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

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Background: the classical approach of continuing the initial empirical antibacterial therapy (EAT) in neutropenic patients with unexplained fever until neutrophil recovering results on unnecessarily prolonged EAT in daily clinical practice and favors bacterial resistance; but available scientific evidence supporting the alternative of stopping EAT before marrow recovery is moderate. The aim of this study is to establish if a clinical approach (apirexia and clinical recovery) is better than and as safe as the standard criteria (recovery from neutropenia) to decide the discontinuation of EAT.

Material/methods:

Randomized, controlled, multicenter and open-labeled phase IV clinical trial. Study period: May-12 to May-16. Inclusion criteria: a) Adult patients (≥ 18 years); b) Hematologic malignancy or autologous or allogeneic hematopoietic stem cell transplantation (SCT) recipients; b) High risk febrile neutropenia (FN). Exclusion criteria: etiological diagnosis of FN. Randomization 72 hours after fever onset to: 1. Experimental group (EG): EAT withdrawal if a) apyrexia ≥ 72 h; plus b) clinical recovery ≥ 72 h; or 2. Control group (CG): EAT withdrawal if, also >500 PMN/mm^3. Follow-up: 28 days from EAT. Efficacy end-point: number of EAT-free days. Safety end-point: total days of fever, crude mortality.

Results:

157 patients were included (EG 78 and CG 79). There were no differences in baseline characteristics or clinical presentation. The most frequent underlying diseases were induction/re-induction chemotherapy for acute leukemia (n=42, 26,7%), autologous SCT (n=42, 45,8%), and allogeneic SCT (n=14, 8,9%). The most frequent clinical presentation was non-focused FN (n=63, 40,1%), abdominal focused FN (n=34, 21,6%) and mucositis (n=31, 19,7%). Fever and neutropenia duration and EAT free days are detailed in Table 1. Recurrent fever frequency was 14,3% (EG) and 17,9% (CG) (*p*=ns) and crude mortality was 1,3% (EG) and 3,8% (CG) (p=ns).

Conclusions:

In hematological patients with febrile neutropenia of unknown origin, EAT withdrawal after 72 hours of apyrexia and clinical recovery regardless neutropenia is safe and reduce unnecessary exposure to EAT.

Table 1. Neutropenia and fever duration and EAT-free days.

Variables **ITT population**	Median (IQ range) **EG (n=78)**	Median (IQ range) **CG (n=79)**	*P*
Neutropenia duration (days)	14 (9,5-24)	11 (8-21)	*p*=ns
Fever duration (days)	4 (2-8)	4 (2-8)	*p*=ns
EAT free days*	18 (12,5-21,5)	16 (9,7-20,2)	*p*=0,047
Per protocol population	**EG (n=66)**	**CG (n=66)**	
Fever duration (days)	4 (1-14)	5 (2-8,2)	*p*=ns
EAT free-days*	19 (14-22)	14,5 (8,7-20)	*p*=0,02
Modified per protocol population #	**EG (n=36)**	**CG (n=30)**	

Fever duration (days)	3 (1-7,2)	3 (1-5,7)	*p*=ns
EAT free-days*	20 (11,2-23)	11,5 (5-16,7)	*P*<0,001

ITT: Intention to treat; EAT: empirical antimicrobial therapy; EG: experimental group; CG: control group. IQ range: interquartile range.
*EAT free-days: days of follow-up (28) – days of EAT.
#That in which clinical recovery visit and neutropenia recovery visit do not match