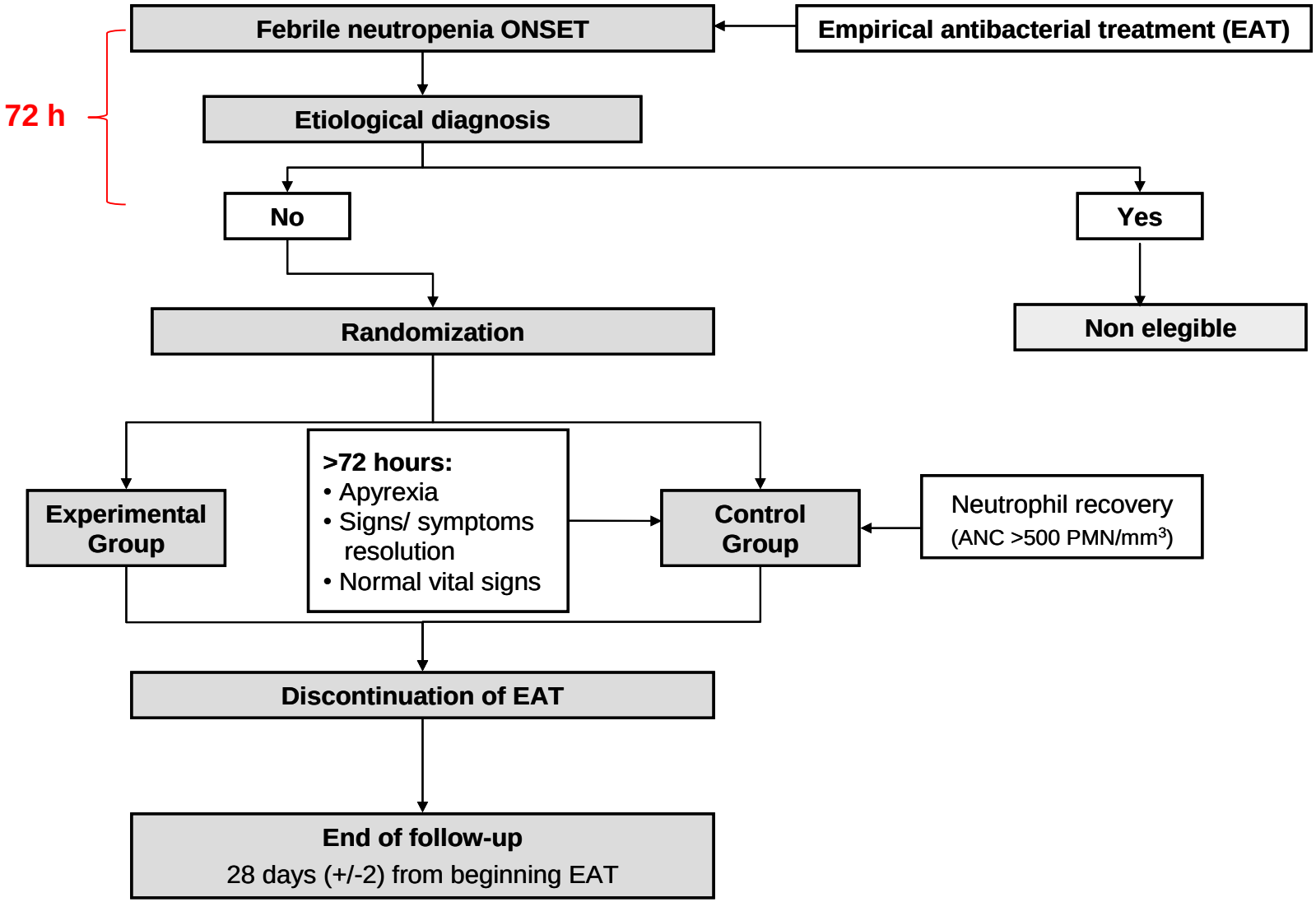
(expected > 7 days and ≤ 100 PMN/mm3)

EXCLUSION CRITERIA

ETIOLOGICAL DIAGNOSIS OF FEBRILE NEUTROPENIA

HIV infection, pregnancy or breastfeeding, renal failure, concomitant therapy with CYP3A4 substratum, epilepsy

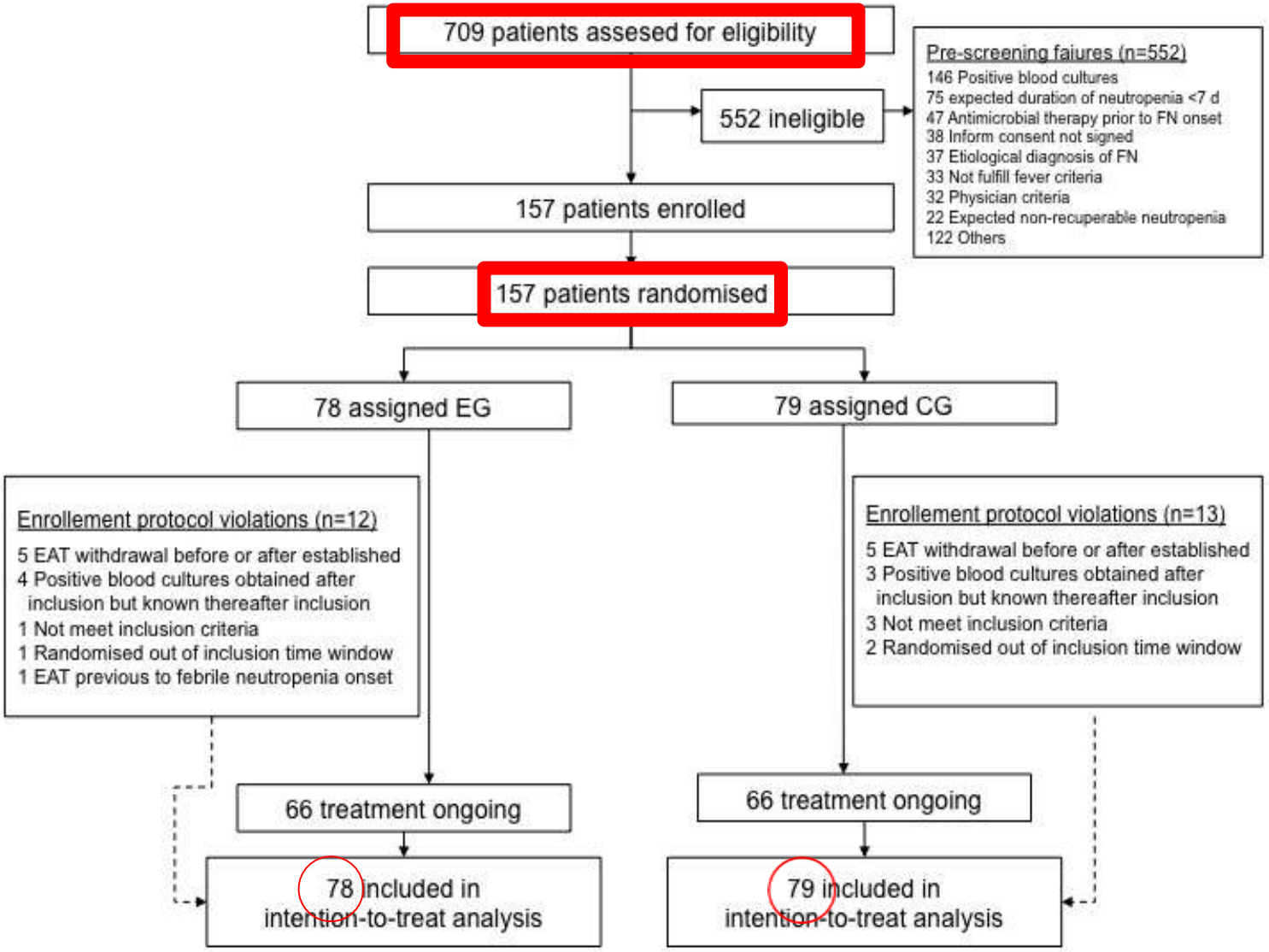
Flow-chart


Febrile neutropenia ONSET
Empirical antibacterial treatment (EAT)
72 h
Etiological diagnosis
No
Yes
Randomization
Non elegible
Experimental Group
>72 hours:
• Apyrexia
• Signs/ symptoms resolution
• Normal vital signs
Control Group
Neutrophil recovery
(ANC >500 PMN/mm3)
Discontinuation of EAT
End of follow-up
28 days (+/-2) from beginning EAT

Material and methods

- All primary analyses were made on an **ITT basis** in all randomized patients and in the **per-protocol population** (PPP).
- A **modified PPP** (patients in which clinical recovery and neutrophils recovery did not coincide) was analyzed separately
- **End-points**
  - **Efficacy:** number of free-days of EAT:
    - 28 - (days of antibacterial treatment)
  - **Safety:** (at 28 days from beginning EAT)
    - Crude (all-cause) mortality.
    - Total days of fever
- **Statistical analyses: descriptive** and **comparative analyses** (Chi square or Fisher exact test, T Student test or U of Mann-Whitney when necessary.
- **Sample Size: 156 patients**

Trial profile



Baseline characteristics

Variable	Experimental Group (n=78)	Control Group (n=79)	p
Age (years)	52 (42-61)	54 (39-63)	*ns*
Female	42 (53.8%)	36 (45.6%)	*ns*
Hematologic disease			
Acute leukemia	40 (51.3%)	31 (39.2%)	*ns*
Lymphoma	23 (26.4%)	29 (36.7%)	*ns*
Chronic Leukemia	2 (2.5%)	-	*ns*
Multiple myeloma	7 (9%)	14 (17.7%)	*ns*
Mielodysplastic syndrome	2 (2.5%)	-	*ns*
Severe aplastic anemia	-	1 (1.3%)	*ns*
Others	4 (5.1%)	4 (5.1%)	*ns*
Summary of treatments			
Chemotherapy	40 (51.3%)	31 (39.3%)	-
Autologus SCT	**29 (37.2%)**	**43 (54.4%)**	**0.04**
Allogeneic SCT	9 (11.5%)	5 (6.3%)	-

SCT: Stem cell transplantation

Clinical characteristics

Variable	Experimental Group (n=78)	Control Group (n=79)	p
Source of fever			
Non focused fever	31 (37.9%)	32 (40.5%)	*ns*
Abdominal	15 (19.2%)	15 (19%)	*ns*
Mucositis	14 (17.9%)	17 (21.5%)	*ns*
Pulmonary	7 (9%)	2 (2.5%)	*ns*
Perianal	2 (2.6%)	5 (6.3%)	*ns*
Others	11 (14.1%)	6 (7.7%)	
Median days of neutropenia (≤ 500 cels/mm^3)	14 (IQR: 9·5-24)	11 (IQR: 8-21·25)	*ns*
Recurrent fever	11 (14·3%)	14 (17·9%)	*ns*
Serious adverse event	11 (14·3%)	26 (32.9%)	*P=0.03*
Infections during follow up	31(39·7%)	23 (29.5%)	*ns*
Bacterial infection	14 (17.9%)	14 (17.7%)	*ns*
Invasive fungal infection	4 (5.1%)	10 (12.7%)	*ns*

IQR: interquartilic range

Efficacy end-point

	Experimental Group N (%)	Control Group N (%)	*P*
Intention-to-treat analyses	**78 (100)**	**79 (100)**	
Efficacy variable			
EAT free days (total) (median, IQR)	18 (12.5-21.5)	16 (9.7-20.2)	0·047
Per protocol population	**66 (84.6)**	**66 (83.5)**	
Efficacy variable			
EAT free days (total) (median, IQR)	19 (14-22)	14.5 (8.7-20)	0,02
Modified per protocol population	**36 (46.1)**	**30 (37.9)**	
Efficacy variable			
EAT free days (total) (median, IQR)	20 (11.2-23)	11.5 (5-16.7)	<0.01

74% increase in antibiotic-free days

EAT: empirical antifungal therapy; IQR: interquartilic range

Safety end-point

	Experimental Group N (%)	Control Group N (%)	*P*
Intention-to-treat analyses	**78 (100)**	**79 (100)**	
Safety variables			
Crude mortality	1 (1.3)	3 (3.8)	n.s
Days of fever	4 (2-8)	4 (2-8)	n.s
Per protocol population	**66 (84.6)**	**66 (83.5)**	
Safety variables			
Crude mortality	0 (0)	2 (3)	n.s
Days of fever	4 (1-14)	5 (2-8.2)	n.s
Modified per protocol population	**36 (46.1)**	**30 (37.9)**	
Safety variables			
Crude mortality	0 (0)	0 (0)	n.s
Days of fever	3 (1-7.2)	3 (1-5.7)	n.s

Conclusion

In hematological patients with febrile neutropenia of unknown origen, **EAT withdrawal after 72 hours of apyrexia and clinical recovery**, regardless of neutropenia reduces unneccesary exposure to antimicrobials and is safe.